Mitochondrial dysfunction in autism and other neurological and psychiatric diseases

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Review of the Literature on Major Mental Disorders in Adult Patients With Mitochondrial Diseases

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Mitochondria are intracellular organelles crucial to the production cellular energy. Mitochondrial disease results from a malfunction in this biochemical cascade. These disorders can affect any organ system, producing diverse signs and symptoms, including psychiatric ones. Several authors argue that mitochondrial dysfunction is related to the pathophysiology of bipolar disorder and schizophrenia. Also, the authors retrieved 19 case reports that describe patients with mitochondrial diseases and psychiatric disorders. Most of these patients have psychiatric presentations that preceded the diagnosis of mitochondrial disease. The most common physical findings are fatigue, muscle weakness with or without atrophy, and hearing loss.

(Psychosomatics 2006; 47:1–7)

Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis

Jacqueline R. Weissman[1], Richard I. Kelley[2], Margaret L. Bauman[3], Bruce H. Cohen[4], Katherine F. Murray[3], Rebecca L. Mitchell[5], Rebecca L. Kern[2], Marvin R. Natowicz[1,4,5,6]*

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Abstract

Background: Previous reports indicate an association between autism spectrum disorders (ASD) and disorders of mitochondrial oxidative phosphorylation. One study suggested that children with both diagnoses are clinically indistinguishable from children with idiopathic autism. There are, however, no detailed analyses of the clinical and laboratory findings in a large cohort of these children. Therefore, we undertook a comprehensive review of patients with ASD and a mitochondrial disorder.

Methodology/Principal Findings: We reviewed medical records of 25 patients with a primary diagnosis of ASD by DSM-IV-TR criteria, later determined to have enzyme- or mutation-defined mitochondrial electron transport chain (ETC) dysfunction. Twenty-four of 25 patients had one or more major clinical abnormalities uncommon in idiopathic autism. Twenty-one patients had histories of significant non-neurological medical problems. Nineteen patients exhibited constitutional symptoms, especially excessive fatigability. Fifteen patients had abnormal neurological findings. Unusual developmental phenotypes included marked delay in early gross motor milestones (32%) and unusual patterns of regression (40%). Levels of blood lactate, plasma alanine, and serum ALT and/or AST were increased at least once in 76%, 36%, and 52% of patients, respectively. The most common ETC disorders were deficiencies of complex I (64%) and complex III (20%). Two patients had rare mtDNA mutations of likely pathogenicity.

Conclusions/Significance: Although all patients' initial diagnosis was idiopathic autism, careful clinical and biochemical assessment identified clinical findings that differentiated them from children with idiopathic autism. These and prior data suggest a disturbance of mitochondrial energy production as an underlying pathophysiological mechanism in a subset of individuals with autism.

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Review

Cognitive decline as a manifestation of mitochondrial disorders (mitochondrial dementia)

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Available online 24 June 2008

Abstract

Mitochondrial disorders, in particular respiratory chain diseases (RCDs), present either as single organ problem or as multi-system disease. One of the most frequently affected organs in RCDs, in addition to the skeletal muscle, is the central nervous system (CNS). CNS manifestations of RCDs include epilepsy, stroke-like episodes, migraine-like headache, ataxia, spasticity, movement disorders, psychosis, demyelination, calcification, but also dementia. Cognitive impairment may be a feature of syndromic as well as non-syndromic RCDs.

ORIGINAL ARTICLE

The Otolaryngological Manifestations of Mitochondrial Disease and the Risk of Neurodegeneration With Infection

Joseph L. Edmonds, MD; Daniel J. Kirse, MD; Donald Kearns, MD; Reena Deutsch, PhD; Liesbeth Spruijt, MD; Robert K. Naviaux, MD, PhD

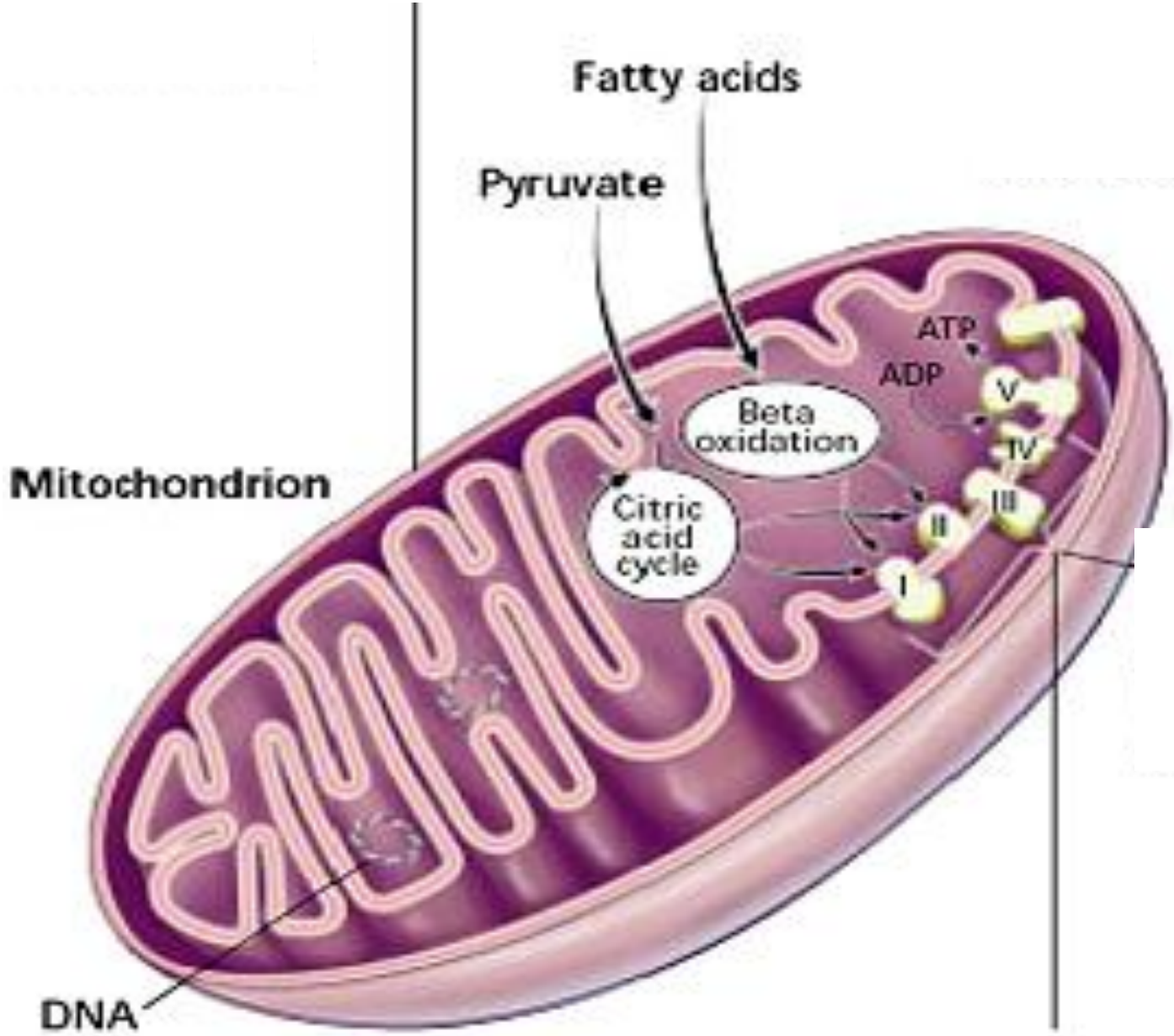
Arch Otolaryngol Head Neck Surg. 2002;128:355-362

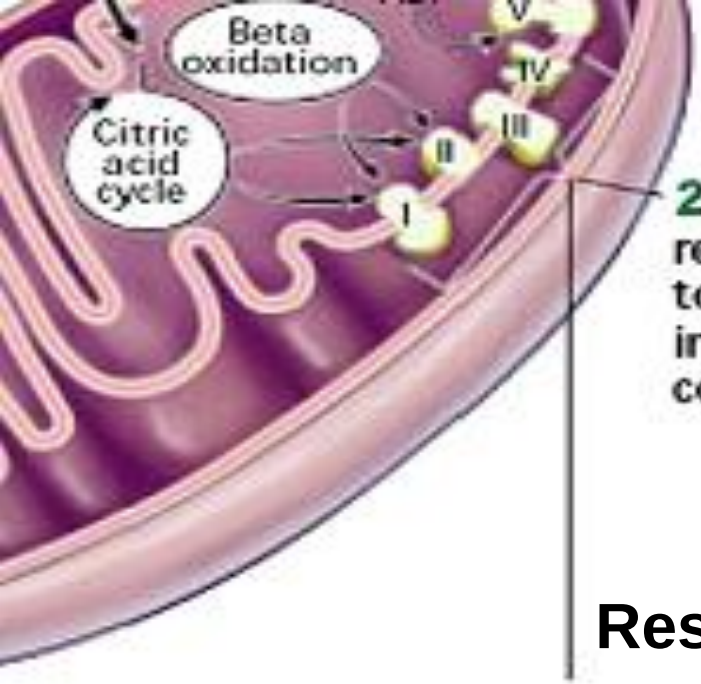
Arch Otolaryngol Head Neck Surg. 2002;128:355-362

