

Role of Mercury Toxicity in Hypertension, Cardiovascular Disease, and Stroke

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Mercury has a high affinity for sulfhydryl groups, inactivating numerous enzymatic reactions, amino acids, and sulfur-containing antioxidants (N-acetyl-L-cysteine, alpha-lipoic acid, L-glutathione), with subsequent decreased oxidant defense and increased oxidative stress. Mercury binds to metallothionein and substitute for zinc, copper, and other trace metals, reducing the effectiveness of metalloenzymes. Mercury induces mitochondrial dysfunction with reduction in adenosine triphosphate, depletion of glutathione, and increased lipid peroxidation. Increased oxidative stress and reduced oxidative defense are common. Selenium and fish containing omega-3 fatty acids antagonize mercury toxicity. The overall vascular effects of mercury include increased oxidative stress and inflammation, reduced oxidative defense, thrombosis, vascular smooth muscle dysfunction, endothelial dysfunction, dyslipidemia, and immune and mitochondrial dysfunction. The clinical consequences of mercury toxicity include hypertension, coronary heart disease, myocardial infarction, cardiac

arrhythmias, reduced heart rate variability, increased carotid intima-media thickness and carotid artery obstruction, cerebrovascular accident, generalized atherosclerosis, and renal dysfunction, insufficiency, and proteinuria. Pathological, biochemical, and functional medicine correlations are significant and logical. Mercury diminishes the protective effect of fish and omega-3 fatty acids. Mercury inactivates catecholamine-*O*-methyl transferase, which increases serum and urinary epinephrine, norepinephrine, and dopamine. This effect will increase blood pressure and may be a clinical clue to mercury-induced heavy metal toxicity. Mercury toxicity should be evaluated in any patient with hypertension, coronary heart disease, cerebral vascular disease, cerebrovascular accident, or other vascular disease. Specific testing for acute and chronic toxicity and total body burden using hair, toenail, urine, and serum should be performed. *J Clin Hypertens (Greenwich)*. 2011;13:621–627. ©2011 Wiley Periodicals, Inc.

There is increasing concern regarding the overall health effects of chronic exposure to various heavy metals in the environment. This is particularly true of mercury and less so with other heavy metals such as cadmium, lead, aluminum, iron, and arsenic. The cardiovascular consequences of mercury toxicity have not been carefully evaluated until recently. This paper will critically review the cardiovascular consequences of mercury toxicity in humans as it relates to hypertension, generalized atherosclerosis, coronary heart disease (CHD), myocardial infarction (MI), cardiac arrhythmias, heart rate variability, sudden death, cerebrovascular accidents (CVA), carotid artery disease, renal dysfunction, and total mortality.

TYPES OF MERCURY

Mercury exists in three basic forms: elemental, inorganic, and organic (Table I).^{1–5} Dental amalgams are the most common source for elemental mercury vapor, which is a stable monoatomic gas. Inorganic mercury, which is a divalent compound, is the toxic species

found in human tissue after conversion from the other forms. Organic mercury in the form of methyl and ethyl mercury is primarily from fish, sea mammals, and thimerosal vaccines. Although dental amalgams have historically been the major source of human exposure, fish and sea mammals are becoming an increasing environment source of potential mercury toxicity.^{1,2,4,5}

MERCURY BIOTRANSFORMATION AND BIOMETHYLATION

Mercury from various sources, including elemental mercury from earth sources or inhaled mercury vapor, methyl and ethyl mercury are converted by biomethylation to inorganic divalent mercury, the toxic form in human organs and tissues (Figure 1).⁴ Divalent mercury is soluble and stable in water and undergoes biomethylation to methyl mercury, which is found in high concentrations in certain fish and sea mammals. It is this source that is becoming the major source of human exposure to mercury.

