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*Via electronic submission to
<https://oehha.ca.gov/comments>*

Monet Vela
Office of Environmental Health Hazard Assessment
P.O. Box 4010
Sacramento, California 95812-4010

Re: Proposed Adoption of New Section Under Article 7: No Significant Risk Levels
Section 25704: Exposures to Listed Chemicals in Coffee Posing No Significant Risk

CERT'S SUBMISSION NO. 4

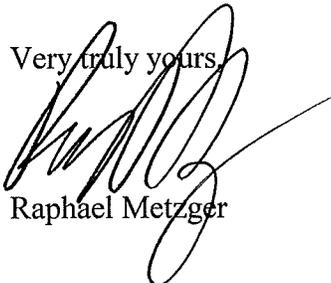
Dear Ms. Vela:

Enclosed herewith are the following documents that are being submitted on behalf of our client, the Council for Education and Research on Toxics (CERT) regarding the Opinions of Dr. Nachman Brautbar Regarding Consumption of Coffee and Chronic Human Diseases.

1. Exhibit A - Opinions of Dr. Nachman Brautbar.
2. Exhibit B - Curriculum Vitae of Dr. Nachman Brautbar.

Kindly include these materials of Dr. Nachman Brautbar in the record for this rulemaking proceeding.

Very truly yours,



Raphael Metzger

RM:ip
encls: as specified

EXHIBIT “A”

OPINIONS OF DR. NACHMAN BRAUTBAR

I. SUMMARY OF OPINIONS

- A. Consumption of coffee has been associated in epidemiologic and other types of studies with increased risks of several chronic diseases, including bone disease (osteoporosis and bone fractures); cardiovascular diseases including coronary heart disease, myocardial infarction, stroke (especially aneurysmal subarachnoid hemorrhage), heart failure, and angina pectoris; connective tissues diseases (rheumatoid arthritis and systemic lupus erythematosus); Type 1 diabetes, fibrocystic breast disease; gastrointestinal disorders (constipation, gallstones, and gastroesophageal reflux disease); and urological conditions (chronic kidney disease, urolithiasis, lower urinary tract symptoms, urinary incontinence, and urinary tract infections); as well as mortality.
- B. Consumption of coffee has generally been associated in epidemiologic studies with decreased risks of a few chronic diseases, the most notable of which are Type 2 diabetes, Alzheimer's disease, and Parkinson's disease. However, it has not been proven that these inverse associations are actually causal. Such inverse associations may be due to numerous confounding factors, including increased water intake (as coffee beverages are comprised of approximately 99% water) among coffee consumers and their consequent likely decreased intake of soft drinks and other unhealthy beverages.

II. Chronic Disease

A. Bone Disease

1. Numerous studies have been published regarding the effects of coffee consumption on bone density and the risk of resultant bone fractures.
2. A community-based cohort study of postmenopausal California women found a significant association between coffee intake and decreased bone mineral density of the hip and spine. The researchers concluded: “Lifetime caffeinated coffee intake equivalent to two cups per day is associated with decreased bone density in older women who do not drink milk on a daily basis.” (Barrett-Connor 1994).
3. A cohort study of coffee consumption and CYP1A2 genotype, found that men who drank ≥ 4 cups of coffee/day had 4% lower bone mineral density at the proximal femur than low or nondrinkers, and that in high consumers of coffee, those with rapid metabolism of caffeine (C/C genotype) had lower bone mineral density at the femoral neck and at the trochanter. (Hallström 2010).
4. A meta-analysis of 10 prospective studies showed an overall 3.5% higher risk of fracture per cup of coffee per day (RR 1.05, 95% CI 1.02 - 1.08) and a dose-response relationship for consumption and risk of fractures for men and women combined and women specifically. (Liu 2012).
5. A meta-analysis of 6 case-control studies and 8 cohort studies reported an overall 30% increase in bone fracture in both sexes combined, with a greater than 50% excess from the 8 studies in women (RR 1.55, 95% CI 1.15 - 2.08). The increased risk for coffee consumption was greatest among those above age 70 (RR 1.40, 95% CI 1.02 - 1.94), especially in North America (RR 1.49, 95% CI 1.49 - 1.90). (Li 2013).
6. A meta-analysis of 9 cohort and 8 case-control studies found an increased risk of fracture in women (RR 1.14, 95% CI 1.05 - 1.24) but not men, especially among women consuming 8 cups per day (RR 1.54, 95% CI 1.19 - 1.99). The risk of osteoporotic fracture was significantly increased in studies of both sexes (RR 1.35, 95% CI 1.06 - 1.73). (Lee 2014).
7. The most recent meta-analysis, based on 10 prospective cohort studies, reported nonsignificant increased risks of fracture for both sexes (RR 1.13, 95% CI 0.86 - 1.48), with higher risks among women (RR 1.27, 95% CI 0.94 - 1.72) and in both sexes when adjustment was made for calcium intake (RR 1.31, 95% CI 0.81 - 2.11). (Li 2015).