Table 2. Presenting Signs and Symptoms of Mitochondrial Disease*

Presenting Symptom	Diagnosis, No. of Patients									Summary, No. (%), (N = 40)	Mean (95% Confidence Interval)
	KSS (n = 1)	COX (n = 5)	NARP (n = 3)	MELAS (n = 10)	PDH (n = 3)	PMPS (n = 1)	CI (n = 5)	3-HIBA (n = 1)	Other (n = 11)		
DD	0	2	2	3	1	0	3	1	4	16/40 (40)	0.40 (0.25-0.57)
SLE	0	1	1	5	1	0	1	0	1	10/40 (25)	0.25 (0.13-0.42)
Ataxia	1	1	0	2	0	0	0	0	1	5/40 (13)	0.13 (0.02-0.23)
Acidosis	0	0	0	0	1	0	0	1	3	5/40 (13)	0.13 (0.02-0.23)
Seizure	0	0	0	1	0	0	1	0	1	3/40 (8)	0.08 (0.00-0.15)
Hearing loss	0	0	0	3	0	0	0	0	0	3/40 (8)	0.08 (0.00-0.15)
FTT	0	1	0	0	0	1	0	0	1	3/40 (8)	0.08 (0.00-0.15)
Blindness	0	0	0	0	0	0	1	0	1	2/40 (5)	0.05 (0.00-0.12)
Ptosis	0	0	0	1	0	0	0	0	0	1/40 (3)	0.03 (0.00-0.08)
Ophthalmoplegia	1	0	0	0	0	0	0	0	0	1/40 (3)	0.03 (0.00-0.08)
Other cranial nerve dysfunction	0	1	1	0	0	0	0	0	1	3/40 (8)	0.08 (0.00-0.15)
Cardiomyopathy	0	0	0	1	0	0	0	0	0	1/40 (3)	0.03 (0.00-0.08)
Vomiting†	0	0	0	0	0	1	0	0	0	1/40 (3)	0.03 (0.00-0.08)
Other	0	0	1	0	0	1	0	0	0	2/40 (5)	0.05 (0.00-0.12)

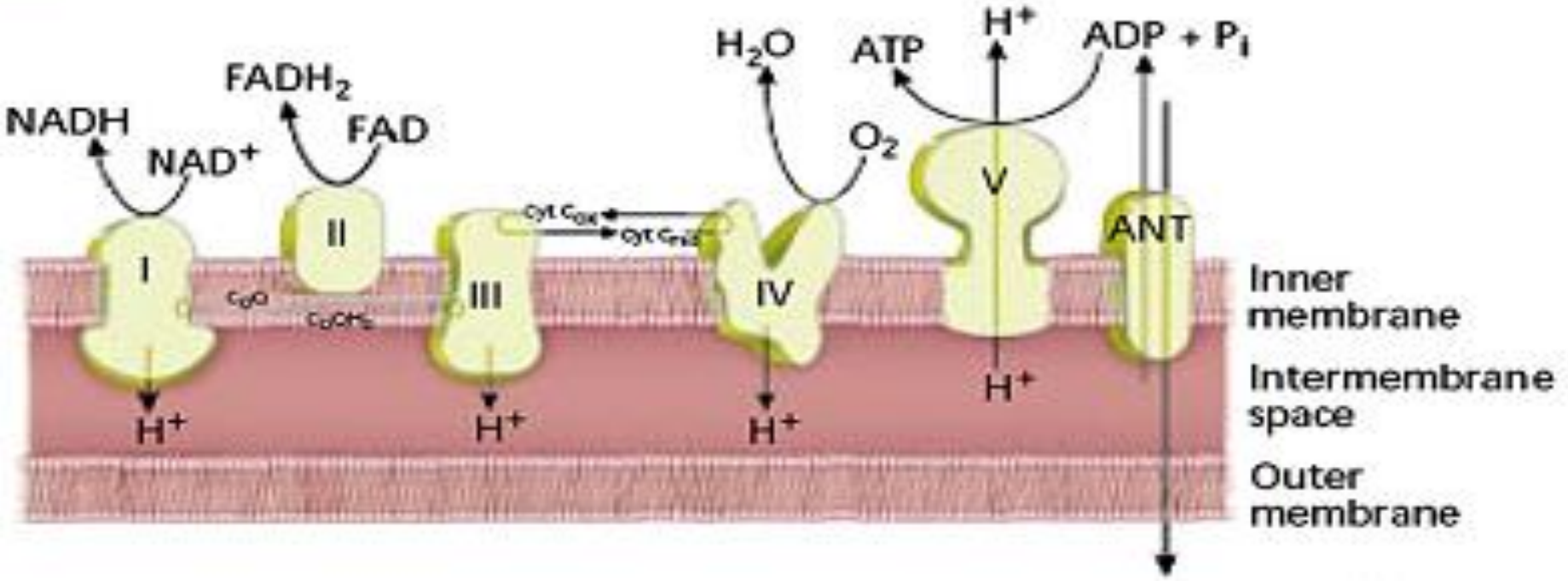
*Only symptoms leading to a mitochondrial evaluation and diagnosis are listed. Most patients had several abnormalities. Abnormalities such as acidosis, seizure disorder, and hearing loss were sometimes present in subclinical forms at the time of diagnosis and were recognized only later after specific testing. Abbreviations are given in Table 1. Gastrointestinal problems and hypotonia were common among patients presenting in the first year of life, but in most cases did not lead to a diagnostic evaluation.


Fatty acids
Pyruvate
Mitochondrion
Beta oxidation
Citric acid cycle
ATP
ADP
V
IV
III
II
I
DNA

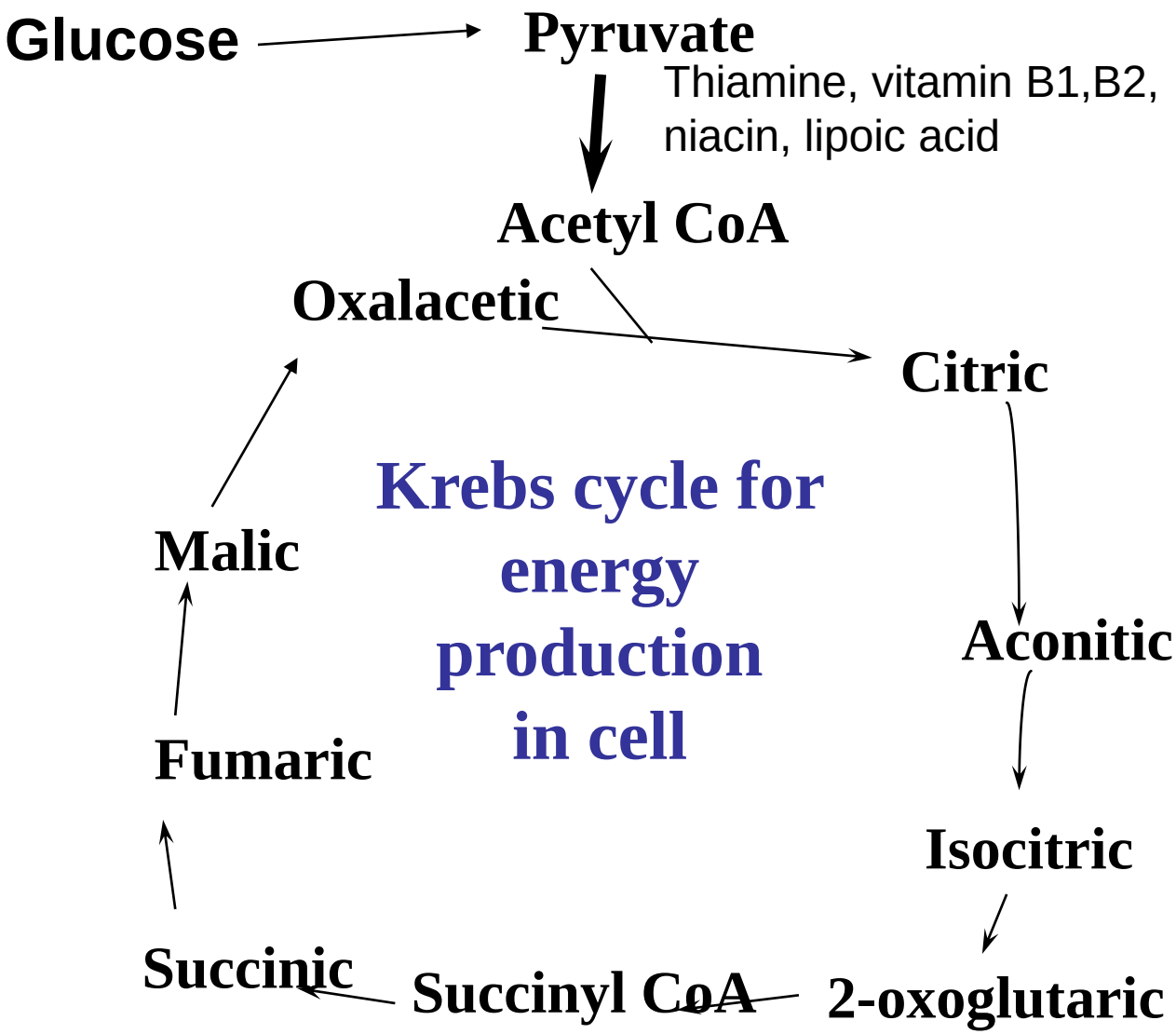


2 The electron transport chain (also called the respiratory chain) uses the energy from the electrons to pump hydrogen ions (protons) into the intermembrane space. The electron transport chain comprises five complexes designated I through V.

Respiratory complexes I-V



Central role of Krebs cycle



Unique mitochondria DNA

- Mitochondria DNA uses different genetic code from nuclear DNA
- Mitochondria DNA not attached to histones, proteins that bind to DNA and regulate the expression of genes
- Histones protect DNA from free radical damage and assist in repairing DNA damage
- Mitochondria DNA does not have this histone protection; more subject to chemical damage and mutations
- Mitochondria may be descendants of bacteria that invaded cells a billion years ago

Unique mitochondria DNA

- Each mitochondrion contains 2 to 10 copies of the mitochondrial DNA (mt DNA).
- Circular, double-stranded DNA molecule 16569 base pairs (bp) in length.
- Mitochondrial DNA encodes only 13 of the more than 1000 proteins required for mitochondrial biogenesis and function.

