The Institute For Natural Dentistry

TOXICOLOGY 101
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MATERIAL CLASSIFICATION

I. OBJECT
II. SUBJECT
III. DIDACTIC
IV. DATA
V. REFERENCES
VI. CONCLUSIONS

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OBJECT

Utilize the fundamentals of toxicology to examine a dental controversy over the stability and safety of its restorative materials.

Further, we wish to examine the research performed by the dental association versus that of peer-reviewed double-blind scientific studies to ascertain the opposing conclusions reached by these parties.

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SUBJECT

I. Definitions
II. Forms of Mercury
  A. Elemental Mercury (Hg)
  B. Organic Hg
  C. Inorganic Hg
III. Heavy Metals
IV. Symptomatology
  A. Neurologic
  B. Mental and Emotional
  C. Cardiovascular
  D. Collagenic
  E. Immunologic
  F. Allergenic
  G. Fetal and Neonatal

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V. Differential Diagnosis
VI. Treatment Goals
VII. The Research
  A. Mercury Absorption
  B. Renal Dysfunction
  C. Alzheimer's Disease
  D. Immune System
  E. Antibiotic Resistance
VIII. Conclusion
IX. References

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DEFINITIONS

Toxicology - "the science of poisons, their effects on the body, various antidotes for their action, and their detection in body fluids and tissues.
(Sax and Haley, 1984)

Acute Toxicity - "implies a single exposure to a toxicant (measured in seconds, minutes, or hours) *that may result in unconsciousness, shock, collapse, severe damage to pulmonary tissue, or even sudden death."
(Sax and Haley, 1984)
*Generally defines as death within 100 days

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Chronic Toxicity - "implies exposure to sublethal quantities of a toxin over a prolonged period of time (measured in days, months, or years) with very few clues as to what the toxicant is doing to vital organs and tissues"

(Sax and Haley 1984)

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Definitions

Acute Mercury Toxicity - results from ingestion of inorganic mercurial salts. This form is very rare in a dental context. At Minimata, acute mercury toxicity (i.e. fatal) was defined as being within 1 year of exposure as opposed to the classic definition of seconds to hours.

Chronic Mercury Toxicity - results from the long-term exposure of sublethal amounts of mercury. Exposure may result from one or the combination of various sources:

- Dental Amalgams
- Air pollution
- Contaminated food sources
- Contaminated water sources

(Queen, 1988)

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Mercury Toxic Patient - one who has symptoms of chronic mercury toxicity

Mercury Sensitive Patient - one who is mercury toxic and has developed a hypersensitivity to mercury (allergic or ideopathic). In some of these individuals, a cross-sensitivity may occur, that is, reactivity to other heavy metals and chemicals.

(Queen, 1988)

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II. FORMS OF MERCURY

Inorganic Mercurial Salts

Mercury Bichloride is the most common form of inorganic mercury. Once ingested it is quickly ionized in the body and becomes highly corrosive. Corrective action must be taken within the first ten minutes after ingestion or as little as one half grain may induce death.

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Elemental Mercury (aka Quicksilver)

Elemental mercury is the form found in dental amalgam. At normal pressure and temperature, it vaporizes easily into "Hg vapor", where in the bloodstream it can bond to proteins and lipoproteins alike, thereby gaining access to hydrophilic and lipophilic body compartments.

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Elemental Mercury (cont)

At room temperature, mercury exists as a volatile liquid. As temperature increases, vaporization increases. Mercury vapor is, incidentally, colorless and odorless.

If access is gained through the Blood Brain Barrier, mercury is readily oxidized in the brain to mercuric ions which then bind to sulfhydryl protein molecules.

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Organic Mercury Compounds

Consists of the Alkylmercurials:

Methylmercury (CH3)

Ethylmercury (CH3- CH2-)

Organomercurials:

Thimerisol (used as a preservative)

Mercuric Chloride (antiseptic; used by people to commit suicide)

Mercurous Chloride ("Calomel" Skin cream)

Mercuric Nitate (used in the felt hat industry)

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III.HEAVY METAL TOXICITY

Those heavy metals most likely to cause a toxic reaction are:

- Mercury
- Lead
- Cadmium
- (Aluminum)

Other Heavy metals which are toxic but rarer in frequency are:

- Nickel
- Silver
- Gold
- Copper
- Iron

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Mercury Toxicity

Sources: Autointoxication (amalgams), food, air and water

Target organs: Brain, CNS, CSF, Liver, Kidney, Teeth, Gingiva, Intestines, Muscle and Bone, Lungs, Spleen and Thymus

Arising conditions: Kidney Toxicity, CNS disturbances, Cardiovascular disturbances, Mental disturbances

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Lead Toxicity

Sources: water (rivers; pipes)
Industrial Products (eg paints)

Target organs:
- Brain
- Digestive Tract
- Bones
- Kidneys

Conditions:
- Headache
- Irritability
- Depression
- Fatigue
- Gout
- HBP
- Kidney disease

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Cadmium Toxicity

Sources: Air pollution (coal combustion); coffee; cigarette smoke

Target organs:
- Liver
- Kidney
- Blood
- Lungs

Conditions:
- HBP
- Iron Deficiency Anemia
- Prostate Hypertrophy
- "Bone Wasting Disease"
- Kidney Diseases (eg albuminuria, hypercalciuria, kidney stones)

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Aluminum Toxicity

Sources:
- Water
- Porcelain crowns
- OTC Stomach Products

Target Organs:
- Brain
- Kidneys

Conditions:
- Alzheimer's Disease

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Other Heavy Metals

NICKEL	Thymus gland	Cancer Immune Suppression
SILVER	Connective Tissue	Agyria (Amalgam tattoo)
GOLD	Blood, Kidneys	High fever Rash
COPPER	Hemoglobin	Anemia
IRON	LIVER, HEART	Fatigue, Hemochromocytosis

(Queen, 1988)

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IV. SYMPTOMATOLOGY

The range of symptoms of chronic mercury toxicity include:

1. Neurologic
2. Mental and Emotional Symptoms
3. Cardiovascular
4. Collagenic
5. Immunologic
6. Allergic
7. Circulatory System
8. Fetal and Neonatal

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NEUROLOGICAL EFFECTS

Methylmercury inhibits acetyltransferase resulting in blocked acetylcholine synthesis thereby causing neurological symptoms (Elhassani, 1983)

Motor Symptoms, the Minimati and Iraqi exposure incidents, included:

Muscular weakness:

Tremors (hands and feet)
Ataxia

Sensory Symptoms included:

Impairment of sight, speech & hearing
pain
numbness
burning sensation

(Rustam and Hamdi, 1974)

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NEUROLOGICAL EFFECTS

Areas and conditions in the Nervous System impaired by methylmercury:

1. Spinal ganglia
2. Nerve / fiber degeneration
   (Cavanagh and Chen, 1971)
3. Myoneural transmission failure
   (resembling Myasthenia gravis)
4. A condition resembling amyotrophic lateral sclerosis (ALS) (Rustam, 1975)
5. Multiple Sclerosis mimicking or exacerbation

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MENTAL AND EMOTIONAL EFFECTS

Autopsies were performed to determine the brain pathology in mercury exposure cases. Acute cases showed cytotoxic brain damage. Chronic cases revealed slow, neurotoxic effects on the brain neurons. Further, chronic cases revealed brain atrophy of up to 49% reduction in brain size. Those dying from chronic exposure (living greater than one year post-exposure clinically reported depression, psychoses, withdrawal and other organic brain disorders correlating with these pathological findings.