B. Cardiovascular Disease

1. Cardiovascular disease generally refers to conditions that involve narrowed or blocked blood vessels that can lead to a heart attack, chest pain (angina) or stroke. Cardiovascular disease includes coronary heart disease, myocardial infarction, stroke, congestive heart failure, and angina pectoris.
2. A meta-analysis regarding coffee consumption and cardiovascular disease was published by Harvard researchers in 2014. They reported risks of cardiovascular disease for different levels of coffee consumption. They found that the risk of cardiovascular disease was reduced 11% for people who drink 1½ cups of coffee per day (RR 0.89, 95% CI 0.84 - 0.94) and was reduced 15% for people who drink 3 cups of coffee per day (RR 0.85, 95% CI 0.80 - .090), but that the risk of cardiovascular disease in people who drink 5.5 cups of coffee per day was reduced only 5% (RR 0.87 - 1.03). The absence of a linear dose-response between coffee consumption and cardiovascular disease renders the association between coffee and cardiovascular disease questionable and difficult to interpret. Moreover, since cardiovascular disease is a collection of different diseases with different causes and risk factors, it would be scientifically more appropriate to evaluate the effect of coffee consumption (and consumption of water) on cardiovascular diseases separately. (Ding 2014)
3. A recent systematic review concluded that studies showed that heavy, but not light, coffee consumption was associated with adverse cardiovascular disease effects. (Lafortune 2016)
4. In a recently published prospective cohort study of 3,042 healthy adults followed for 10 years, Greek researchers reported a J-shaped relationship between coffee consumption and cardiovascular disease. Comparing those consuming more than 250 milliliters of coffee per day with those consuming no coffee, the risk of cardiovascular disease was more than doubled for each of three analytical models (Model 1: HR 2.81 (95% CI 1.84 - 4.23, Model 2: HR 2.62, 95% CI 1.67 - 4.09), Model 3 (HR 2.48, 95% CI 1.56 - 1.93). (Kouli 2017).
5. In recently published Mendelian randomization analyses of coffee consumption and cardiovascular disease in 95,366 Danes and 223,414 individuals, U-shaped associations between coffee intake and cardiovascular disease and all-cause mortality were observed, confirming an increased risk of cardiovascular disease for high consumption of coffee with a lower risk for medium consumption of coffee. (Nordestgaard 2017)
6. A study by government researchers used data from 1991 Medicare files to analyze the contribution of dehydration to mortality. They reported that Medicare beneficiaries hospitalized with dehydration had significantly increased risks of death from cancer compared to those without

dehydration. Among those who died within 30 days of hospitalization, the risk of cardiac mortality was more than doubled among those hospitalized with dehydration (RR 2.19, 95% CI 20.7 - 2.31). Among those who died within one month to one year of hospitalization, the risk of cardiac mortality was increased more than 75% among those hospitalized with dehydration (RR 1.78, 95% CI 1.69 – 1.88). (Warren 1994).

a. Coronary Heart Disease.