Mitochondria general

- 16-100,000 mitochondria per cell
- 16 in tail of sperm-none enter fertilized egg
- 100,000 in oocyte- all mitochondrial DNA comes from mother
- Mitochondria found in all cells except red blood cells
- Produce 90% of the energy in the cell
- Uses 85% oxygen in the cell
- Krebs cycle and electron transport chain (ETC) are 2 major biochemical functions
- Highest number in heart and skeletal muscle, liver, and brain which are organs that require greatest amount energy

CLEVELAND CLINIC JOURNAL OF MEDICINE
VOLUME 68 • NUMBER 7 JULY 2001 625-642

TABLE 7

Vitamins, supplements, and medications used in mitochondrial diseases

SUPPLEMENT	DAILY DOSE	COMMENTS
Coenzyme Q_{10}	5–15 mg/kg in divided doses	Variable gastrointestinal absorption dependent on formulation Maximal benefit may take months
L-carnitine	30–100 mg/kg in divided doses	Prescription brand Carnitor IV and oral preparations available
Thiamine (vitamin B_1)	100–800 mg	
Riboflavin (vitamin B_2)	400 mg	
Niacinamide (vitamin B_3)	100–500 mg	Avoid niacin form, as it can cause uncomfortable flushing
Folate	1–10 mg	
Vitamin E	400–1200 IU in divided doses	May interfere with CoQ_{10} absorption
Selenium	25–50 µg	
Lipoic acid	200–600 mg in divided doses	
Prednisone	5–60 mg	Symptomatic improvement noted on patients, but should be used sparingly as withdrawal of treatment may lead to recurrence of symptoms

Signs of mitochondrial dysfunction Cohen and Gold, 2001

- Muscles-low muscle tone, weakness, low exercise tolerance, muscle pain, cramps
- Brain-developmental delay, mental retardation, autism, dementia, seizures, migraines, stroke
- Nerves-nerve pain, absent deep tendon reflexes, lack of or excessive sweating, abnormal temperature regulation
- Gastrointestinal problems-reflux, constipation,

Diseases associated with mitochondrial disorder

- Autism
- Diabetes
- Cancer
- Alzheimer's
- Anxiety
- Chronic fatigue syndrome
- Exercise intolerance
- Parkinson's
- Bipolar disorder
- Aging
- Schizophrenia
- Heart disease
- Toxic chemical exposure

CLIN. CHEM. 40/10, 1879–1883 (1994) • Molecular Pathology

Tiglylglycine Excreted in Urine in Disorders of Isoleucine Metabolism and the Respiratory Chain Measured by Stable Isotope Dilution GC-MS

Michael J. Bennett,[1,4] Susan Powell,[1] Daniel J. Swartling,[2] and K. Michael Gibson[3]

Tiglylglycine is specific Marker for mitochondrial function

Tiglylglycine (TG), an interm… olism of isoleucine, is increase… with β-ketothiolase deficiency or … pionate metabolism. It is also impl… diagnostic marker in disorders of the r… We present a method for the synth… tiglyl[^{13}C,^{15}N]glycine and the developme… tope dilution mass spectrometric assay … pare data from controls with that from su… tothiolase deficiency and propionyl-C… deficiency, and with six patients with e… disorders of the respiratory chain. TG w… the urine from all of the patient groups. The … excretion did not persist in one patient with a respiratory chain defect, which suggests that, in some patients, multiple sample analysis may be necessary to identify a respiratory chain defect. This is the first urinary compound to be implicated as a potential marker of disorders of the respiratory chain.

Indexing Terms: *organic acids/reference range/mitochondrial en-*

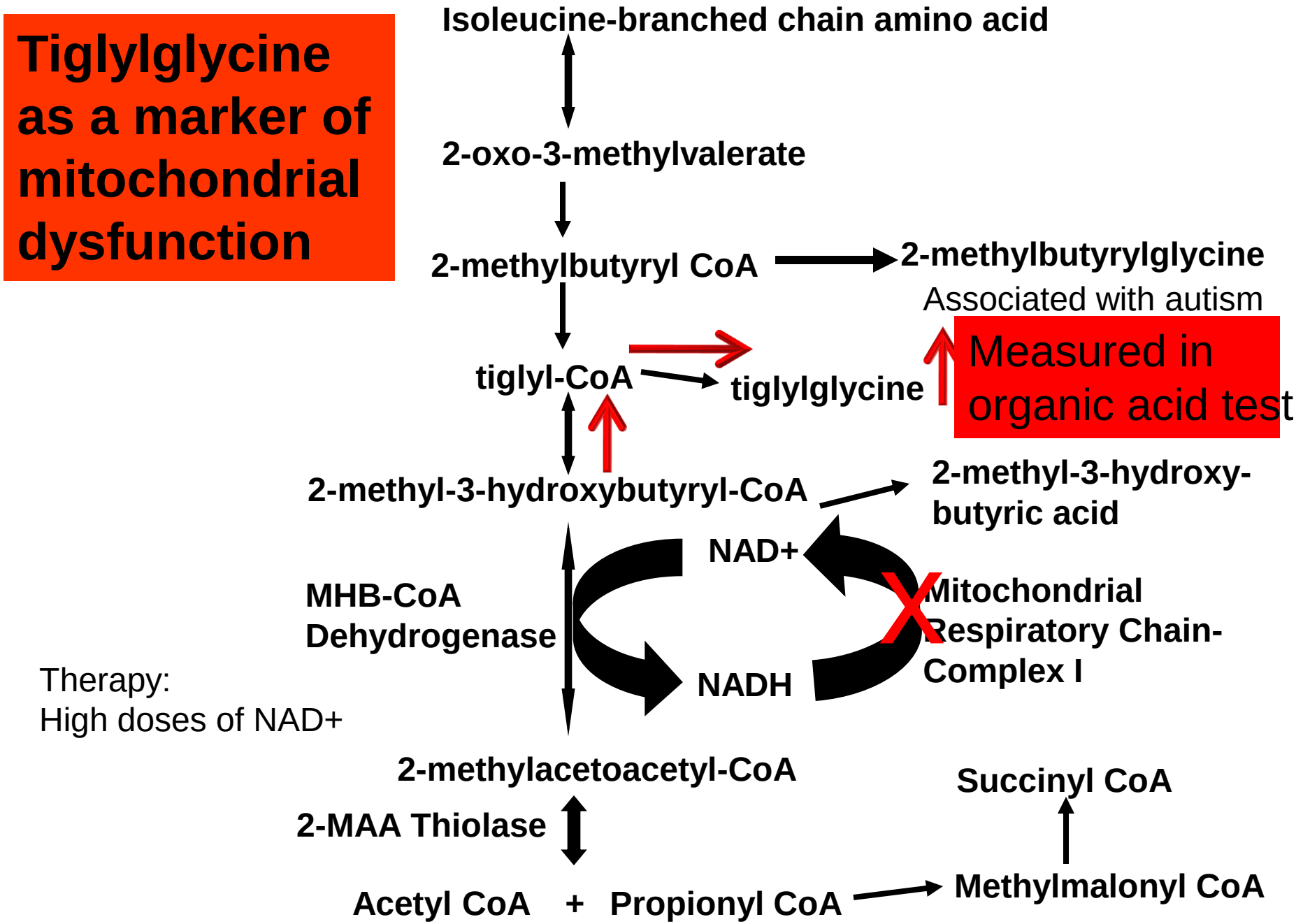
…ary lactic ac-
…able has hin-
…tative assay.
…and of stable-
…^{5}N]TG), and
…sitive stable
…pectrometric
… excretion of
…ses including
… in patients
…atory chain.

Materials and Methods

Synthesis of Labeled and Unlabeled TG

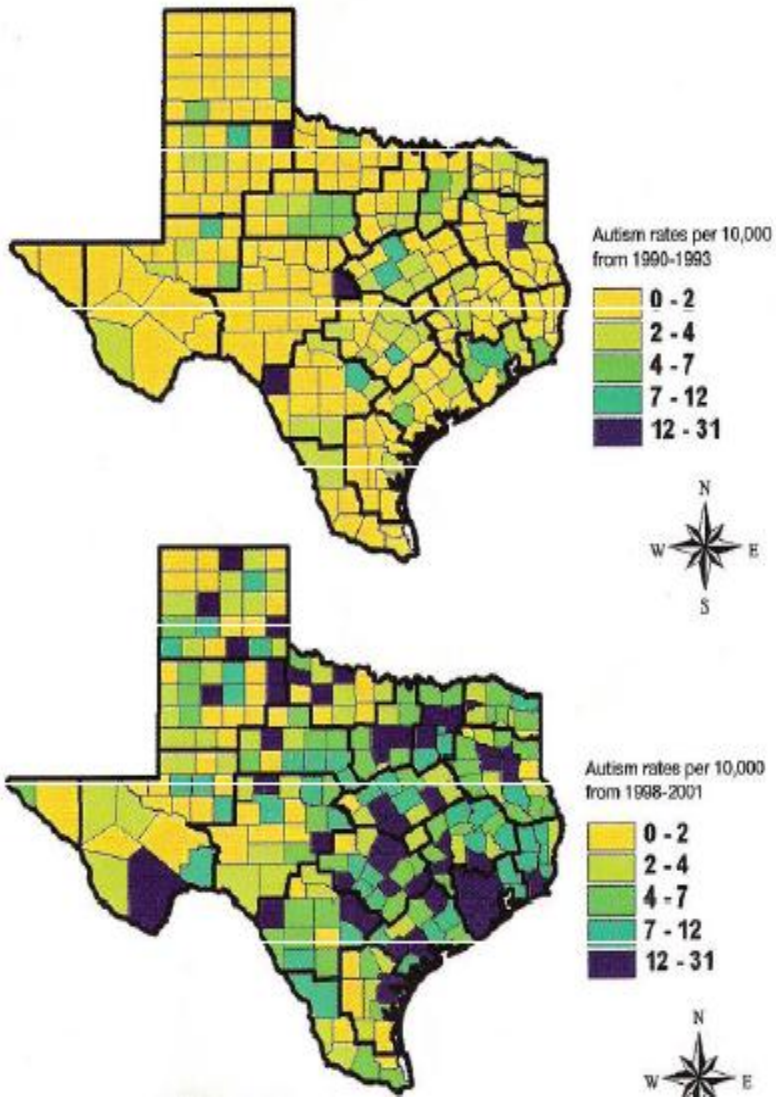
[^{13}C,^{15}N]Glycine (99 atom % pure) was obtained from Merck, Sharpe and Dohme (Montreal, Canada). TG was synthesized by a modification of the procedure described by Rowley and Gerritsen (*6*). Tiglylchloride was prepared from tiglic acid according to Yamada (*7*) by reflux with thionyl chloride and distillation. Glycine (labeled