(Takeuchi, 1982)

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CARDIOVASCULAR EFFECTS

Saytanov, 1974 - Exposed rabbits to mercury vapor and found electrocardiogram (EKG) changes characterized by a lowering and broadening of the P-waves.

Damluji, 1976 - studying the 1970 mercury outbreak in Iraq noted abnormal changes caused to the S-T segment of EKGs.

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COLLAGENIC EFFECTS

The following are lists of effects of chronic mercury toxicity also studied at Minimata which mimic collagen diseases such as:

Periodontal Disease

Malocclusion

Lupus Erythomatosis

Scleroderma

Lower back pain

Various Forms of arthritis

Dermatitis

(Queen, 1988)

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IMMUNOLOGIC EFFECTS

Thymus Cells Studies have found methylmercury to cause atrophy of the thymic cortex, thereby preventing maturation of T-cells to respond to immune system threats

(Hirakawa and Hayashi, 1980)

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ALLERGIC EFFECTS

One effect of mercury is believed to be the inactivation of enzymes, including digestive enzymes.

Food allergies, in part, have been identified with food particle size (Cutler, Bioset 2002). It is postulated that once digestive enzymes are inactivated, proteins, which cause most allergies, cannot be broken down into smaller subunits which then elicit an allergic response

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CIRCULATORY SYSTEM EFFECTS

Chronic fatigue is one of the most commonly reported clinical symptoms. Generally, fatigue is caused by low levels of hemoglobin or iron.

Chronic mercury, lead and cadmium can all cause fatigue and because part of the differential diagnosis if blood tests reveal normal hemoglobin and iron levels.

(Queen, 1988)

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FETAL AND NEONATAL EFFECTS

Fetuses and infants are more susceptible to chronic mercury exposure than are adults. In Japan, toxic infants were born to mothers showing no visible or outward signs of chronic exposure.

Studies have indicated those areas most susceptible in fetuses are neurons, astrocytes (Choi, 1978) and fetal hemoglobin (Tejning, 1968)

Tedeschi found mother's milk contained roughly 10% of the mother's mercury blood levels.

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V. DIFFERENTIAL DIAGNOSIS

Whether testing for acute or chronic mercury toxicity, the physical examination and history is the most reliable means of diagnosis (Arena, 1986)

Urine, blood and hair analysis can be used, if desired, as confirmatory physical testing.

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Other Techniques For Chronic Mercury Toxicity Detection:

- Mercury Vapor Analyzer
- Mercury Patch Test
- Porphyrin Blood Testing
  (Lead and Mercury Applications)
- Biocompatibility Testing
- Electroencephalogram

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VI. TREATMENT GOALS

Detoxification Strategies

Mercury has an affinity to lipoproteins, hence, it binds to lipoproteins in the blood and to other lipoidal tissues in the body, notably brain and nerve cells.

The Competitive Equlibrium Concept theorizes for mercury to be released from binding sites, adequate amounts of selenium and sulfhydryl proteins need to

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surpass "Competitive Equilibrium" to "de-bond' mercury from those sites.

Once mercury is free, it can become redistributed (the toxic ping - pong effect) or be excreted. Excretion would depend on adequate amounts of lipoproteins and cholesterol, which in turn are dependent upon adequate and proper EFA ingestion, absorption and distribution in the body.

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Recommendations For Chronic Mercury Toxicity Patients

- High Protein
- High Fat (EFA)
- Mercury chelating herbs
- Spa detoxification

note: a low-fat and low-cholesterol diet is contra-indicated in mercury toxicity patients
(Queen, 1988)

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VII. RESEARCH

A. Mercury Absorption

Proof of Mercury Vapor Release From Amalgams

Lorscheider (1985) proved Hg vapor is constantly released from amalgams & is increased with stimulation

Results:

Gum chewing, 6x increase from control

Tooth brushing (lasted for 90 minutes)

NOTE: David Kennedy has produced a video showing mercury vapor release from amalgam restorations.

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Proving Absorption of Hg Vapor

The Sheep Study

Study: Six sheep with twelve readioactively tagged fillings (which were over carved to minimize mercury release)

3 days later - fecal excretion of Hg

29 days later - full body xrays revealed full body distribution

Heaviest concentrations:

GI > Kidney > Liver > Brain >
Jaw bone > Gingiva > Trachea

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Physical Tests:	ng Hg / gram
Urine Tests	4.5
Blood Tests	9.0
Kidney	7438.0
Stomach	929.0
Liver	772.1
Periodontal bone	318.2
Gingival Tissue	323.7
Tracheal lining	121.8
Feces	4489.3

Conclusion: Areas of exposure are highest as well as areas of elimination

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Criticism of the Studies

The Dental Associations criticized the study by claiming humans and sheep have different chewing patterns. The heavier chewing patterns of sheep, they contend, biases the study by generating more mercury migration than would occur in humans.

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The Monkey Study

Tissue concentrations of monkeys 28 days after amalgams placement (12-16 occlusal fillings)

Tissue	Conc (ng Hg / gm)
Whole blood	5.8
Urine	17.7
Feces	3490.2
Gingiva	4190.4
Periodontal Bone	7756.1
Tongue	253.3
Oral Mucosa	86.6
Parotid	1.6
Trachea	12.6

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The Monkey Study

Tissue	Conc (ng Hg / gm)
Stomach	18.4
Small Intestine	68.9
Brain- Frontal cortex	7.2
- Occipital cortex	12.6
- Thalamus	9.9
- CSI	1.9
-Pituitary	83.6
-Spinal cord	0.0

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The Monkey Study

Tissue	Conc (ng Hg / gm)
Glands - Thyroid	4.1
-Adrenal	31.3
-Pancreas	15.6
-Gonads	12.7
Heart (ventricles)	6.6

note: microgram = 1 part / million
nanogram = 1 part / billion

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The Monkey Study

Tissue	Conc (ng Hg / gm)
Liver	133.1
Bile	243.1
Large Intestine	983.1
Colon	482.7
Feces	3490.2
Kidney	3053.5
Spleen	15.6

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The Monkey Study

Since primates and humans are similar, it was believed absorption of Hg would be lower and elimination would be more efficient than in sheep. The results show the contrary to be true.