- (1) Coronary heart disease is a disease in which plaque builds up inside the coronary arteries. It distinguished from other heart conditions that affect the heart muscle, valves or rhythm, which are considered forms of heart disease.
- (2) “Coronary heart disease (CHD) is one of the leading causes of mortality in industrialized countries. CHD is responsible for about 19% of all deaths in the United States and UK in recent years, and is rapidly becoming a major cause of death worldwide.” (Wu 2009)
- (3) One meta-analysis of coffee consumption and coronary heart disease, based on 13 case-control studies and 10 cohort studies, reported a significantly increased risk of coronary heart disease for consumption of 3 to 4 cups of coffee per day (OR 1.33, 95% CI 1.04 - 1.71; $p < 0.0001$) with an even higher risk for consumption of more than 4 cups of coffee per day (OR 1.83, 95% CI 1.49 - 2.24; $p < 0.0001$) (Sofi 2007). Another meta-analysis, based on 21 prospective cohort studies, reported lesser risks of coronary heart disease. As compared to light coffee consumption, under the random-effects model, the pooled relative risks for all studies were 0.96 (95% CI 0.87 - 1.06) for moderate consumption, 1.04 (95% CI 0.92 - 1.17) for heavy consumption, and 1.07 (95% CI 0.87 - 1.32) for very heavy consumption. (Wu 2009). Rather than demonstrating decreased risks of coronary heart disease from coffee consumption, these studies actually reflect increased risks of coronary heart disease with a dose-response.
- (4) Associations between fatal coronary heart disease and intake of water and fluids other than water were examined among the 8,280 male and 12,017 female participants aged 38-100 years who were without heart disease, stroke, or diabetes at baseline in 1976 in the Adventist Health Study, a prospective cohort study. Water was the fluid consumed in greatest amounts among the participants. Compared with the national averages, the Adventist Health Study population drank more water, milk, and fruit juices and less

coffee, tea, and carbonated and alcoholic beverages. A total of 246 fatal coronary heart disease events occurred during the 6-year follow-up. High daily intake of water (five or more glasses) compared with low (two or fewer glasses) daily water intake was associated with a relative risk of 0.46 (95% CI 0.28 - 0.75; p trend = 0.001) in men, and a relative risk of 0.59 (95% CI: 0.36, 0.97) in women. A high versus low intake of fluids other than water was associated with a relative risk of 2.47 (95% CI: 1.04, 5.88) in women and of 1.46 (95% CI: 0.7, 3.03) in men. All associations remained virtually unchanged in multivariate analysis adjusting for age, smoking, hypertension, body mass index, education, and (in women only) hormone replacement therapy. (Chan 2002).

- (5) The Chan study shows an approximate 50% reduction of coronary heart disease for high water intake, but an approximate doubling of the risk of coronary heart disease from consumption of beverages other than water. This study provides strong evidence for a protective effect of high water intake on coronary heart disease in contrast to other beverages which included coffee.

b. Myocardial Infarction

- (1) Myocardial infarction, commonly known as a “heart attack,” occurs when blood flow stops to a part of the heart, causing damage (often necrosis) to the heart muscle.
- (2) In 1993 Sander Greenland published a meta-analysis of 22 studies of coffee consumption and myocardial infarction or coronary death. Eight of the included studies were case-control studies and fourteen of included studies were cohort studies. Comparing those who drank 5 cups per day with non-drinkers, a significantly increased risk of myocardial infarction or coronary death was found in the 8 case-control studies (RR 1.42, 95% CI 1.30 - 1.55) and a lesser, but significantly increased risk was found in the nine cohort studies published in 1986 or later (RR 1.27, 95% CI 1.17 - 1.39). (Greenland 1993).
- (3) In 2013 Canadian researchers published a cross-sectional analysis in which they used data from the National Health and Nutrition Examination Survey (NHANES) to assess cardiovascular disease risks from water intake. Compared with participants who had the highest water intake, those with lowest intake were more likely to report a history of myocardial infarction (1.4% vs. 3.1%). The prevalence of

myocardial infarction was 3.08 among participants with low (< 2.0 liters/day) water intake, 2.54 among participants with moderate (2.0 to 4.3 liters/day) water intake, and 1.44 among participants with high intake (>4.3 liters/day). (Sontrop 2013).