Tiglylglycine as a marker of mitochondrial dysfunction

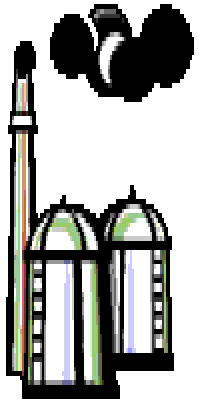


Therapy:
High doses of NAD+

Autism rates in Texas

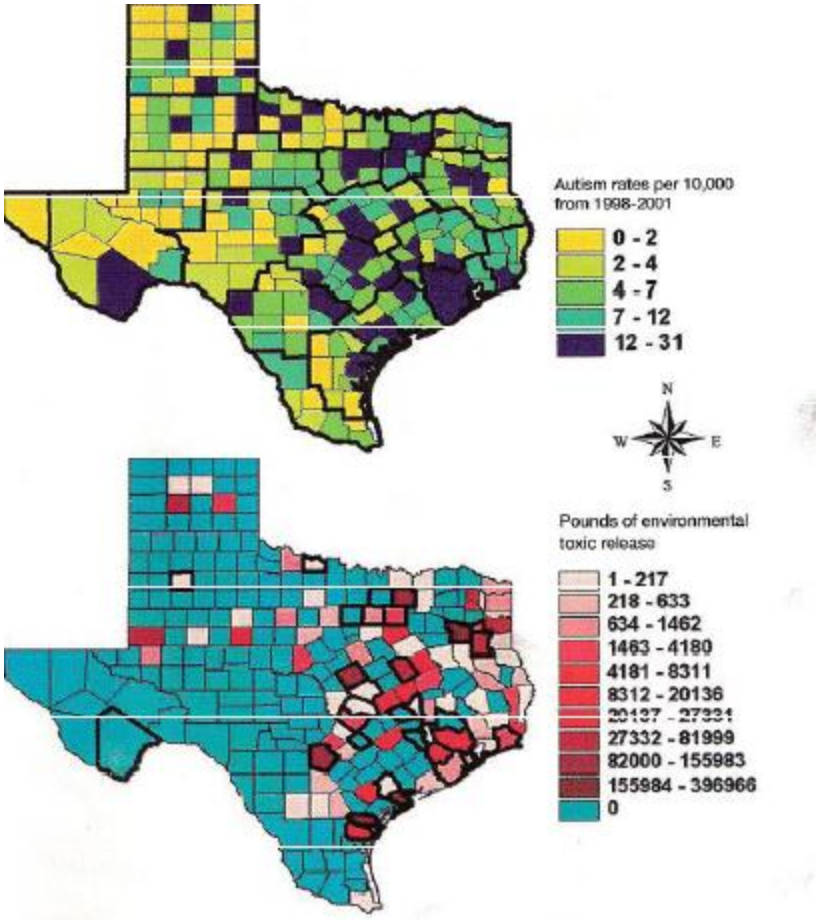


1990-1993



1998-2001

Comparison of autism rates and industrial pollution in Texas



Autism rate1998-2001

Pounds of industrial toxic release

Environmental mercury release, special education rates, and autism disorder: an ecological study of Texas

Raymond F. Palmer[a,*], Steven Blanchard[b], Zachary Stein[a], David Mandell[c], Claudia Miller[a]

[a]*University of Texas Health Science Center, San Antonio Department of Family and Community Medicine, 7703 Floyd Curl Drive, San Antonio, Texas 78229-3900, USA*

[b]*Department of Sociology, Our Lady of the Lake University, San Antonio, Texas, USA*

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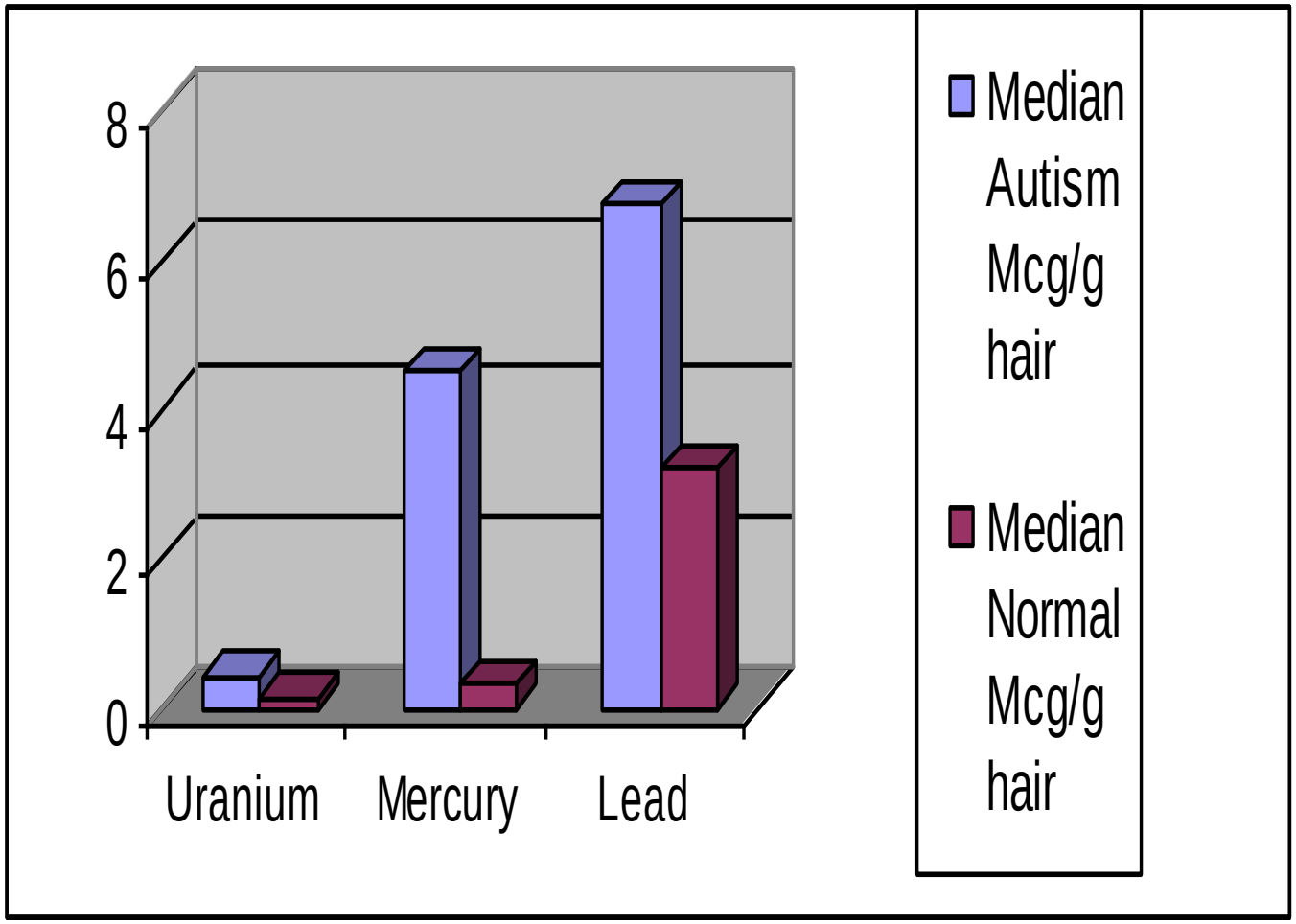
Accepted 1 November 2004

Environmental mercury release, special education rates, and autism disorder: an ecological study of Texas
Raymond F. Palmer, et al

- There has been a significant increase in the proportion of children in special education and autism associated with mercury released into the environment.
- For every 1000 lb of mercury liberated into the environment, there has been a 43% increase in the rate of special education students and a 61% increase in the percentage of students with autism.