In fact, amalgams caused changes in kidney and intestinal function.

Further, there were changes in gingival flora cultures.

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Second Sheep Study on Kidney Function:

Six sheep each were given 12 occlusal fillings totalling 5100mg / Hg per sheep (425 mg/tooth).

Two control sheep received glass ionomer fillings.

Renal clearance tests were given to all animals pre-operatively, then 30 days and 60 days post-operatively.

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Renal Clearance

	Pre-Op	30 days	60 days
Controls	WNL	WNL	WNL
Exper	WNL	46% function	40% function

Conclusion: A significant decline in kidney function resulted with no physiological tissue changes and no clinical signs or symptoms noted.

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Renal Clearance

	Controls	Experimented
Urine Sodium clearance	24.8	93.0
Urine Protein clearance	82.2	30.1

Conclusions: Hg causes increased salt excretion by bucking normal sodium reabsorption in the proximal tubules.

Note: for each Na(+) and Cl (-) transported (ie: either reabsorbed or excreted) 370 water molecules follow to maintain osmotic equilibrium.

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This would result in salt cravings and dehydration.

Further, low serum sodium levels stimulates renin release, which functions to increase blood pressure, thereby creating a mechanism in which hypertension could develop.

Low sodium levels can also stimulate an electrolyte imbalance which can cause muscle weakness, fatigue and cardiac irregularities.

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Alzheimer's Disease

(quote)

Staging of Alzheimer's Disease

Reisberg, Ferris, DeLeon and Cook

Journal of Psychiatry, 1982.

Stage 1

Normal behavior; no signs or symptoms

Stage 2

"the forgetfulness of normal aging";

classification is age-dependent (eg. 45 vs 65)

Stage 3

"borderline stage" characterized by confusion and mild cognitive decline

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Stage 4

"Late Confusion", "mild AD" stage showing marked cognitive decline, that is, complex tasks such as book-keeping, mathematics and once accomplished complex skills may no longer be performed.

Stage 5

"Early dementia", "Moderate AD". The patient may be able to function in a social situation but cannot live on their own without assistance.

NOTE: The diagnosis is made through persistent direct questioning.

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Stage 6:

"Middle Dementia" "Advanced AD"

Severe cognitive decline is evident and cannot be hidden. Institutional care is necessary due to the inability to perform simple functions involving shoes, shoelaces, buttons, clothes etc. Physical, mental and behavioral derangements such as violence, delusions, paranoia, loss of inhibition, irrelevant conversation, et cetera, now occur.

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Stage 7

"Late Dementia"

Stage 7 is characterized by severe cognitive decline - speaking is reduced to grunts and incontinence may occur. Psychomotor skills such as walking with one's feet or using one's hands to eat or perform any acts of manual dexterity are diminished. One, in essence, is reduced to a helpless infant. "AD seems to progress in the reverse order of normal development. It is the smile that goes last."

(Reisberg et al, 1982)

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Genetic Relations to AD

Allen D. Moses of Duke University, linked clinical AD to genetic susceptibility involving apolipoprotein E (ApoE) consisting of E2, E3 and E4 genomes.

Initial Study:

64% AD patients had ApoE

31% controls had ApoE

Further study with AD patients:

ApoE patients with 2 E4 genes had an average AD onset of age 68

ApoE with one E4 and one E3 had average AD onset at age 75

ApoE with no E4 had an average onset of 84

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Environmental Factors

The environment factors affecting expression of genetic susceptibility seem to be toxic metals:L

Arsenic	Iron
Aluminum	Manganese
Beryllium	Mercury
Cadmium	Nickel
Copper	Titanium

Studies involving identical twins show if one twin was environmentally exposed to heavy metals, he or she alone, not the other twin, developed AD. This established the conclusion there exists an environmental causative factor.

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Amyloid Beta-Protein

Initially, brain "plaques" were discovered in those suffering from AD. These are now classified as amyloid beta protein and are common in AD, Parkinson's and Down's Syndrome patients (21st chromosome contains ApoE)

The Amyloid protein will develop in all tissues of the body. However, the plaques cause the most damage in the hippocampus (memory) and cerebral cortex (reasoning).

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Prevailing AD Hypothesis

1. Genetic susceptibility (ApoE4 gene)
2. Amyloid Plaque (containing Amyloid Beta-protein)
3. Environmental Factors such as heavy metals stimulating gene expression:
   - Aluminum (water)
   - Arsenic (water)
   - Cadmium (coffee; smoking)
   - Mercury (amalgam; vaccines)

What is the scientific mechanism for this proposal?

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UK Brain Autopsy Studies

Three U. of Kentucky psychiatrists, Dr. Wenstrup, Ehmann and Markesberry performed autopsies on 10 clinically diagnosed AD patients and 12 controls with "Instrumental Neutron Activation Analysis" (INAA) which can determine trace concentrations of selected elements which included:

Bromine	Potassium
Cesium	Rubidium
Chromium	Selenium
Cobalt	Silicon
Iron	Silver
Mercury	Zinc

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UK Brain Autopsy Study

The study found the most significant elevation was mercury. Further, significant elemental ratios were discovered:

1. Increased mercury / selenium mass ratio (in nuclear and microsomal fractions)
2. Increased mercury / zinc mass ratio (in microsomal fractions)
3. Increased zinc / selenium mass ratio (in mitrochondrial fractions)

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UK Brain Autospy

The highest elevation of mercury was found in the nucleus basalis of Maynert in the AD patients.

The implication here was memory loss occurred as a result of mercury concentration

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UK Conclusions of Mechanism of Action

The toxic reaction to mercury is the AD patients were classified as:

1. Nuclear functions with elevated mercury showed decreased levels of DNA and RNA synthesis (no new neuron synthesis)
2. Microsomal Fractions demonstrated decreased protein synthesis (no repair and maintenance of existing neurons).
3. Mercury binds to beta-tubulin disrupting microtubules and neural cytoskeletons (axon collapse and degeneration)

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UK Conclusions

4. Mercury binds to neuron cell membranes disrupting sodium-ATPase and potassium ATPase allowing heavy metals to enter the cell membrane and bind to the sulfhydryl group rich nuclear membrane (and enter the nucleus to disrupt DNA and RNA synthesis)
5. Mercury may cause fatigue because of its accumulation in the mitochondria with the resulting depletion of zinc and selenium

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UK Conclusions

(note: "zinc fingers" along with cysteine insert into the wide groove of the DNA helix. These proteins assist DNA transcription to form mRNA.)

6. The authors concluded the source of the mercury was from dental amalgam fillings and ingestion of seafood.

Wenstrup, Ehmann and Markesberry,
"Trace Element imbalances in isolated subcellular fractions of AD brains."
Brain Research 553:125-131, 1990.

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What is the Total Mercury bioburden from amalgams? (Aposhian et al, 1992)

Subjects were divided between those with amalgams and those without. The subjects with amalgams were classified as to the amount of total mercury in their fillings.