c. Stroke

- (1) A stroke occurs when brain cells suddenly die due to a lack of oxygen from obstructed blood flow, which can result from a blocked artery (ischemic stroke) or a ruptured blood vessel (hemorrhagic stroke). The two types of hemorrhagic stroke are intracerebral (within the brain) and subarachnoid, which results from bleeding into the subarachnoid space, usually due to a ruptured aneurysm.
- (2) Some case-control studies have reported increased risks of stroke associated with consumption of coffee or caffeine.
 - (a) In a case-control study of 1,714 Americans diagnosed with intracerebral hemorrhage at age 18 to 49, the adjusted risk for intracerebral hemorrhage was significantly increased among those who consumed more than 5 caffeinated drinks per day (OR 1.73, 95% CI 1.08 - 2.79). (Feldmann 2005).
 - (b) In a multicenter case-crossover study of 390 subjects, the relative risk of acute ischemic stroke in the hour after consuming coffee was doubled (RR 2.0, 95% CI 1.4 - 2.8, $p < 0.001$). The association between ischemic stroke in the hour after coffee consumption was only apparent among those consuming 1 cup of coffee per day or less, but not for patients who consumed coffee more regularly (p -trend = 0.002). The investigators concluded that coffee consumption transiently increases the risk of ischemic stroke onset, particularly among those who drink coffee infrequently. (Mostofsky 2010).
 - (c) In a multicenter case-control study in South Korea of 940 patients with acute hemorrhagic stroke aged 30 to 84 years without a history of stroke, those who consumed caffeine-containing medicines had more than double the risk of all hemorrhagic stroke (OR 2.23, 95% CI 1.41 - 3.69). (Lee 2013).
- (3) Some cohort studies have reported increased risks of stroke in association with increased consumption of coffee.

- (a) In a cohort study of 37,514 Dutch adults who were followed for 13 years, on multivariate analysis, the risk of stroke increased with increasing coffee consumption: 1 to 3 cups/day (RR 0.86, 95% CI 0.39 - 1.87), 3.1 to 6 cups/day (RR 1.20, 95% CI 0.59 - 2.47), more than 6 cups per day (RR 1.34, 95% CI 0.49 - 3.64). (De Koning Gans 2010).
 - (b) In the Netherlands Cohort Study 120,852 adults aged 55-69 years were followed for 10 years. On multivariate analysis, consumption of more than 67 cups of coffee per day was associated with a slight increased of mortality from stroke among men (RR 1.15, 95% CI 0.74 - 1.77) and women (RR 1.10, 95% CI 0.63 - 1.90). (Leurs 2010).
 - (c) In a cohort study of Hawaiian men at high risk of cardiovascular disease who were followed for incident stroke over a 25-year period, the risk of thromboembolic stroke, adjusted for other factors, was more than doubled for men who consumed 3 cups of coffee per day compared to nondrinkers (RR 2.1, 95% CI 1.2 - 3.7). (Hakim 1998).
- (4) Three meta-analyses regarding consumption of coffee and stroke, all based on prospective cohort studies, have been published. (Larsson 2011, Kim 2012, Zhang 2012). These reported reductions in risk of stroke ranging from 7% to 17%, depending on consumption levels. In one study, the greatest risk reduction (17%) was found for consumption of 3 to 4 cups of coffee per day, with lesser reductions in risk for higher consumption: 13% risk reduction for 6 cups/day and 7% reduction for 8 cups/day. (Larsson 2011).
- (5) While studies regarding coffee consumption and ischemic and hemorrhagic stroke are mixed, the risk of subarachnoid hemorrhagic stroke has been reported to be increased with consumption of coffee and/or caffeine in most studies. Isaksen 2002: more than 5 cups of coffee per day (OR 3.86, 95% CI 1.01 - 14.73); Broderick 2003: 5 or more caffeinated drinks per day (OR 1.94, $p < 0.0001$); Jiménez-Yepes 2008: OR 1.48, 95% CI 0.86 - 2.55); Larsson 2008: 8 or more cups of coffee per day in men (RR 1.18, 95% CI 0.63 - 2.20); Sugiyama 2010: 1 cup of coffee per day (RR 1.32, 95% CI 0.44 - 3.95); Vlak 2011: coffee consumption (RR 1.7, 95% CI 1.2 - 2.4); Larsson 2011: 5 or more cups of coffee per day in women (RR 0.27, 95% CI 0.11 - 0.67);

Lee 2013: caffeine-containing medicines (OR 2.24, 95% CI 1.08 - 4.66); Sakamaki 2016: 5 or more cups of coffee per day (RR 3.79, 95% CI 1.19 - 12.05).