The Environmental Protection Agency has determined the safe daily intake of mercury to be <0.1 µg/kg/d.⁴ However, 12% of women have hair mercury above the level at which stopping consumption of highly contaminated fish would be advisable (1.0 µg/g).⁴ It is estimated that one dental amalgam filling releases about 3 µg to 17 µg of mercury vapor per day. The typical amalgam is

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1. Elemental	Mercury vapor (Hg^0), a stable monoatomic gas	Dental amalgams
2. Inorganic	Divalent mercury (Hg^{2+})	Toxic species in human tissue after conversion
3. Organic	Methyl mercury (CH_3Hg^+) Ethyl mercury ($CH_3CH_2Hg^+$)	Fish, sea mammals Thimerosal vaccines

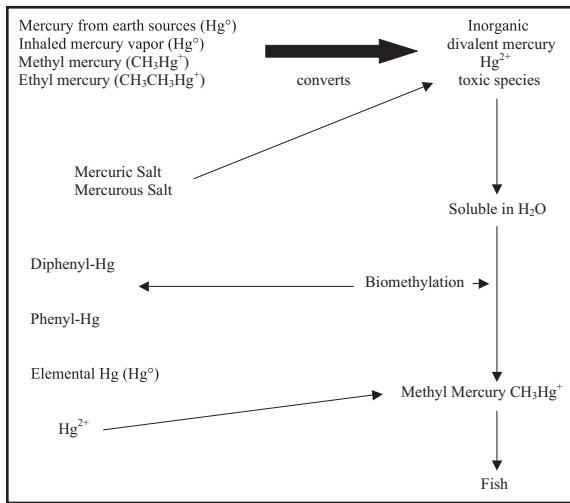


FIGURE 1. Mercury biotransformation and biomethylation.

composed of 50% mercury, 25% silver, and 25% tin, copper, and nickel.^{4,6,7} Fish and sea mammals provide about 2 µg/d to 3 µg/d depending on the type and amount consumed.^{1,2,4,5} The long-lived large predatory fish such as swordfish, tilefish, shark, and king mackerel contain about 1 µg of methyl mercury per gram. Pike, whale, bass, tuna, and trout are about 0.1 µg to 0.5 µg of mercury per gram. Nine vaccines that contain thimerosal (50% mercury) as a preservative would give an estimated exposure of 62 µg of organic mercury.^{1,2,4,5} All other sources of mercury provide about 0.3 µg/d.^{1,2,4,5}

IMPORTANT FACTS ABOUT MERCURY

Mercury is the most dangerous of all the heavy metals.⁸ It will modify the distribution and retention of other heavy metals.⁹⁻¹¹ Mercury has no known physiologic role in human metabolism, and the human body has no mechanisms to actively excrete mercury.¹² Mercury thus accumulates during life so that the average 165-lb person has a total body burden of about 13 mg of mercury.⁸ Mercury has a high affinity for sulfhydryl groups, various enzymes and amino acids, N-acetyl cysteine (NAC), alpha lipoic acid (ALA), and glutathione (GSH), which provide about 10% to 50% of the plasma protein antioxidant capacity.^{8,12,13} Both NAC and ALA, as well as cysteine, are precursors for glutathione, which is the most potent intracellular

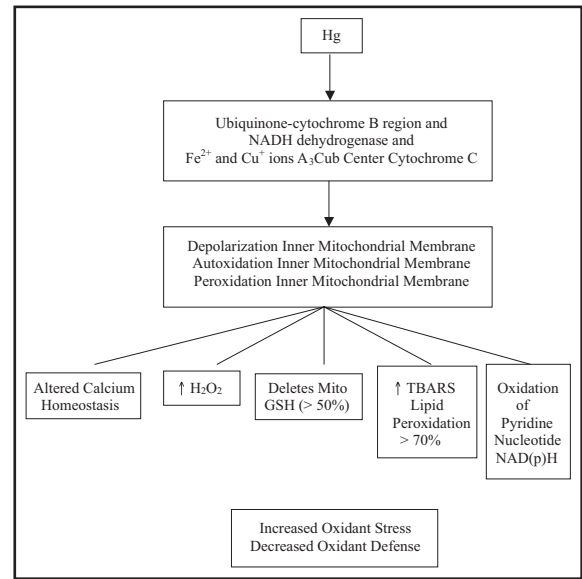


FIGURE 2. Pathophysiologic basis of mercury toxicity, mitochondrial dysfunction, and oxidative stress.