Hair metals in boys with autism

n=40 boys per group, age matched



Autism 9:290-298,2005

COMMENTARY-SPECIAL ISSUE

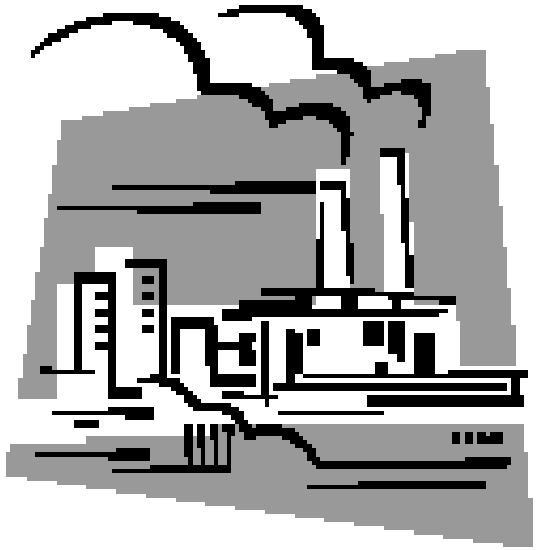
Autism Spectrum Disorders and Identified Toxic Land Fills: Co-Occurrence Across States

Environmental Health Insights 2008:2 55–59

Xue Ming[1], Michael Brimacombe[2], Joanne H. Malek[3], Nisha Jani[2] and George C. Wagner[3]

[1]Departments of Neurosciences and Pediatrics, UMDNJ-New Jersey Medical School, Newark, NJ. [2]Department of Preventive Medicine, UMDNJ-New Jersey Medical School, Newark, NJ. [3]Department of Psychology, Rutgers University, New Brunswick, NJ.

The area of highest ASD cases coincides with the highest density of toxic landfill sites while the area with lowest ASD cases has the lowest density of toxic landfill sites.



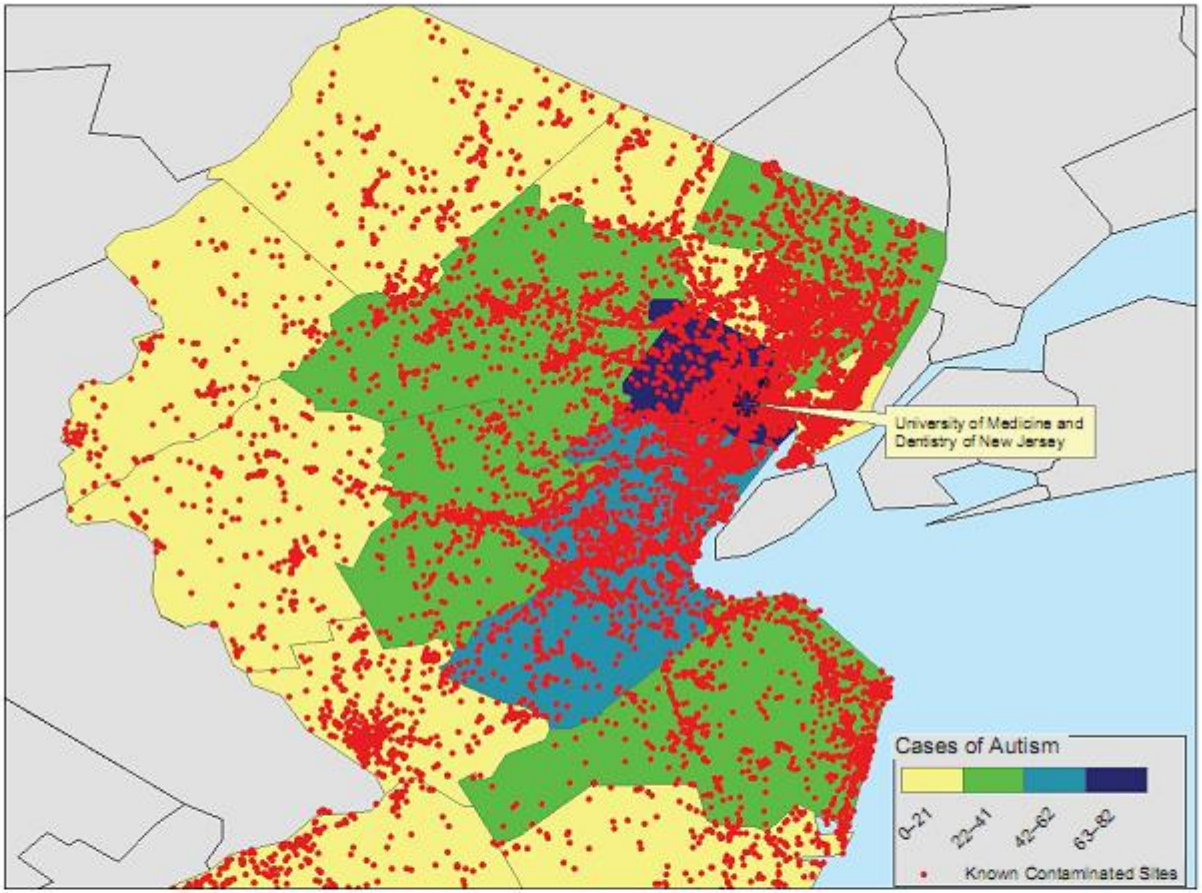


Figure 1. The Distribution of Toxic Landfill Sites and the ASD Cases by Zip Code.
From: http://www.state.nj.us/dep/srp/kcs-nj/The number of the autism spectrum disorders cases in a specific county is color coded according to the density scale in the insert. These data represent the cases seen at the Autism Center from 1998 to 2006, not population based prevalence. Each red dot represents a toxic landfill site.

Polish Journal of Environmental Studies Vol. 13, No. 4 (2004), 397-401

Chlorfenvinphos, an Organophosphate Insecticide, Affects Liver Mitochondria Antioxidative Enzymes, Glutathione and Hydrogen Peroxide Concentration

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Received: 10 September 2003
Accepted: 26 November 2003

Abstract

Impaired mitochondrial energy metabolism and neuronal apoptotic cell death after chronic dichlorvos (organophosphate) exposure in rat brain.

NeuroToxicology Volume 28: 1208-1219,2007

- Decreased mitochondrial electron transfer activities of cytochrome oxidase (complex IV) along with altered mitochondrial complex I, and complex II activity
- An increase in lipid peroxidation, and as well as protein and mtDNA oxidation.
- All this could have been because of enhanced oxidative stress, decreased GSH levels and also decreased Mn-SOD activity in the mitochondria
- Evidence of impaired mitochondrial bioenergetics and apoptotic neuronal degeneration after chronic low-level exposure to dichlorvos

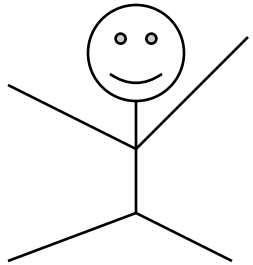
Pesticide Application

E. Guillette et al, "An Anthropological Approach to the Evaluation of Preschool Children Exposed to Pesticides in Mexico," ENVIRONMENTAL HEALTH PERSPECTIVES 106: 347-353,1998.

The pesticide-exposed children

Far less physical endurance in a test to see how long they could keep jumping up and down

Inferior hand-eye coordination



Could not draw a simple stick figure of a human being, which the nonexposed children could readily do.

E. Guillette et al, "An Anthropological Approach to the Evaluation of Preschool Children Exposed to Pesticides in Mexico," ENVIRONMENTAL HEALTH PERSPECTIVES 106:347-353,1998.

"Some valley (pesticide-exposed) children were observed hitting their siblings when they passed by, and they became easily upset or angry with a minor corrective comment by a parent. These aggressive behaviors were not noted in the [pesticide-free] foothills [children]."

Eric M. Roberts, et al **Maternal Residence Near Agricultural Pesticide Applications and Autism Spectrum Disorders among Children in the California Central Valley** Environ Health Perspect. 115(10): 1482–1489, 2007

- Children exposed to pesticides called organophosphates used to kill insects had more than twice the risk of developing pervasive developmental disorder (PDD).
- For organochlorines,there was 7X autism rate
- Mothers exposed to such pesticides were also likely to have shorter pregnancies and their children to have impaired reflexes .

Environmental Health Perspectives Vol 114, Sept 2006 Autism Spectrum Disorders in Relation to Distribution of Hazardous Air Pollutants in the San Francisco Bay Area G. C. Windham,et al

- Objective: To explore possible associations between autism spectrum disorders (ASD) and environmental exposures, we linked the California autism surveillance system to estimated hazardous air pollutant concentrations compiled by the U.S. EPA
- The individual compounds that contributed most to ASD associations included mercury, cadmium, nickel, trichloroethylene, and vinyl chloride.

Mitochondrial changes in hepatocytes of rats chronically exposed to vinyl chloride and ethanol M. L. Miller Environmental Research Volume 29, 1982, Pg 272-279

- Chronic exposure of male rats to 600 ppm vinyl chloride (VC) or VC and 5% ethanol (EtOH) in drinking water induced ultrastructural changes in the mitochondria of hepatocytes
- In animals receiving VC alone, large floccular densities in the mitochondrial matrix were seen occasionally after 6 months of VC inhalation.
- The numbers and severity of changes in mitochondria increased with duration of exposure and age.