- (6) A few studies have evaluated the risk of stroke in association with water intake and dehydration.
- (a) A study by Dutch investigators evaluated the relationship between total fluid (and specific beverage) intake and stroke mortality in the Netherlands Cohort Study (NLCS). In 1986, 120,852 participants aged 55-69 years were enrolled into the NLCS. Mortality data were collected over a 10-year follow-up period. Analysis was done through a case-cohort approach, and it was based on the subjects without a history of heart disease, stroke or diabetes at baseline. A total of 708 stroke mortality cases occurred during the follow-up. In the multivariate analysis, the highest level of coffee consumption (> 6 cups/day) increased the risk of stroke mortality in men (HR 1.15, 95% CI 0.74 - 1.77) and women (HR 1.10, 95% CI 0.63 - 1.90), but the highest level of water consumption (> 500 ml/day) reduced the risk of stroke mortality in men (HR 0.85, 95% CI 0.31 - 2.20 and women (HR 0.49, 95% CI 0.19 - 1.24). Thus, in the Netherlands Cohort study, high water intake reduced the risk of stroke mortality, whereas high coffee intake increased the risk. (Leurs 2010).
- (b) A case-control study by Israeli researchers sought to evaluate risk factors associated with stroke that occurred in patients hospitalized for other illnesses. The cases were all patients who suffered an ischemic stroke while hospitalized for a condition other than stroke; the controls were patients admitted during the same period who were matched for age and sex to the study patients. Of 2,247 consecutive patients with ischemic stroke, the stroke had occurred during hospitalization not related to any surgical procedure in 80 patients. On logistic regression analysis, the risk of stroke was increased more than five-fold among the dehydrated patients (OR 5.3, 95% CI 1.5 - 1[0].9) and was highly significant ($p = 0.0006$). (Nadav 2002).
- (c) A recent study by researchers affiliated with the Myocardial Infarction Data Acquisition System

(MIDAS), a repository of in-patient records from New Jersey hospitals, used 1,282,787 records of hospitalizations for atrial fibrillation to assess the impact of dehydration on the risk of ischemic stroke. Within 10 days of discharge for atrial fibrillation, patients 18-80 years old with comorbid dehydration had a 60% higher risk of ischemic stroke compared to atrial fibrillation patients without comorbid dehydration (RR 1.60, 95% CI 1.28 - 2.00). Patients in the same age group also had a 34% higher risk of ischemic stroke in days 11-20 post-atrial fibrillation discharge (RR 1.34, 95% CI 1.04 - 1.74). The researchers concluded that dehydration may be a significant risk factor for ischemic stroke in patients 18 to 80 years old with atrial fibrillation. (Swerdel 2016).

d. Heart Failure

- (1) Heart failure, often referred to as congestive heart failure, occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs.
- (2) In 2012 researchers from Boston published a meta-analysis of coffee consumption and the risk of heart failure that was based on five prospective cohort studies and included 6,522 heart failure events and 140,220 participants. They observed a statistically significant J-shaped relationship between coffee consumption and heart failure. Compared with no consumption, the pooled relative risk for heart failure was 0.96 (95% CI 0.90 - 0.99) for 1 to 2 servings per day, 0.93 (95% CI 0.86 - 0.99) for 2 to 3 servings per day, 0.90 (95% CI 0.82 - 0.99) for 3 to 4 servings per day, 0.89 (95% CI 0.81 - 0.99) for 4 to 5 servings per day, 0.91 (95% CI 0.83 - 1.01) for 5 to 6 servings per day, 0.93 (95% CI 0.85 - 1.02) for 6 to 7 servings per day, 0.95 (95% CI 0.87 - 1.05) for 7 to 8 servings per day, 0.97 (95% CI 0.89 - 1.07) for 8 to 9 servings per day, 0.99 (95% CI 0.90 - 1.10) for 9 to 10 servings per day, 1.01 (95% CI 0.90 - 1.14) for 10 to 11 servings per day, and 1.03 (95% CI 0.89 - 1.19) for 11 servings per day. Thus, dose-response was J-shaped with the strongest inverse association being seen for 4 servings per day. (Mostofsky 2012).
- (3) In 2013 Canadian researchers published a cross-sectional analysis in which they used data from the National Health and Nutrition Examination Survey (NHANES) to assess cardiovascular disease risks from water intake. Compared