For one month, they consumed no fish, seafood or any food which could have mercury contamination.

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Aposhian et al, 1992

The results: the subjects with no amalgams, on average, excreted one-third of the amount of mercury (after a DMPS challenge).

The conclusion was two-thirds of the total mercury bioburden is from amalgam.

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UK's Boyd Haley

In one study, Dr Haley studied brain cell tissue growth in cultures and found the combination of mercury and EDTA (Ethyline diamine tetracetic acid) inactivated tubulin and resulted in nerve cell formations resembling "neurofibrillary tangles" (NFTs) found in AD brain tissue.

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Haley, Vimy and Lorscheider

In a study, they fed rats inorganic mercury (mercuric chloride) for 6 months. They found increased brain levels but no marked behavioral disturbances.

Next, they exposed the rats to mercury vapor in the equivalent amount to a human inhaling vapors from his/ her fillings. The findings were dramatic- all the rats experienced behavioral deterioration. Autopsy conclusively established a tubulin deformation consistent with human AD brains.

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Haley on ApoE protein

ApoE is a cholesterol transport protein which functions to remove LDL cholesterol from the brain to CSF, then to the plasma for elimination.

Current Statistics:

E2 (2 copies) 30% chance of AD by 85

E4 (2 copies) 70% chance of AD by 65

Mechanism:

Apo E2, at its binding site contains two cysteines (bind Hg and remove it).

Apo E4, has two arginines which cannot bind mercury.

Apo E3 has one cysteine and one arginine.

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Immune System

In 1984, David Eggleston published a study in which he secured the cooperation of 3 patients:

Patient#1: A woman had her amalgams replaced with composite. Her T-cell count rose from 47% to 73% (55.3%) increase.

The plastic fillings were then replaced with amalgams in which case the T-cells fell to 55% (a 24.7%) decrease.

Patient#2: A composite filling was replaced with a nickel containing crown. His T-cells went from 63% to 56.7% and back to 73% when the crown was removed.

Patient#3: Chronic MS patient; her T-cell count went from 60% to 71% after amalgam removal.

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Autoimmune Disease

(Pollard et al, 1994)

A study was performed on mice in which amalgams and silver, non-mercury alloys were placed in the mice bodies.

Both amalgams and silver alloys created autoimmune reactions mimicking scleroderma and SLE, that is, both were found to produce auti-nuclear antibodies. The response was also quantitative, the greater the amounts of alloy and the larger the exposure, the stronger the immune response.

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Antibiotic Resistance & Mercury

Summers, Lorscheider, Vimy et al, 1993)

This team had been assembled to test the theory that mercury resistance derived from fillings might also create antibiotic resistance.

Six monkeys had amalgams placed and were tested to rule out pre-existing resistance.

The experiment discovered mercury resistance developed followed by antibiotic resistance.

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Antibiotic Resistance & Mercury

Mercury fecal excretion was recorded at 100ppm (well above EPA regulation levels of 0.2 ppb).

After 8 weeks, glass ionomer fillings were placed. The monkeys continued to excrete significantly high levels of mercury and antibiotic resistant bacteria for another 8 weeks.

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Neurobiology Laboratory
Psychiatric University Hospital
Basel, Switzerland (2000)

A study demonstrated that neuroblastoma cells exposed to mercury show and increase in production of amyloid protein.

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Lorscheider
University of Calgary

This team has produced a video which shows direct visual evidence of mercury's effect on neurons.

Neurons were cultured from snail brains in which growth cones of the neurons were shown to exhibit Alzheimer's-like neurodegeneration where exposed to mercury ions.

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Blood and Bone Sensitivity

Studies at Colorado University indicate blood and bone cells are highly sensitive to mercury.

40 parts per billion - lethal to WBC

0.4 parts per million - lethal to bone cells

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Biomaterials Unit
School of Dentistry
University of Birmingham (UK)
(2000)

For this study, rat bone cells were exposed to amalgam. Mercury, followed by copper, followed by silver were osteotoxic to bone producting osteoblasts.

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UK - College of Dentistry

(Saxe et al, 1999)

Studied 68 subjects with AD and 33 controls without AD to determine mercury levels in multiple brain regions at autopsy to determine a correlation with the placement, location and duration of amalgam restorations in the mouth.

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Saxe et al

The Findings:

1. No correlation between AD and amalgams
2. No difference in brain levels of mercury between controls and ADs.

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Saxe

"This study demonstrates that dental amalgam is not a major public health risk factor for AD... This is the first thorough clinical pathological correlative study of humans to show that mercury in dental amalgam restorations does not appear to be a neurotoxic factor in the development of AD."

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Commentary

A proper control group was NOT established, that is, a proper control should have NOT had any amalgams. Multiple amalgam restorations in the controls would NOT show a difference from AD patients.

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CONCLUSIONS

"It follows that the practice of using amalgams as tooth restorative materials cannot be defended by claims that they are safe, for there is no basis for such a statement. It can be motivated based on a judgement that, as in the case of pharmaceuticals, the benefits outweigh the risks."

Weiner & Nylander, Aspects of Health Risks of Mercury From Dental Amalgams; Toxicology of Metals (?), 469-486, 1996.

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The Institute For Natural Dentistry

TOXICOLOGY 102: Physiological Response to Mercury Exposure

Institute For Natural Dentistry
January 2004

1

I. OBJECT
II. SUBJECT
- A. Mercury Exposure
- B. Biotransformation
- C. Inhalation
- D. Blood Biochemical Reactions
- E. Barriers
- F. Distribution
- G. Compartmentalization
- H. Elimination
- I. Molecular Biochemical Reactions

III. CONCLUSION: Treatment Protocols for Holistic Dentistry

2

1.OBJECT

Placement and removal of dental amalgams results in Hg vapor exposure to patients, Dr. and staff.

The purpose and primary intent of the genre of holistic dentistry is to deliver SAFETY to the patient, that is: safe elimination, safe placement of biocompatible material and restoration of pre-mercury exposure health.

3

II. SUBJECT

A. Exposure

The primary cause of exposure in the dental setting is through the mechanism of Hg vaporization. This phenomenon can be measured and is quantified and found to occur:

1. Amalgam Placement
2. Amalgam Removal
3. Chewing
4. Brushing
5. Consumption of hot beverages
6. Clenching
7. Teeth at rest via corrosion of the amalgam

4

Exposure During Removal

Precautions and the amount of exposure from various precautionary protocols:

Exposure	Technique
80%	HVA
70%	HVA / rubber dam (RD)
65%	HVA / RD / HEPA Filtration
50%	Clean Sweep
30%	Clean Sweep / RD
25%	Clean Sweep / RD / HEPA Filter

(Memoli, 2003)

5

Definition: the "chronically" exposed:
Those constantly subjected to the same toxin; usually seen in cases of autointoxication whereas a toxic substance is directly implanted into a person and constantly gives off toxic dose.