G Model
NEUTOX-965; No of Pages 10

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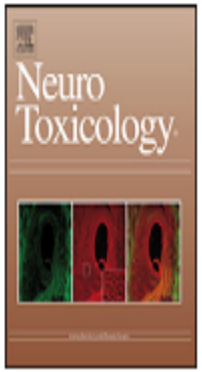
NeuroToxicology xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

NeuroToxicology



Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6–8 years of age

Malin Larsson [a], Bernard Weiss [b], Staffan Janson [a,e], Jan Sundell [c,d], Carl-Gustav Bornehag [a,c,f,*]

[a] *Karlstad University, Health and Environmental Sciences, Sweden*
[b] *Department of Environmental Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA*
[c] *Technical University of Denmark, International Centre for Indoor Environment and Energy, Denmark*
[d] *University of Texas at Tyler, USA*
[e] *County Council of Värmland, Sweden*
[f] *SP Technical Research Institute of Sweden, Sweden*

An analysis of the associations between indoor environmental variables in 2000 as well as other background factors and the ASD diagnosis indicated five statistically significant variables:

(1) maternal smoking

(2) male sex

(3) economic problems in the family

(4) condensation on windows, a proxy for low ventilation rate in the home

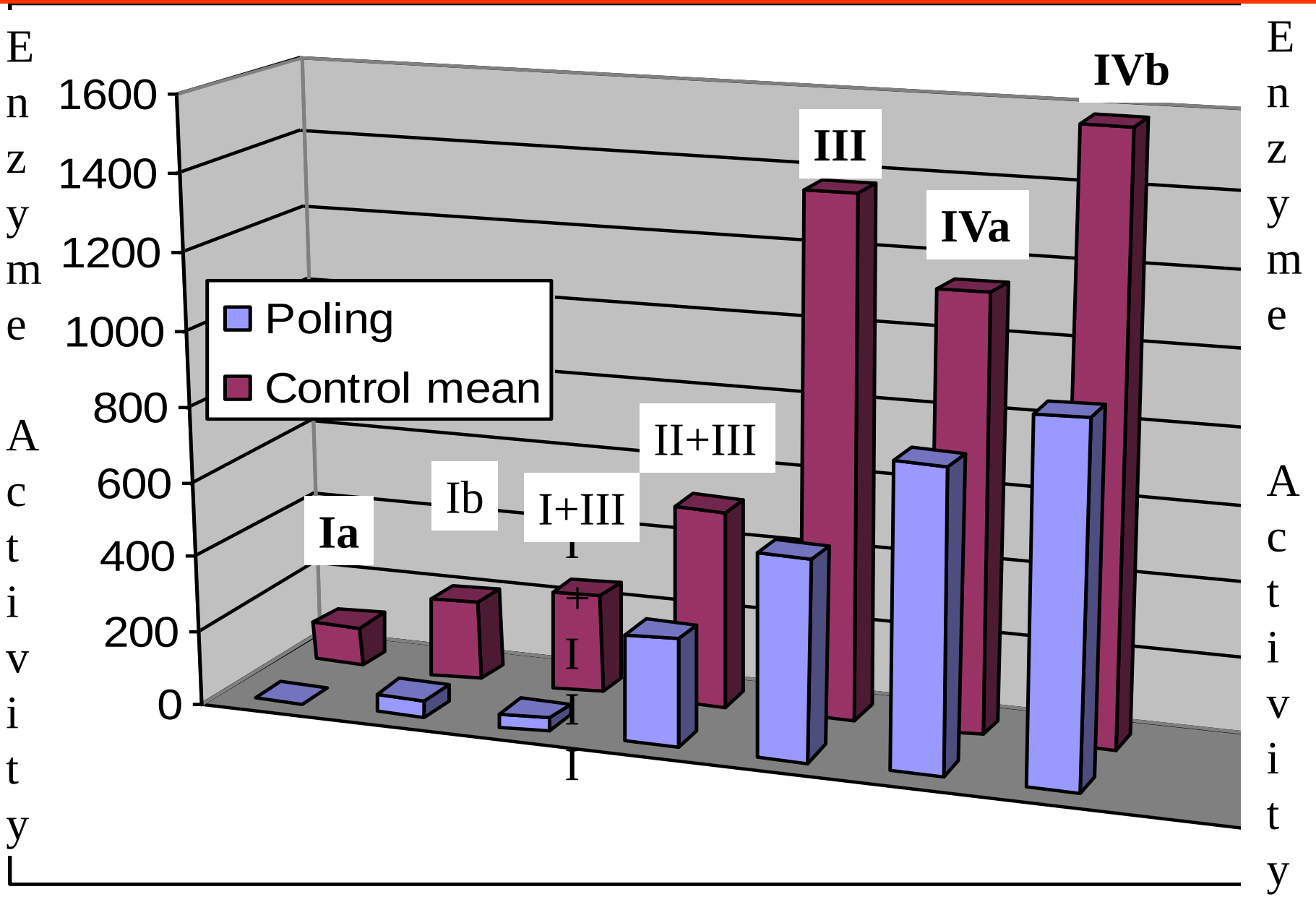
(5) PolyVinylChloride (PVC) flooring, especially in the parents' bedroom.

Hannah Poling Case

Poling JS, et al. J Child Neurol 2006;21(2):170-172

A 19-month-old girl was born after a normal full-term pregnancy. There was no family history of autism or affective, neuromuscular, or hearing disorders. Her development was progressing well, with normal receptive and expressive language and use of pre-linguistic gestures, such as pointing for joint attention. Imaginary play and social reciprocity were typical for age. She used at least 20 words and could point to five body parts on command..

Defective respiratory complexes (I,II,III,IV) in Hannah Poling's biopsy



Hannah Poling case

- In Hannah Poling's case , a muscle biopsy revealed deficiencies of the mitochondrial respiratory chain in three of the four respiratory complexes in the mitochondria with the value for the fourth complex near the lower limit of normal.

How common is mitochondria dysfunction in autism?

- Dr. Oliveira in Portugal tested 69 children with autism and found that five of them (7.2%) had proven mitochondrial disorders.
- Fourteen of the children (20.2%) had high amounts of lactic acid in the blood, a characteristic of mitochondrial disorders. 11 of the 14 children with high lactic acid had a muscle biopsy performed on them.
- Five of the 11 children had subnormal values for the mitochondrial respiratory chain enzyme deficiencies (the critical machinery that generates energy) and thus proven mitochondrial defects, but mitochondrial abnormalities could not be ruled out in the other 6.
- Another study found that lactic acid was absent in 50% mitochondrial disease.
- Thus, 40% of individuals with autism may have mito disorder

Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis

Jacqueline R. Weissman[1], Richard I. Kelley[2], Margaret L. Bauman[3], Bruce H. Cohen[4], Katherine F. Murray[3], Rebecca L. Mitchell[5], Rebecca L. Kern[2], Marvin R. Natowicz[1,4,5,6]*

1 Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, Cleveland, Ohio, United States of America, **2** Department of Pediatrics, Johns Hopkins University Medical Center and Division of Metabolism, Kennedy Krieger Institute, Baltimore, Maryland, United States of America, **3** Department of Pediatrics and Learning and Developmental Disabilities Evaluation and Rehabilitation Services (LADDERS), Massachusetts General Hospital, Boston, Massachusetts, United States of America, **4** Neurological Institute and Pediatrics Institute, Cleveland Clinic, Cleveland, Ohio, United States of America, **5** Genomic Medicine Institute, Cleveland Clinic, Cleveland, Ohio, United States of America, **6** Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio, United States of America

Abstract

Background: Previous reports indicate an association between autism spectrum disorders (ASD) and disorders of mitochondrial oxidative phosphorylation. One study suggested that children with both diagnoses are clinically indistinguishable from children with idiopathic autism. There are, however, no detailed analyses of the clinical and laboratory findings in a large cohort of these children. Therefore, we undertook a comprehensive review of patients with ASD and a mitochondrial disorder.

Methodology/Principal Findings: We reviewed medical records of 25 patients with a primary diagnosis of ASD by DSM-IV-TR criteria, later determined to have enzyme- or mutation-defined mitochondrial electron transport chain (ETC) dysfunction. Twenty-four of 25 patients had one or more major clinical abnormalities uncommon in idiopathic autism. Twenty-one patients had histories of significant non-neurological medical problems. Nineteen patients exhibited constitutional symptoms, especially excessive fatigability. Fifteen patients had abnormal neurological findings. Unusual developmental phenotypes included marked delay in early gross motor milestones (32%) and unusual patterns of regression (40%). Levels of blood lactate, plasma alanine, and serum ALT and/or AST were increased at least once in 76%, 36%, and 52% of patients, respectively. The most common ETC disorders were deficiencies of complex I (64%) and complex III (20%). Two patients had rare mtDNA mutations of likely pathogenicity.

Conclusions/Significance: Although all patients' initial diagnosis was idiopathic autism, careful clinical and biochemical assessment identified clinical findings that differentiated them from children with idiopathic autism. These and prior data suggest a disturbance of mitochondrial energy production as an underlying pathophysiological mechanism in a subset of individuals with autism.

Table 4. Enzymology and Genetic Data.

	Number of patients	Percent of patients	Mutations
Complex I defect	16	64	
Complex II defect	2	8	
Complex III defect	5	20	
Complex IV defect	1	4	
mtDNA tRNA mutation	1	4	
mtDNA sequence variants of probable pathogenicity	2	8	3397A>G 4295A>G
mtDNA sequence variants of unclear pathogenicity	4	16	3394T>C; 10394C>T; 11809T>C; 11984T>C

Table 2. Biochemical and Neuroimaging Data.

	Number abnormal	Number tested	Percent of tested who were abnormal
Increased blood lactate level	19	25	76
Increased blood pyruvate level	9	17	53
Increased plasma alanine level	9	25	36
Increased serum AST and/or ALT level	13	25	52
Increased serum CK level	8	25	32
Abnormal urinary organic acid analysis	10	24	42
Increased fibroblast lactate: pyruvate ratio	3	15	20
Biochemical evidence of mitochondrial disease with any of the above tests	24	25	96
Abnormal cranial MRI	10	21	48
Increased lactate on cranial MRS	2	5	40

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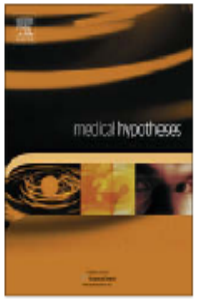

Environmental risk factors for autism: Do they help cause de novo genetic mutations that contribute to the disorder?