antioxidant and protects against oxidative stress, inflammation, and cardiovascular disease.^{3,4,5,8,9,12} This mercury-induced reduction in oxidant defense and increase in oxidative stress increase the risk for CVD and CVA. Selenium antagonizes some of the adverse effects of mercury by forming a seleno-mercury complex in tissue that is less toxic.^{9,14-20} Higher intake of selenium reduces mercury-related CVD and CVA.

PHYSIOLOGIC BASIS OF MERCURY TOXICITY

Mercury induces mitochondrial dysfunction and oxidative stress.^{21,22} The primary mitochondrial dysfunction occurs at the ubiquinone-cytochrome B region and with NADH dehydrogenase causing displacement of Fe²⁺ and Cu⁺ ions in the a₃Cub center of cytochrome C (Figure 2). This results in depolarization and auto-oxidation of the inner mitochondrial membrane with lipid peroxidation and severe mitochondrial dysfunction. Physiologic consequences include increased hydrogen peroxide, depletion of mitochondrial glutathione by more than 50%, increased lipid peroxidation markers such as TBARS by more than 70%, oxidation of pyridine nucleotides such as NAD(p)H, and altered calcium homeostasis.^{21,22} This severe mitochondrial dysfunction increases oxidant stress and reduces oxidant defenses, which has enormous health implications.

The primary three sources of mercury-induced lipid peroxidation include the Fenton reaction, affinity for sulfhydryl groups, and selenium deficiency.⁸ Mercury serves as a direct catalyst in Fenton-type reactions and as an indirect catalyst via iron stimulation, which

TABLE II. Vascular Biologic Effects of Mercury

1. Increased free radical production and increase in oxidative stress
2. Inactivation of antioxidant defenses
3. Mitochondrial dysfunction
4. Binds to thiol-containing molecules (sulfhydryl groups)
5. Binds to SE forming Se-Hg complex-mercury selenide, which decreases Se available for cofactor with glutathione peroxidase
6. Inactivates glutathione, catalase, superoxide dismutase
7. Increases lipid peroxidation in all organs
8. Increases oxidation of low-density lipoprotein and oxidation of low-density lipoprotein immune complexes
9. Increased platelet aggregation and thrombosis
10. Increased coagulation and thrombosis: increases Factor VIII, platelet factor 4, and thrombin and reduces protein C
11. Inhibit endothelial cell formation and migration and decreases endothelial repair
12. Decreases nitric oxide bioavailability
13. Endothelial dysfunction
14. Increase apoptosis
15. Reduced monocyte function and phagocytosis
16. Immune function is impaired
17. Increased vascular inflammation with increase tumor necrosis factor α and interleukin 6
18. Stimulation of vascular smooth muscle cells
19. Inactivation of paraoxonase and other high-density lipoprotein proteins and enzymes
20. Translocation of membrane phosphatidyl serine
21. Activates phospholipase A2
22. Activates phospholipase D

TABLE III. Summary of the Overall Vascular Biologic Effects of Mercury

1. Oxidative stress
2. Inflammation
3. Thrombosis
4. Vascular smooth muscle proliferation and migration
5. Endothelial dysfunction
6. Dyslipidemia (oxidation of high-density lipoprotein and paraoxonase)
7. Immune dysfunction
8. Mitochondrial dysfunction

increases the production of radical oxygen species and superoxide anion.⁸ Mercury's high affinity for SH, such as glutathione, NAC, and ALA, which comprise much of the antioxidant capacity of plasma, reduces both membrane and plasma antioxidant defense. Finally, insoluble complexes of mercury with selenium reduces selenium availability, which is a necessary cofactor for glutathione peroxidase (GPx) activity to break down hydrogen peroxides and various other toxic peroxidation products, which further increases risk for CVD and CVA. Plasma and intracellular antioxidant capacity are both reduced.⁸