6

B. Biotransformation

Biotransformation is the process, in bacteria, of converting elemental mercury to methylmercury and vice versa. That is, certain flora in the mouth and intestines have been found to methylate and demethylate (methylmercury).

Some of the species found to "biotransform" Hg include:

Streptococcus mitior
Streptococcus mutans
Streptococcus sanguis

(Heintze, et al 1983)

7

C. Inhalation

Of the percentage of Hg vapor which escapes our precautions, approximately 30% will end up in the brain due to its proximity in the mouth and the other 70% will be inhaled into the lungs.

(Memoli, 2003)

8

Inhalation

Once inhaled, 74% remains in the lungs whereas 7-26% is eliminated by the next and following exhalations.

Within 10 minutes of inhalation, approximately 30% of the vapor dissolves and enters the blood stream.

That remaining in the lungs breaks down quickly. The half-life of Hg vapor is 18 hours.

(Hursh, Clarkson et al, 1976)

9

D. Blood Biochemical Reactions

Once elemental Hg vapor enters the blood stream, one of several reactions may occur:

1. Oxidation Hg vapor is oxidized, that is, it undergoes ionization to become mercuric ions:

Location:

84% of oxidation occurs in the Red Blood Cells (RBC's)

16% occurs equally in:

- hemoglobin molecules
- plasma albumin

[note: vitamin C greatly enhances oxidation]

10

2. Bonding

Hg vapor may combine with ligands such as hemoglobin or other organic compounds.

Likewise, Hg vapor may form inorganic compounds by bonding to elements such as chlorine or bromine etc.

3. Intracellular Exposure

Hg vapor may penetrate, under certain conditions, the cellular membrane.

11

E. Barriers

"Barriers" are protected areas of the body to prevent toxic element or micro-organism incursion into key vital "compartments".

12

Barriers of Mention:

Blood Brain Barrier
Blood Cerebral Spinal Fluid Barrier
The Placenta
The Breast (Milk) Barrier

Cell Membrane
Nuclear Membrane

13

Barriers

Methylmercury and Hg vapor are believed to be able to penetrate all barriers.

Mercuric ions, it is believed, cannot penetrate the BBB and placenta.

(Goodman and Gillman, 1980)

14

F. Distribution

Distribution may be dependent upon the body's capacity to oxidize mercury:

Whole blood uptake: 0.5 ug | hr | ml
Plasma uptake: 0.11 ug | hr | ml
Hemoglobin uptake: 1.0 ug | hr | ml

15

G. Compartmentalization

Compartmentalization is a process whereby excess mercury, that is, that mercury exceeding the body's ability to process, is stored in the body's compartments to prevent acute exposure and toxicity which could harm or potentially kill the organism.

16

In the human organism, the major compartment is the cell. In essence, this serves almost as a backup defense system in order to prevent incursions into barriers by those agents or toxins capable of disabling the host.

Compartmentalization may be the body's mechanism by which it handles constant, chronic exposure (eg dentist; fish consumers; H2O) when first line defenses are exhausted and dietary and physiological responses cannot by replenished before the next exposure (Hg overspill)

17

Compartmentalization

Because of this phenomenon, we simply cannot refer to mercury bioburden as being a singular entity. In fact, because of compartmentalization and the associated problem of trying to "chelate" out the Hg bioburden, we really need to refer to at least three distinct types of mercury:

18

1. Extracellular Compartments

Hg in the ECF and elimination organs / channels; seen primarily in amalgam placement and removal. Possibly responsible for the symptoms we see in acute and chronic exposures.

Most chelators, natural and pharmacological, and most Hg removal protocols address and remove this type of mercury.

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2.Intracellular Compartments

Toxins in the cell as a result of the compartmentalization phenomenon.

For the most part, IC toxins do not produce overt symptoms because of the cells ability to handle the bioburden. The price for this may be decreased energy production and cell dysfunction.

No chelators I have tested remove this bioburden.

20

3. Brain and Nervous System

Toxins must transgress the BBB and the BCSFB to gain access to brain cells, neurons and spinal ganglia.

As a result of many of the effects of Hg acting in this compartment it is characterized as an 'acute neurotoxin'.

No chelators I have tested remove this bioburden.

21

H. Elimination

There are two major strategies the body has to eliminate Hg:

1. Natural decay (half-life)
2. The body's own elimination channels and organs

22

Half-life

Hg Vapor 18 hour half-life in the lungs

Methylmercury - approx 65 days

Bound Hg (eg in the brain) 18-22 years

note: as long as chronic exposure is occuring, we are defeating the half-life potential to eliminate Hg

23

Elimination Channels

Studies on animals with mercury exposure clearly exhibited Hg concentrations in areas of exposure (mouth, trachea, stomach, periodontal bone and gingiva) and areas of elimination (such as the liver, colon, lungs and kidneys)

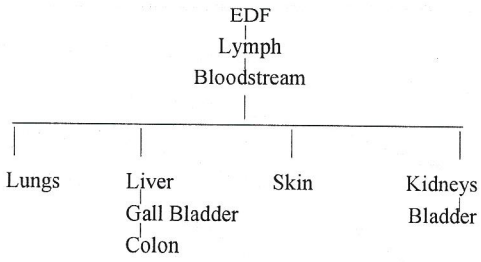
24

The bloodstream is the major elimination channel because it can carry Hg directly to the elimination organs such as the skin, lungs, liver and kidneys.

For that Hg in the ECF, or inside the cells or that penetrating barriers such as in the brain or nervous system - complicated biochemical processes necessitating optimal body and nutritional conditions are necessary in order to effect elimination. This may be impossible for the chronically exposed patient.

25

Overview of Elimination Channels and Organs



Note: Cellular and N.S. elimination are more complicated and less understood.

26

I. Molecular Biochemical Reactions

Hg exposure will activate an acute or chronic inflammatory response.

1-10 ug/m3 of Hg vapor is sufficient to inhibit protein synthesis.

(Goldschmidt, et al, 1976)

27

Elemental mercury vapor, mercury salts (Hg ions), and organic mercury all have a high affinity for sulfur in its various bonding capabilities:

Sulfhydryl bonds (-SH)
Eg. GSH, cysteine, Coenzyme A
Disulfide bonds (-SS)
Eg. cysteine
Sulfide bonds (-S)
Eg. most proteins and enzymes

28

Once Hg vapors enter the bloodstream, the status of the blood proper, liver and kidneys determines the level of elimination (i.e., whether it is eliminated, compartmentalized or breaches a barrier).

29

Glutathione (GSH), a tripeptide consisting of cysteine, glycine and glutamine, may be the most important determinant in elimination.

The free sulfhydryl group on the cysteinyl residue has a propensity to form complexes with strongly electrophilic metal ions such as Hg.