with participants who had the highest water intake, those with lowest intake were more likely to report a history of congestive heart failure (0.9% vs 1.1%). The prevalence of heart failure was lowest (0.94%) among participants with high water intake (> 4.3 liters/day). (Sontrop 2013).

e. Angina Pectoris

- (1) Angina pectoris is chest pain due to inadequate supply of oxygen to the heart muscle, usually resulting from , usually resulting from inadequate blood flow as a result of obstruction or spasm of the coronary arteries. The pain is typically severe and crushing, and is characterized by a feeling of pressure and suffocation behind the breastbone.
- (2) Two studies published in 1995 evaluated the risk of angina pectoris in relation to consumption of coffee.
 - (a) In a case-control study of nonfatal myocardial infarction among Massachusetts women aged 45-69 years, 858 cases with first infarctions were compared with 858 community controls matched on age and town precinct. Detailed information on coffee drinking, cigarette smoking, and other factors was obtained by telephone interview. On multivariate analysis, consumption of caffeinated coffee increased the risk of angina pectoris in a dose-response manner: 1-2 cups/day (RR 1.4, 95% CI 0.5 - 3.8), 3-4 cups/day (RR 2.9, 1.0 - 8.6), ≥ 5 cups/day (RR 4.0, 95% CI 1.2- 13). (Palmer 1995).
 - (b) The association between coffee consumption and self-reported angina pectoris or and its symptoms was studied in 11635 men and 11785 women, aged 40-54 years. Angina pectoris was reported by 201 men and 102 women. Symptoms of angina pectoris were reported by 241 men and 395 women. The univariate analysis showed a positive association between number of cups of coffee and self-reported angina pectoris. After adjusting for major coronary risk factors, risk of angina pectoris was increased in men (RR 1.4, 95% CI 0.8 - 2.7) and in women (RR 2.7, 95% CI 1.1 - 6.7). (Stensvold 1995).
- (3) Two studies have evaluated the risk of angina pectoris in relation to consumption of water.

- (a) In 2013 Canadian researchers conducted a cross-section analysis of the 2005-2006 National Health and Nutrition Examination Survey to evaluate the association between water consumption and the risk of cardiovascular disease. Of 3,427 participants, 18% had cardiovascular disease. Compared with participants who had the highest water intake, those with lowest intake were more likely to report a history of angina pectoris (1.3, vs. 1.6%). However, angina pectoris was not associated with low water intake in multivariable analysis. (Sontrop 2013).
- (b) In 2016 Korean researchers published a study regarding water intake and heart disease using data from the 2012 Korea National Health and Nutrition Examination Survey. Participants were divided into 2 groups: above adequate intake (736 participants) and below adequate intake (4,819 participants). Participants with more than adequate water intake had a slight nonsignificant reduced risk of angina pectoris (OR 0.94, 95% CI 0.47 - 1.86). (Jang 2016)

7. **Connective Tissue Diseases**

- a. Connective tissue diseases include inherited disorders and autoimmune diseases, in which the body's normally protective immune system produces antibodies that target the body's own tissues for attack. These diseases include polymyositis and dermatomyositis, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic lupus erythematosus, and vasculitides - more than 20 conditions characterized by inflammation of blood vessels.
- b. Studies regarding coffee consumption and autoimmune connective tissues diseases have only been published regarding rheumatoid arthritis and systemic lupus erythematosus.
- c. **Rheumatoid Arthritis.**
 - (1) Rheumatoid arthritis is an autoimmune disorder in which the immune system mistakenly attacks the synovium, a soft tissue that lines the joints, leading to inflammation.
 - (2) In 2000, Finnish researchers published a study about coffee consumption and rheumatoid factor and rheumatoid arthritis. They assessed rheumatoid factor in a cross-sectional study and rheumatoid arthritis in a cohort study. In the former, daily coffee consumption was proportional to the prevalence of rheumatoid factor positivity. In the

latter, the relative risk of rheumatoid factor-positive rheumatoid arthritis for consumption of 4 or more cups of coffee per day versus less coffee consumption was doubled. (RR 2.20, 95% CI 1.13 - 4.27). (Heliövaara 2000).