VASCULAR BIOLOGIC EFFECTS OF MERCURY

Numerous toxic effects of mercury have been demonstrated in vitro and in animal and human studies (Table II). Mercury increases free-radical production^{3,23-29}; inactivates antioxidant defenses^{3,23,24}; binds to thiol-containing molecules^{3,23-25,30}; binds to selenium forming seleno-mercury complexes, reducing selenium availability for GPx activity^{3,23,24,27,31}; inactivates glutathione, catalase, and superoxide dismutase^{25-27,30}; increases lipid peroxidation^{28,32,33}; increases oxidation of LDL (oxLDL); and increases plasma oxLDL complexes.⁸ Thrombosis is potentiated by increased platelet aggregation,³³ increases in Factor VIII, platelet

factor 4,²⁴ and thrombin with reductions in protein C.^{33,34} Endothelial cell formation and migration are reduced, which decreases vascular endothelial repair, decreases nitric oxide, and causes endothelial dysfunction.³⁵ Apoptosis is increased,²⁵ monocyte function and phagocytosis are impaired,²⁵ immune function is reduced,²⁵ and vascular inflammation is increased with elevations of tumor necrosis factor α and interleukin 6.²⁵ There is increased production and release of superoxide anion from human neutrophils and monocytes,^{23,25} depolarization of the inner mitochondrial membrane with severe mitochondrial dysfunction,^{21,22} and disruption of plasma membrane lipid integrity by translocation of phosphatidyl serine (PS).²⁵ Mercury stimulates proliferation of vascular smooth muscle cells³⁶ and inactivates paraoxonase, an extracellular antioxidative enzyme related to high-density lipoprotein (HDL), CHD, and MI risk.^{37,38} The clinical consequences of these and other pathophysiologic mechanisms explains the wide variety of cardiovascular diseases caused by mercury including CHD, MI, arrhythmias, abnormal heart rate variability, generalized atherosclerosis, sudden death, CVA, carotid artery stenosis, renal dysfunction, and hypertension.^{4,5,6,7,8,9,13,15,19,26,28,39-70} Mercury activates phospholipase A2 (PLA-2) and induces formation of arachidonic acid metabolites such as total prostaglandins, thromboxane B2, and 8-isoprostane in vascular endothelial cells and activates vascular endothelial cell phospholipase D.^{26,51-54} Many of the cardiovascular consequences of mercury are mitigated by concomitant intake of fish containing omega-3 fatty acids and by the intake of selenium.^{8,45-50} Even very low levels of chronic mercury exposure promote endothelial dysfunction as a result of increased inflammation, oxidative stress, reduced oxidative defense, reduction in nitric oxide (NO) bioavailability, which increases the risk of CVD and CVA.²⁶

In summary, the overall vascular effects of mercury include oxidative stress—decreased oxidative defense, inflammation, thrombosis, VSM proliferation and migration, endothelial dysfunction, reduced NO bioavailability, dyslipidemia, immune dysfunction, and mitochondrial dysfunction (Table III). All of these

abnormalities have the potential to increase the risk for hypertension, CVD, and CVA.