30

Hg decreases GSH levels by several mechanisms in which irreversible bonding occurs:

1. Direct binding to GSH
   note: 2 GSH molecules bind to 1 Hg
2. GSH Reductase inactivation
   note: reduces oxidized GSH
3. GSH Synthetase inactivation
   note: synthesizes new GSH

31

Metals that remain longer in plasma tend to be excreted by the kidney. The kidney can handle one-tenth the amount of excretion the colon can.

Further, the kidneys are limited by the amount of Hg they can handle because of nephrotoxicity and possible renal failure.

32

"In all these various renal systems, a threshold effect is generally observed, in that no cellular necrosis (death) is observed up to a certain dose. Above that dose, however, cellular death progresses rapidly, and in some systems an all-or-none response is observed. This does not mean biochemical or physiological effects. One possible explanation for the threshold effect and the subsequent steep dose-response curve is that endogenous ligands, such as glutathione, bind mercury and may act as a buffer to prevent

33

functional changes from occurring. Above a certain dose or concentrations of mercury, the buffer becomes depleted, and mercuric or mercurous ions can bind more readily to critical nucleophilic groups in the cell, thereby causing functional impairment. Intracellular sulfhydryl-containing proteins such as metallothionein or low-molecular-weight thiols, in particular glutathione, likely function in such a capacity.

Zalups and Lash, "Interactions between GSH and mercury in the kidney, liver and blood." Toxicology Edita-Chang, p 145-163, 1996.

34

Erythrocytes-1st Line of Defense

Hg plasma levels appear to be determined by the RBCs, which have the capacity to synthesize GSH de novo.

Further, they contain significant GSH enzymes such as GSH S-transferase and GSH peroxidase.

RBCs are therefore "equipped to handle plasma oxidants and reactive electrophiles. These can then be processed by the liver.

35

"Although the liver is a primary site of the excretion of mercury, little hepatotoxicity is generally observed *in vivo*. This suggests that the mercury that is taken up by hepatocytes for transport across the sinusoidal plasma membrane does not interact significantly with hepatocellular thiols or macromolecules. Rather, the mercury that is taken up by the hepatocyte must be efficiently delivered into the bile across the canalicular plasma membrane for excretion in to the intestine."

Zalups and Lash, 1996[36]

III. CONCLUSION

Holistic Dental Goals
(Distant Early Warning)

1. Decrease exposure at time of mercury removal.
2. Improve the ability of the RBCs to handle exposures. (1st line of defense) in order to prevent compartmentalization and Barrier penetration.

37

3. Open elimination channels to allow for Hg "movement" to the elimination organs.
4. Strengthen the elimination organs to effectively process and eliminate Hg.

38

Holistic Dental Protocols

...create a protocol designed to meet the holistic dental goals before dental procedures are formed.

Further, create a protocol designed to reduce exposure after mercury removal (eg: exercise, baths, protein, vitamin C etc) to assist the physiologic action post-exposure.

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Complementary and Integrative Dentistry

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Toxicology 103: Introduction to the Blood Brain Barrier and its Clinical Significance in Dental Medicine
IND; January 2004

1

I. OBJECT
II. SUBJECT
- A. Definitions
- B. Misconceptions
  1. "Opening" and "Closing" the BBB
  2. "Permeability" concept of the BBB
  3. Adult vs Fetal BBB
- C. Endothelial Cells
- D. BBB Structure
  1. Tight Junction Microanatomy
  2. Electrical Resistance

2

II. Subject (cont)
- E. BBB Function
  1. Receptors
  2. Transporters
  3. Genetic
- F. BBB Micro Pathophysiology
  1. Hg and Heavy Metals
  2. Fluoride
- G. BBB Macro Pathophysiology
  1. Multiple Sclerosis
  2. Cerebral Amyloid Angiopathy
  3. Hemostasis and CV Ischemia
  4. "HIV"
  5. Hypertension

3

II. Subject (cont)
- G.
  6. Brain Tumours
  7. Traumatic Brain Injury
  8. Cerebral Malaria
  9. Bacterial Meningitis

III. CONCLUSIONS
- A. BBB in General
- B. BBB with specific relation to dental protocol

IV. REFERENCES

4

I. OBJECT

The question of interest which arises for the holistic dentist is this:

"How does Hg get into the brain?"

This question in itself raises two highly relevant, significant, controversial and overlooked questions:

"How can we prevent this during our procedures?"

"How can we get it out of the brain?"

5

II. SUBJECT
A. Definitions

The BBB comprises the interface between the bloodstream and the brain, thereby, determining what gets into the brain (Gate-Keeper Concept.

The BBB functions both to protect the brain from non-essential, potentially toxic substances and to allow essential nutrients in.

6

An understanding of the BBB is central to the development of procedures and conditions which could potentially threaten the realm of the Brain and Nervous System causing irreparable damage to the patient.

Further, an understanding of the BBB is necessary to address conditions such as Alzheimer's Disease, Muscular Sclerosis, Parkinson's Disease et cetera. Major pharmaceutical research is being conducted on the BBB and neurochemicals in order to create a new generation of neuropharmaceuticals capable of transgressing intact BBBs.

7

The BBB is formed by brain capillary endothelial cells (EC). Brain ECs are nondistinct microscopically from systemic ECs, however, their function is based on selectivity whereas systemic ECs are relatively nondistinct in their function.

8

Origin of ECs

ECs are specialized connective tissue cells arising from undifferentiated mesenchymal cells. Although ECs morphologically resemble epithelial cells, they originate and retain mesenchymal properties.

9

B. Misconceptions of the BBB

"We need to open the BBB in order to get Hg / toxins out of the brain."

"The ECs have dual function, ie, they are specific at the luminal side whereas at the abluminal side they are relatively nonspecific (ie transporting out of the brain and into the bloodstream anything the brain wishes to export).

10

"We need to close the BBB in order to prevent Hg entry during Hg removal procedures."

"The terms "open" and "closed" are metaphors referring to the patency of ECs and technically are not correct terms.

Our goal is to create the proper physiological environment conducive to proper functioning of the BBB.

11

"The BBB has selective permeability."

Again, "permeability" conjures up an image of specific function, specifically related to the cellular fluid mosaic model which clearly is not indicative of the BBB function.

12

"The BBB in fetuses is nonfunctional and therefore susceptible to interactions from drugs and toxins eg. Hg."

FINDINGS: A study concluded Junctional Epithelial Patency, in the fetal brain, is completed by the first trimester in utero."

REF: Mollgard and Saunders, 1975.

13

C. Endothelial Cells

ECs became BBB-ECs when two distinct features are developed:

1. A low rate of fluid phase endocytosis occurs, that is, "selective endocytosis".
2. High electrical resistance Tight Junctions are developed. These function to prevent any gaps between cells that would allow for blood-borne hydrophilic substances to pass into the Brain ECF.