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Point mutations are associated with low dose mercury, mitochondria more susceptible to mutations

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ABSTRACT

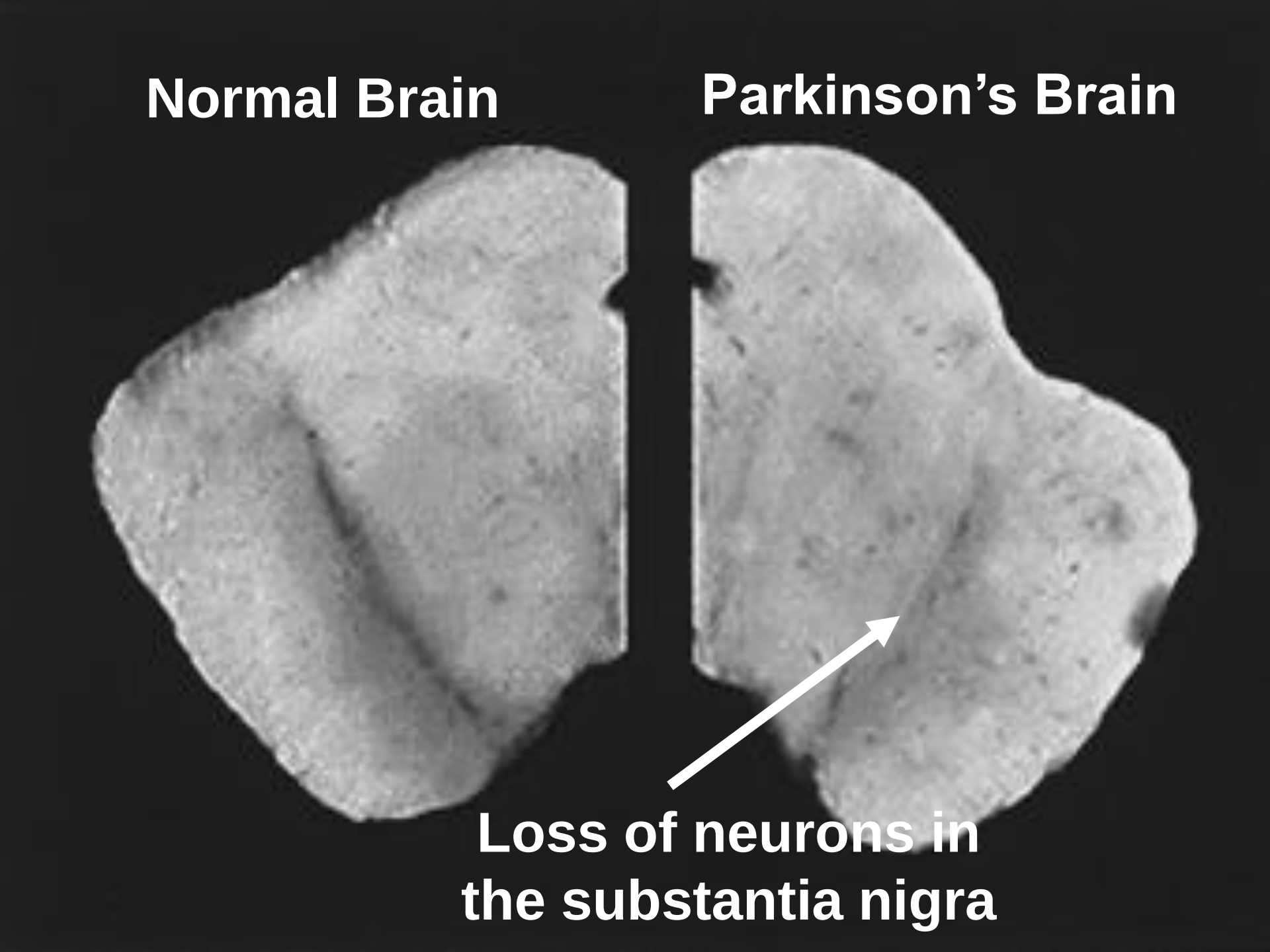
Recent research has discovere… …o mutations. Advanced parental age at the … …autism and de novo mutations. We inves… …ociated with increased risk for autism migl… …novo mutations. A survey of the research literature ide… …environmental factors for which increased pre-con-

Properties of tetrachloroethylene (TCE)

- Dry cleaning agent, pharmaceutical manufacturing, metal degreaser, grain fumigant.
- Contamination of ground water from industrial contamination
- Dermatitis, irritation of the eyes, nose, and throat.
- Acute exposure has been known to cause depression of central nervous system.
- Malaise, dizziness, headaches, increased perspiration, cardiac arrhythmias, renal injury, carcinogenic

Tetrachloroethylene (PERC) toxicity

- Tetrachloroethylene is a dry-cleaning agent and industrial degreaser that often goes under the name perchloroethylene (PERC).
- The National Institute of Occupational Safety and Health estimates that 650,000 U.S. workers are exposed to PERC annually.
- PERC enters the environment through evaporation or through transport into groundwater and drinking water supplies.
- Through widespread use it has become a frequent drinking water contaminant, and it is present in approximately half of the nation's Superfund sites.


Normal Brain
Parkinson's Brain
Loss of neurons in
the substantia nigra

Gash DM et al. Trichloroethylene: Parkinsonism and complex 1 mitochondrial neurotoxicity. Ann Neurol. 2008 Feb;63(2):184-92.

- Workers exposed to trichloroethylene (TCE) by chronic inhalation and dermal exposure from handling trichloroethylene-soaked metal parts had Parkinson's disease.
- Nearby coworkers receiving chronic respiratory exposure, displayed many features of parkinsonism, including significant motor slowing.
- TCE was toxic to animals exposed for 6 wks. The animals had selective complex 1 mitochondrial impairment in the midbrain with striatonigral fiber degeneration and loss of dopamine neurons, simulating human Parkinson disease.
- TCE, used extensively in industry and the military and a common environmental contaminant, joins other mitochondrial neurotoxins and some pesticides, as a risk factor for parkinsonism.

Gash DM et al. Trichloroethylene: Parkinsonism and complex 1 mitochondrial neurotoxicity Ann Neurol. 2008 Feb;63(2):184-92.

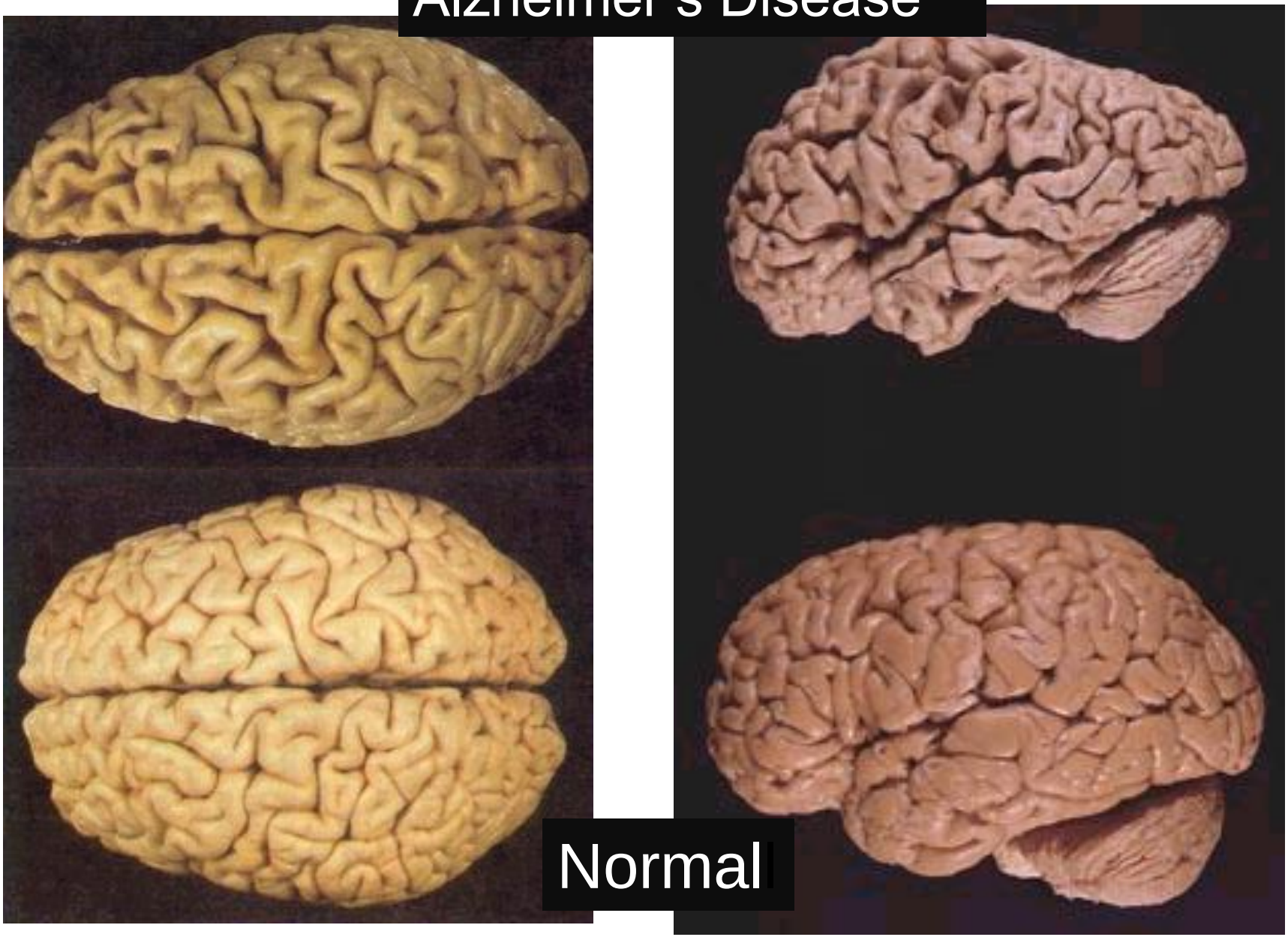
- Eddie Abney worked for more than 20 years at a factory in Kentucky which used trichloroethylene (TCE) to remove grease from equipment,
- He had little protection and absorbed the solvent by inhalation and direct contact with the skin
- At night in bed, he reeked of the smell of TCE.
- Developed severe Parkinson's disease
- Two coworkers who also were exposed developed Parkinsons
- 27 other people nearby developed neurological symptoms like tremors

Gash DM et al. Trichloroethylene: Parkinsonism and complex 1 mitochondrial neurotoxicity Ann Neurol. 2008 Feb;63(2):184-92.