CLINICAL VASCULAR CONSEQUENCES OF MERCURY TOXICITY

The clinical consequences of mercury toxicity include hypertension,^{13,27,39,40,55–59,67–70} CHD,^{5,15,41,60,61} MI,^{19,39,41,60,61} reduction in heart rate variability,⁷⁰ increase in carotid intima-media thickness (IMT)⁶⁹ and carotid obstruction,¹³ CVA,^{39,68} generalized atherosclerosis,⁴ renal dysfunction, and proteinuria,⁴ and an overall increase in total and cardiovascular mortality.^{4,68} Gomez and colleagues⁶⁸ followed 3998 workers in mercury mines exposed to inorganic mercury from 1895 to 1994 and found a 2.78-time increased incidence of hypertension, 1.17-time increased risk of stroke and 1.51-time increased risk in total cardiovascular mortality, but no increase in CHD. In a study of Faroese whaling men, both toenail and hair mercury levels were significantly associated with increased carotid IMT and hypertension.⁶⁹ Evidence from these and other epidemiologic and clinical studies suggest that people with high levels of urine, hair, blood, and toenail mercury have an increased risk of cardiovascular diseases.^{5,8,8,50,56,59,60,67–69}

CORONARY HEART DISEASE AND MYOCARDIAL INFARCTION

In rabbits exposed to inhaled mercury vapor, the cardiovascular and cardiac pathology includes bradycardia, thrombosis in small and medium caliber arteries, focal necrosis with thickening of the endocardium of the perivalvular regions, papillary muscles and valves, endothelial proliferation with inflammatory foci and focal edema, inflammation, and fibrosis of the ascending aorta.⁴²

In a case control study in 9 counties of 684 men with their first MI, there was a significant association of toenail mercury content, adipose tissue DHA, and first MI.⁵ There was a 15% higher toenail mercury content as assessed by neutron activation analysis (NAA) in the men with their first MI compared with the control group (95% confidence interval [CI], 5–25). The risk-adjusted odds ratio [OR] for MI was 2.16 in highest vs the lowest quintile ($P=.006$, 95% CI, 1.09–4.29). The adipose DHA was directly proportional to the mercury toenail content ($P<.001$), and the DHA content was inversely correlated to MI with an OR of 0.59 in the highest vs the lowest quintile ($P=.02$; 95% CI, 0.30–1.19). This important study concluded that there exists a positive monotonic increase in the risk of MI with mercury toenail content above the 0.25 $\mu\text{g/g}$ level, which was even steeper when adjusted for the DHA adipose tissue content. Mercury diminishes the cardiovascular protection of fish consumption. Another study substantiated these results in which the highest quartile of DHA with the lowest quartile of mercury was associated with a 67% reduction in CHD ($P<.016$).⁴³

In another large nested case control study of 33,733 male health care professionals between the ages of 40 to 75 years (Health Professionals Follow-Up Study), however, no association between mercury toenail content assessed by NAA and CHD was found.⁹ Yet, if dentists were excluded, there was a nonsignificant correlation of toenail mercury and CHD. Also, patients with the highest tertile of mercury and the lowest serum selenium level had a significant increase in CHD.

Other human studies have shown mixed results.^{6,8,39,40,44} Mercury miners showed no relationship between CHD and serum mercury levels.²⁷ However, another study of European mercury miners showed a significant relationship of mercury exposure to total mortality (increase 8%), hypertension (increase 46%), CHD (increase 36%), renal disease (increase 55%), and CVA (increase 36%).³⁹ A Finnish study found a significant relationship between hair mercury, 24-hour urine mercury and cardiovascular events.⁸ In patients with hair mercury in the highest tertile ($>2.0 \mu\text{g/g}$) and increased 24-hour urinary mercury, CHD, and MI risk was increased 2-fold ($P=.005$), cardiovascular death increased by 2.9 times ($P=.014$), and circulating oxLDL and immune complexes to oxLDL increased significantly ($P=.01$). The Gothenburg Study showed no relationship between serum mercury content and the number of amalgam fillings and CHD or MI.⁶ The National Health and Nutrition Examination Survey (NHANES) from 1999 to 2002 found levels of DHA and EPA and other nutrients in fish, even with elevated mercury levels, helped to offset the risk of CHD and MI.⁶² The fish intake resulted in lower levels of C-reactive protein and higher serum HDL cholesterol as well.⁶² The risk of hypertension over 10 years was highly correlated in a group of chemical factory workers exposed to mercury vapor.⁶³