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D. BBB EC Structure

EC Tight Junction Microanatomy

Tight Junction formation, as in all cells, is mediated by the endothelial cytoskeleton consisting of microtubules, microfilaments and intermediate fibers composed primarily of tonofilaments.

EC microtubules are oriented along the long axis of the cell from the apical to basal surfaces of the cell.

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EC Tight Junction Microanatomy

The Tight Junctions, which impart selective endocytosis consists of the following subunits and components:

1. The cytoskeleton structure itself
2. Occludin - a transmembrane protein found in all ECs
3. Cytoplasmic - occludin bonding proteins designated as ZO-1, ZO-2, cingulin and P130.
4. E-Cadherin - imparts calcium regulation

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EC Tight Junction Microanatomy

The anatomy structurally is composed of 3 main elements:

1. Occludin - situated in the actual tight junction themselves.
2. Cytoplasmic Proteins, ZO-1 and ZO-2, which bond to the occludin at the tight junction and to the cytoskeleton.
3. The Cytoskeleton - which stabilizes the entire structure, the ZO-1 and ZO-2 cytoplasmic

Proteins selectively bind to actin filaments found in the microfilaments and tonofilaments.

17

Regulation: the binding of membrane and cytoplasmic proteins to each other and the cytoskeleton is regulated by calcium and mediated by the E-cadherin family of adhesion molecules binding to catenins (cytoplasmic transducers).

REF: Ando-Akatsuka et al, 1996.
Staddon and Rubin, 1996.
Balda et al, 1996.
Hirase et al, 1997.
Nagafuchi and Takeichi, 1988.
Ozawa et al, 1989.

18

Electrical Resistance

Electrical resistance may confer selective endocytosis in the BBB-ECs.

FINDINGS: The electrical resistance in vitro BBB ECs demonstrates ranges from 50-500 ohm-cm2 and, at times, upwards to 1000 ohm-cm2.

QUESTION: can this resistance repel ionic mercury?

19

Interestingly enough, intra-parenchymal brain capillaries, which lack BBB qualities, exhibit electrical resistance of 3000 to 8000 ohm-cm2.

REF: Butt and Jones, 1992.
Smith and Rapaport, 1986.

20

E. BBB Function
Receptors

Receptors, beyond those attributed to growth and maintenance, tell us the function of a cell. In the case of the ECs, they inform us of the very nutrients and mediators the brain itself is looking for.

Selective endocytosis occurs partly by the mechanism of receptor-mediated transcytosis.

21

Receptors

The following are receptors identified to date on the EC:

- Insulin
- IGF-1 (Insulin Growth Factor)
- IGF-2
- Transferrin
- Leptin
- Albumin
- Histones
- Cationized antibodies

REF: Kumagi et al, 1987
Triguero et al, 1989
Pardridge et al, 1989
Pardridge and Boado, 1991

22

EC Transcellular Transport System

By virtue of the existence of the BBB, it was hypothesized (Crone, 1965) that if substrates could only enter the brain through the EC, then those cells (and possibly all cells) must possess a transcellular transport system (especially to mediate hydrophilic molecules).

23

EC Transporters

Once receptors are activated, "transporters" are responsible for intracellular transport. These transporters accomplish this task with "intelligence", that is, intracellular pathways are utilized (roads), "targets" are specific (end points), all of which occur in a temporal specific manner delivering the product in the right amount, at the right time, at the right place and in a specific amount of time.

24

Transcellular Barrier Transporters

GLUT-1 - is the primary glucose transporter and is located on both sides (luminal and abluminal) of the EC.

Amino Acid Transport Systems consist of sodium-dependent and sodium independent systems. Amino acids such as glutamate, aspartate, glycine and GABA operate as neurotransmitters and are predominant in 90% of CNS synapses (Smith & Cooper, 1992)

25

Transporters (cont)

Essential amino acids, [that is, those that cannot be synthesized in the brain but are necessary for function] have transporters and includes:

Arginine	Isoleucine
Lysine	Valine
Tryptophan	Methionine
Leucine	Phenylalanine

26

Transporters (cont)

Some also serve as precursors for brain protein synthesis:

Serotonin (tryptophan)

Nitric Oxide (arginine)

Catecholamines (tyrosine)

(Smith & Cooper, 1992)

27

Transporters (cont)

P-glycoprotein (the "Guardian of the Brain") This drug-exporting transporter is concentrated on the brain side of the EC and extrudes drugs found in Brain ECF. P-gp is believed to explain the low Brain ECF saturation of highly lipophilic drugs targeted for the brain. P-gp inhibitors are now being developed but have the undesired side effect of serious toxicity.

(Boret and Schinkel, 1996)

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Transporters (cont)

Lipoprotein Receptors

LDL receptors have been discovered on ECs.

Although the brain can synthesize cholesterol de novo, plasma LDLs are actively transported into the brain (~85%).

Apolipoprotein (apo) E and apoEI have been discovered to bind at this site, but are limited to ECs within the gray matter associated with neuronal cell populations.

(Pitas et al, 1987).

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Transporters (cont)

Other notable transporter systems:

Fatty Acid Transporters

Specifically for Palmitate, Docosahexaeonate and Arachidonate.

LysoPtdCho

Specifically for Phosphatidylcholine

Ion Transport Channels

To regulate BBB function and ion concentrations (eg K+, Ca2+ and H+) in the brain.

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Genetics

Molecular biology studies on the BBB has found its properties, particularly its ability to keep out micro-organisms and peripheral neurotransmitter, cytotoxins to be a result of genetic expression.

Further, it has been discovered that down regulation of specific genes such as GLUT-1 and gamma-GTP to result in a lack of barrier function and brain tumour activity.

(Boado, 1996)

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F. BBB Micropathophysiology

A classic model for Hg induced BBB dysfunction begins with mercury vapor entering the bloodstream. Once oxidized, it now bonds to LDL which bind to the EC LDL cell receptor.

The EC cell will selectively uptake LDLs at the rate necessary for proper brain function. It can be theorized that if cholesterol is lacking in the brain, its uptake in the ECs will be

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increased thereby transporting Hg bound LDL into the brain.

BBB Dysfunction

As stated earlier, patency of BBB ECs is determined by the Tight Junctions. Tight Junctions, for their part, are regulated by the cytoskeleton, occludin, and the cytoplasmic occludin bonding proteins - all of which are regulated by calcium.

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The cytoskeleton is known to be composed of microtubules, microfilaments and tonofilaments. Microtubules contain the dimer Tubulin A and B.

The A and B subunits, both around 55 kilodaltons, are non-covalently bonded by hydrogen bonds.

Polymerization of microtubules occurs on the end called the nucleation site where A and B subunits are alternately arranged to promote growth.

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Tubulin Binding Sites

1. GTP nucleotide: GTP is an assembly cofactor and has two binding sites on the B subunit.
2. Magnesium 48 binding sites.
3. Calcium 1 high affinity site
4. Vinblastine two sites per dimer
5. Colchicine - has known bonding sites.