- Rats were exposed to TCE and were found to have mitochondria damage.
- Complex 1, a mitochondria enzyme important in energy production, was significantly reduced in the substantia nigra, the brain area damaged in Parkinson's syndrome.
- Dopamine neurons in this area also showed degenerative changes following TCE administration

Alzheimer's disease

- Alzheimer's disease is by far the most common form of adult onset dementia, affecting over 4 million individuals in USA.
- Approximately 14 million individuals in the US alone will have AD by the year 2050 unless preventive measures are found.
- The economic burden of AD is estimated to be over 100 billion dollars per year.
- AD is not the only adult onset dementia but its prevalence reflects approximately 60% to 75% of all cases, given that AD often coexists with other dementia disorders.


Alzheimer's Disease
Normal

Freed DM, Kandel E. Long-term occupational exposure and diagnosis of dementia. Neurotoxicology 1988;9(3):391–400.

- Serum levels of tetrachlorethylene, dry cleaning solvent (745 parts per billion) were approximately 15 times that seen in a normal population.
- Man worked as a dry cleaner for over 30 years and was subsequently diagnosed with probable Alzheimer’s Disease.

Kukull WA, et al. Solvent exposure as a risk factor for Alzheimer's disease: a case-control study. Am J Epidemiol 1995;141(11):1059–79

- 139 individuals diagnosed with Alzheimer's disease and 243 controls
- History of exposure to one or more solvent groups (benzene and toluene, phenols and alcohols, and ketones plus other solvents) resulted in an adjusted Alzheimer's Disease odds ratio of 2.3 for both sexes
- For men the odds ratio increased to 6.0 (95% CI, 2.1–17.2).

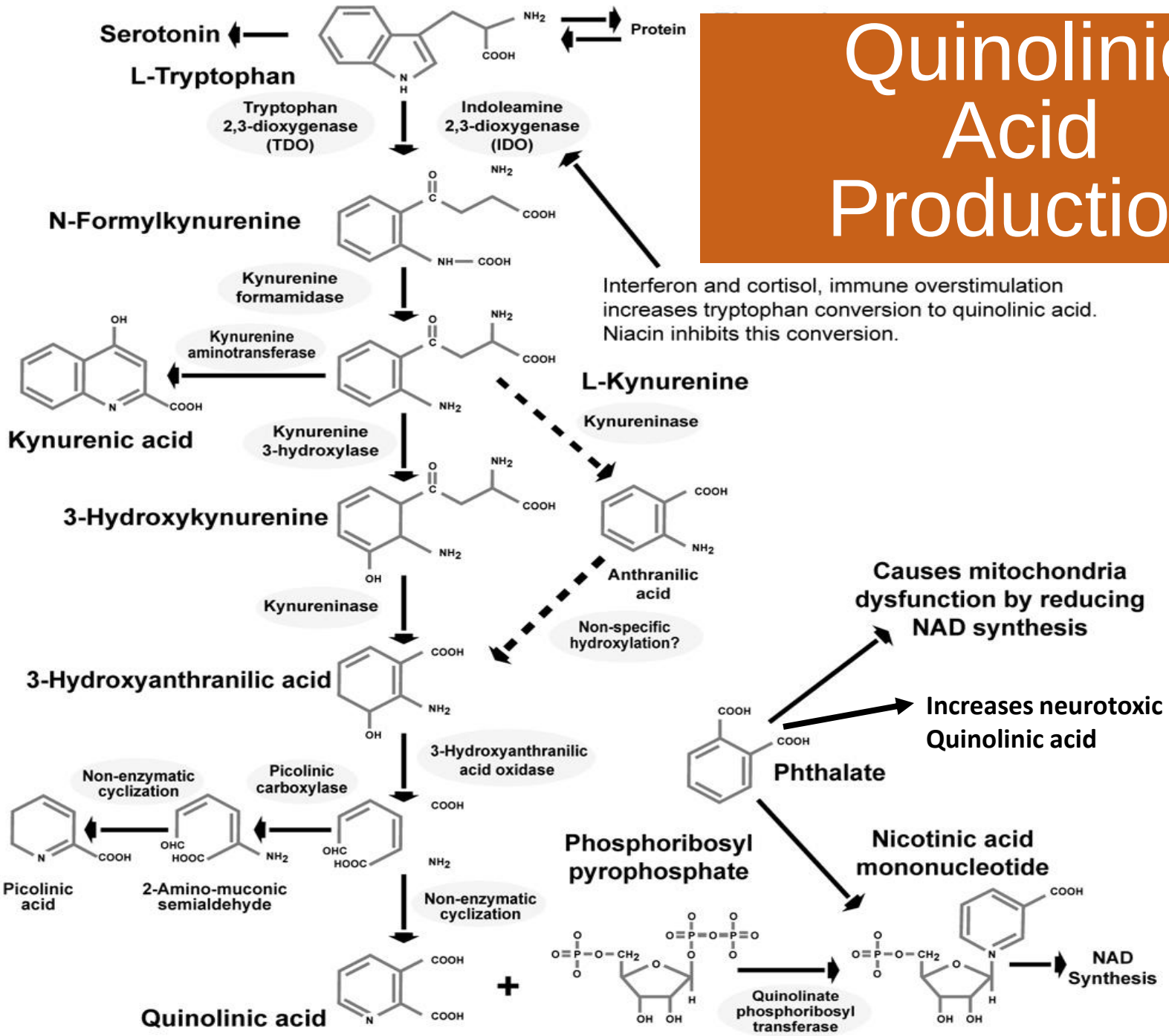
Toxicol Pathol. 2008 Mar 18 Long-Term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain-Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid {beta}-42 and {alpha}-Synuclein. Calderón-Garcidueñas L et al (PMID: 18349428)

- Performed brain pathology studies on deceased residents in highly polluted cities.
- Exposure to air pollution should be considered a risk factor for Alzheimer's and Parkinson's diseases.
- Carriers of the APOE 4 allele could have a higher risk of developing Alzheimer's disease if they reside in a polluted environment.

Mitochondria, metabolic disturbances, oxidative stress and the kynurenine system, with focus on neurodegenerative disorders. Sas K et al. J Neurol Sci. 2007 257:221-39.

- Quinolinic acid is a specific agonist at the N-methyl-d-aspartate receptors, and a potent neurotoxin with a marked free radical-producing property.
- Implicated as major neurotoxin in Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS),schizophrenia
- Kynurenine protects against quinolinic acid damage

Quinolinic Acid Production



Implications of the kynurenine pathway and quinolinic acid in Alzheimer's disease. GUILLEMIN Gilles J. ; BREW Bruce J.

- Aβ 1-42, a cleavage product of amyloid precursor protein, induces production of quinolinate, in neurotoxic concentrations, by macrophages. and, more importantly, microglia.
- Senile plaques in Alzheimer's disease are associated with evidence of chronic local inflammation (especially activated microglia).
- Major aspect of quinolinate toxicity is lipid peroxidation and markers of lipid peroxidation are found in Alzheimer's disease.
- These data imply that quinolinate may be one of the critical factors in the pathogenesis of neuronal damage in Alzheimer's disease.

JOURNAL OF VIROLOGY, June 2005, p. 7768–7776 Vol. 79, No. 12
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Indoleamine 2,3-Dioxygenase Mediates Cell Type-Specific Anti-Measles Virus Activity of Gamma Interferon

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Gamma interferon (IFN-γ) has been shown to after vaccination, to exhibit protective functions i and to mediate a noncytolytic clearance of measles intracellular antiviral activity in the absence of IFN-γ-induced effects on MV replication in variou sensitive to IFN-α/β than are wild-type strains, I endothelial, and astroglial cells, but not in lymph IFN-γ correlates with the induction of indolea degradation pathway known to mediate antiviral γ-induced antiviral activity can be overcome by th a specific role of IDO in the anti-MV activity. Ou important antiviral role in MV infections of epithelial, endothelial, and astroglial cells.

Measles virus causes the Induction of Indoleamine 2,3 dioxygenase which induces production of toxic quinolinic acid

Suggested treatments to lower quinolinic acid

- Avoid tryptophan supplementation which increases quinolinic acid. Use 5-hydroxytryptophan instead. Not converted to quinolinic acid.
- Use niacin (causes flushing) or flush-free niacin inositol (hexaniacinate) that reduces conversion of tryptophan to quinolinic acid
- Reduce stress in your life

Organic acid testing

- 96 different metabolites
- Additional screening for 73 different non-metal toxic chemicals that form organic acids including trichloroethylene, vinyl chloride, and organophosphates
- Quinolinic acid
- Tiglyglycine-most sensitive mitochondrial marker
- 5-hydroxyindoleacetic acid-serotonin marker
- Nutritional deficiencies-B12, B6, biotin, vitamin C,
- Genetic disorders
- Other Mitochondrial markers
- Comprehensive interpretations
- Markers for metal toxicity (HVA, VMA)


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