STROKE AND CAROTID ATHEROSCLEROSIS

High hair mercury content increases carotid IMT and carotid atherosclerosis.¹³ A study of 1014 men between the ages of 42 to 60 years found an increase in mean carotid IMT over 4 years related directly to hair mercury content ($P=.0007$).¹³ Each increase in 1 μg in hair mercury content equaled a 0.008-mm increase in carotid IMT, a 7.3% increase over the mean. There was a 0.042 mm per 4 years in the highest quintile vs the lowest quintile, which correlated with a 32% greater increase ($P<.05$). In addition, mercury hair content was proportional to blood pressure (BP), fibrinogen levels, waist/hip ratio, and low HDL cholesterol (all significant at $P=.0002$). Many studies on the risk of fish intake, mercury, and stroke have been inconclusive. Different stroke types have often not been separated. In a population-based cohort, mercury levels and relative content of fatty acids were determined in erythrocyte membranes in the population consuming one meal per week as fish.⁶⁴ In women, there was a nonsignificant decrease in stroke

risk with increasing fish intake (OR, .90). The risk for stroke in men rose with increasing fish intake (OR, 1.24). The corresponding risk for mercury in men was 0.99 and for the sum of proportions of EPA and DHA was 1.08. This study suggested that the risk for stroke between sexes differs with increasing fish intake, EPA, and DHA consumption, but there was no association between stroke risk and mercury at these lower levels of one meal of fish per week. There are many basic mechanisms by which mercury can increase the risk for stroke as discussed earlier in this paper. The increases in both BP and pulse pressure,^{13,39,40,44,55,56-60,67} the increased thrombotic risk related to increased platelet aggregation,³³ increase in Factor VIII, thrombin, and platelet factor 4²³ and reduction in protein C^{33,34} as well as endothelial dysfunction from reduced NO bioavailability³⁵ may account for much of the observed elevation in CVA risk with mercury. One recent study showed that mercury increases thrombotic risk by enhancement of procoagulant activity in erythrocytes by protein thiol depletion-mediated phosphatidyl serine exposure and microvesical generation.⁶⁵

HYPERTENSION

The association of mercury toxicity and hypertension in humans is convincing.^{13,39,40,44,55-60,67} Mercury miners were found to have significant increases in systolic BP ($P < .01$) that correlated with lipid peroxidation and overall oxidative stress ($P < .01$).²⁷ European mercury miners had a 46% greater incidence of hypertension vs aged-matched controls. Other studies have shown significant correlations with hair mercury content, hypertension, and carotid IMT.¹³ In a study of 251 persons in the Brazilian Amazon, BP was significantly associated with total hair mercury levels. The OR for elevated systolic BP with total hair mercury $>10 \mu\text{g/g}$ was 2.91 (1.26–7.28).⁵⁶ In 101 participants in the Wisconsin Sleep Cohort study, those in the upper quartile of blood mercury were 1.9 times more likely to be hypertensive ($P = .023$) and those in the upper quartile of hair mercury were 4 times more likely to be hypertensive ($P = .02$), but there was no change in brachial artery flow-mediated vasodilation or the middle cerebral artery reactivity to CO_2 .⁵⁷ In 732 Inuit adults, blood mercury level was correlated with systolic BP and pulse pressure ($P = .0004$) and diastolic BP ($P = .069$).⁵⁸ In a comparative population study, long-term methyl mercury exposure, as measured by hair mercury levels, was associated with a risk of hypertension of 1.4 to 1.6 times in 833 patients.⁵⁹ In a sample of 1240 women aged 16 to 49 who participated in the NHANES 1999 to 2000, Vupputuri and colleagues⁶⁰ found a significant increase in systolic BP with increasing levels of blood total mercury, but only among non-fish consumers. There was a 1.83-mm Hg increase in systolic BP for each 1.3 $\mu\text{g/L}$ increase in total blood mercury (95% CI, 0.36, 3.30; interaction $P = .02$).