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Microtubules impart two functions:

1. Intracellular transport
   - Axoplasmic transport in neurons
   - Chromosomal movement in mitosis (centriole growth is mediated by a tubulin nucleation site)
   - intracellular vesicular movement (eg: ER to golgi to cell membrane)
2. Cell Structure

   Disruption of microtubules causes an immediate morphological change in cell shape with disruption of function.

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Mercury ions have been found to attach to the GTP binding sites on the B subunit of tubulin resulting in both nucleation site and microtubule disruption.

It can be theorized that mercury can promote BBB dysfunction allowing other toxins and agents normally prohibited from the brain to enter. A physiological disruption thus occurring would be difficult to trace to its root cause.

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Further, the Wenstrup, Ehmann and Markesberry study indicating DNA transcription disruption could also adversely effect the function of the BBB EC.

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Fluoride

Fluoride can transverse the BBB. It is not known under what conditions this can occur, as to whether the BBB is functioning normally, is dysfunctional or nonfunctional.

However, fluoride appears to have a tendency to concentrate in the lobular regions of the brain, especially the frontal lobes.

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G. BBB Macropathophysiology

We will discuss certain conditions in which the BBB may be adversely affected.

Such affected individuals seeking amalgam removal could, under certain pathological conditions, exacerbate their existing condition or predispose themselves to other neurological conditions.

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Pathophysiology
Cerebral Amyloid Angiopathy

There are various forms of CAA. One , however is associated with the BBB and coincidentally, Alzheimer's Disease.

This version, called "CAA associated with AD/SDAT (Senile Dementia Alz-type)" shows amyloid deposition exclusively in brain microvessel walls. The link with the BBB, although coincidental, has not been scientifically researched and has been labeled "multifactorial".

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Multiple Sclerosis (MS)

MS is characterized as a chronic inflammatory demylelinating disorder of the CNS.

The etiology is unknown (possible over-riding emotional component).

It is believed to be an "autoimune attack on the CNS myelin." Lesion show macrophages and lymphocytes attacking venules primarily in the white matter.

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MS (cont)

Normal Physiology - the net negative charge of the ECs tends to repel leukocytes restricting immune cell access to the CNS.

Apparently, during immune-mediated and imflammatory events, BBB function terminates, leukocytes enter the CNS resulting in vasogenic edema.

REF: Brosnan, Claudio and Martiney (1992) The BBB during immune responses Sewin, Neurosci 4, 193-200.

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MS

Conclusion: "Alterations in BBB function correlates with MS disease activity...the results indicate that therapies that target events occurring at the BBB are likely to significantly ameliorate or halt progression...

REF: (IBID) Brosnan and Claudio

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Hemostasis and CV Ischemia

Cerebral Vascular Accidental Patients

Thrombi are perceived as originating outside the CNS, bypassing the BBB, and then causing intracranial CVAs.

It is now known the BBB has a unique hemostatic regulatory capacity.

CLIN: patients with compromised blood coagulation factors may have a compromised BBB (Inc. increased PT times)

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"HIV" Infection

Patients with AIDS in studies comparing AIDS with HIV Encephalitis and AIDS without HIV Encephalitis both show a BBB leak... Moreso, these vascular leaks were always associated with necrosis induced by cerebral infarcts, opportunistic infections and the HIV Encephalitis itself.

CLIN: Mercury Removal

REF: Petito and Cash (1992). BBB Abnormalities in AIDS: Immunohistochemical localization of server proteins in postmortem brain. Ann. Neuro., 32, 658-66.

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Hypertension

BBB dysfunction is observed after an acute increase in blood pressure caused by an increase in systemic pressure exceeding 60mm Hg or certain vasoactive drugs

Johansson et al, 1970

Johansson, 1984

In chronic hypertension, renal hypertension is more likely to cause BBB dysfunction and brain edema than genetic hypertension.

Johansson and Lindu, 1980, 1981
Meuller and Loft 1982

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Brain Tumours

In all brain tumours, with the notable exception of gliomas, the BBB is permeable.

The significance is not understood but most brain tumours grow by angiogenesis in which the tumour actually occurs in the BBB or brain microvasculature.

CLIN: for Brain tumours, a significant decrease in BBB permeability is not possible (even with drug use)

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Traumatic Brain Injury

Injury, slight, moderate and severe, invokes a change in BBB permeability. Macromolecules are seen to enter the brain at the site of injury and at remote microvascular foci.

Experimental evidence ranges from rapid BBB opening to delayed closure, reopening at times and unpredictable closing. It appears that repair of the BBB is multifactorial in nature. Dental procedures should be delayed in cases of head injury (eg whiplash).

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Cerebral Malaria

Human malarial infections, unlike other CNS infections such as bacterial meningitis, directly attacks the BBB and does not enter the brain parenchyma.

Malaria is caused by four known plasmodium parasites, P. falciparum being most common and most pathogenic. These parasites are prevalent in South America, Africa and Asia.

Dental procedures are again contraindicated until these pathogens are eliminated.

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Bacterial Meningitis (BM)

The most common agents in adults are Haemophilus Influenzae, Neisseria meningitis, and Streptococcus Pnueumoniae. In neonatal patients, causative organisms most common are Escherichia Coli and Streptococcus agalactiae.

BM In its most common clinical manifestation attacks the nasopharynx. Colonization results in epithelial penetration and bacteremia which can enter the subarachnoid space (CSF) causing cerebral edema.

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Bacterial Meningitis (BM)

CSF penetration causes the release of cytokines which then cause BBB dysfunction.

H. influenzae, it is understood, is now believed to directly attack BBB ECs.

NOTE: Many of these infections are antibiotic resistant and may persist subclinically.

Dental procedures in clinically benign and asymptomatic cases need to be evaluated in terms of BBB permeability.

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III. CONCLUSIONS

THE BBB Proper:

The BBB, although highly rigorous and dynamic, is clearly susceptible to certain factors:

1. Systemic conditions
2. Certain Microorganisms
3. The possibiltiy of mercury and other heavy metal (lead, cadmium, aluminum) induced dysfunction
4. Penetration by fluoride with unknown long term effects.

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The BBB with specific relation to dental protocol:

1. Certain indicated systemic conditions may be relative contra-indications for mercury removal.
2. BBB dysfunction itself is a contraindication.
3. Phase I examination should include an assessment of the BBB.

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3. Phase I Assessment (cont)

A. Dietary recommendations need to reflect brain and BBB health.

B. Protocols need to be established to correct BBB dysfunction.

C. Therapeutic end points need to be determined to establish proper BBB function for safe mercury removal.

D. Lastly, an assessment should be made of the ApoE genome to assess one's ability to clear mercury from the brain.

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IV. REFERENCES

Dr. Joer G. Huwyer maintains a BBB website:

http://www.med.ucla.edu/divisions/endo/namepage.html

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