Pederson and colleagues⁶⁷ found an increase in pulse pressure using 24-hour ambulatory BP monitoring (54 mm Hg vs 50 mm Hg, $P < .0001$) that was related to blood mercury levels ($\rho = .272$, $P < .01$) in a group of Greenlanders consuming more fish than a group of Danes. Mercury is also significantly associated with reduced heart rate variability in addition to increased pulse pressure and hypertension.⁷⁰ Reduced heart rate variability may predispose to ventricular fibrillation and sudden cardiac death, as well as being associated with angina, MI, CHD, CHF, and all-cause mortality.⁷⁰

In acute and probably chronic mercury intoxication, mercury binds to the sulfhydryl group S-adenosyl methionine and inactivates this enzyme, which is a necessary cofactor for catecholamine-*O*-methyl transferase, the enzyme needed to convert norepinephrine, epinephrine, and dopamine by methoxylation.⁴⁰ This results in a clinical syndrome that resembles a pheochromocytoma crisis with malignant hypertension in acute mercury intoxication and significant increases in urinary catecholamines in chronic mercury toxicity. This can be a helpful clinical clue to mercury-induced hypertension. It would be important to measure baseline and provoked 24-hour urine mercury levels in patients with hypertension with a history or clinical evidence of possible mercury exposure. Measurement of timed baseline and provoked urine collections for heavy metals is cost-effective, at about \$150 for most laboratories, and is reimbursed by insurance with proper coding. Mercury also induces renal dysfunction and proteinuria, which contribute to sodium retention and hypertension.^{26,39,40,45} Studies have shown an increase in renal insufficiency in mercury miners by 55%.³⁹ Mercury concentrates in the renal tubules and in the glomerulus and results in proteinuria, fibrosis, chronic renal dysfunction, and renal insufficiency.^{26,44}

SUMMARY

Mercury has a high affinity for sulfhydryl groups, which inactivate numerous enzymatic reactions, amino acids, and sulfur-containing antioxidants (NAC, ALA, GSH) with decreased oxidant defense and increased oxidative stress. Mercury binds to metallothionein and substitute for zinc, copper, and other trace metals, reducing the effectiveness of metalloenzymes. Mercury also induces mitochondrial dysfunction with reduction in ATP, depletion of glutathione, and increased lipid peroxidation. Oxidative stress and decreased oxidative defense are common (especially with mercury). Selenium and fish high in omega-3 fatty acid content antagonize mercury toxicity. The overall vascular effects of mercury include increases in oxidative stress and inflammation, reduction in oxidative defense, thrombosis, vascular smooth muscle dysfunction, endothelial dysfunction, dyslipidemia, and immune and mitochondrial dysfunction. The clinical consequences of mercury toxicity include hypertension, CHD, MI, cardiac arrhythmias, sudden death, reduced heart rate variability, increased carotid IMT and carotid artery

obstruction, CVA, generalized atherosclerosis, and renal dysfunction, insufficiency, and proteinuria. Pathological, biochemical and functional medicine correlations are significant and logical. Mercury diminishes the protective effect of fish and omega-3 fatty acids. Mercury inactivates catecholamine-0-methyl transferase, which increases serum and urinary epinephrine, norepinephrine, and dopamine. This effect will increase BP and may be a clinical clue to mercury toxicity. Mercury toxicity should be evaluated in any patient with hypertension, CVD, CHD, CVA, or other vascular disease and who have a clinical history of exposure or clinical evidence on examination of mercury overload. Specific testing for acute and chronic toxicity and total body burden using hair, toenail, urine, and serum should be performed. The 24-hour urine measurements should be done with baseline and provoked samples.

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