- (3) In 2002, a prospective cohort study of women evaluating coffee consumption and rheumatoid arthritis was published. Compared with nondrinkers, women consuming 4 or more cups of decaffeinated (but not caffeinated) coffee per day had a 2½ fold increased risk of rheumatoid arthritis (RR 2.58, 95% CI 1.63 - 4.06). (Mikuls 2002).
- (4) In 2006, Danish researchers published a case-control study of risk factors for serologic subtypes of rheumatoid arthritis. Risk of anti-CCP-positive rheumatoid arthritis was doubled among those drinking >10 cups/day coffee vs. none (OR 2.18, 95% CI 1.07 - 4.42). (Pedersen 2006).
- (5) The following year the same researchers reported an extremely high (greater than 50-fold increased) risk of anti-CCP-positive rheumatoid arthritis in SE homozygotes who were heavy coffee drinkers (OR 53.3, 95% CI 15.5-183) compared with SE noncarriers who were not coffee drinkers. (Pedersen 2007).
- (6) In 2014 Korean researchers published a meta-analysis of studies regarding coffee and tea consumption and the development of rheumatoid arthritis. The analysis included five studies (three cohort studies and 2 case-control studies, including 134,901 participants (1,279 cases of rheumatoid arthritis and 133,622 non-cases). Meta-analysis of the cohort studies revealed a trend of an association between total coffee intake and rheumatoid arthritis incidence. Comparing the highest versus lowest exposure group, the risk was increased four-fold (RR 4.148, 95% CI 0.792 - 21.73, $p = 0.092$). Meta-analysis of case-control studies showed a significant association between total coffee intake and rheumatoid arthritis incidence (RR 1.201, 95% CI 1.058 - 1.361, $p = 0.005$). Combining the data of the cohort and case-control studies showed a significant association between total coffee intake and rheumatoid arthritis incidence (RR .426, 95% CI 1.060 - 5.554, $p = 0.036$). Meta-analysis stratified by seropositivity indicated a significant association between coffee consumption and seropositive rheumatoid arthritis risk (RR 1.329, 95% CI 1.162 - 1.522, $p = 3.5 \times 10^{-5}$), but not seronegative rheumatoid arthritis risk (RR 1.093, 95% CI 0.884 - 1.350,

$p = 0.411$). No association was found between tea intake and rheumatoid arthritis incidence (RR 0.880, 95% CI 0.624 - 1.239, $p = 0.463$). The authors concluded that their meta-analysis suggests that high coffee consumption is associated with an elevated risk of rheumatoid arthritis. The association between coffee and rheumatoid arthritis was found in seropositive rheumatoid arthritis, but not in seronegative rheumatoid arthritis. (Lee 2014).

d. Systemic Lupus Erythematosus.

- (1) Systemic lupus erythematosus is an autoimmune disorder that causes inflammation in many parts of the body, including the joints, skin, kidneys, blood, lungs, heart, and brain.
- (2) In 2013, Colombian researchers published a study of 310 Colombian patients with Systemic Lupus Erythematosus to determine the prevalence of and associated risk factors for cardiovascular disease. They found that the risk of cardiovascular disease was almost doubled among Systemic Lupus Erythematosus patients who drink coffee (OR 1.94, 95% CI 1.19 - 3.18, $p = 0.019$). (Amaya-Amaya 2013).
- (3) In 2014, Japanese investigators reported the results of a study investigating the effects of alcoholic and caffeinated beverages on the risk of Systemic Lupus Erythematosus. They found an increased risk of Systemic Lupus Erythematosus in association with consumption of coffee (OR 1.57, 95% CI 0.95 - 2.61) and consumption of black tea (OR 1.88, 95% CI 1.03 - 3.41). (Kiyohara 2014).
- (4) In 2016, Colombian researchers conducted a cross-sectional analysis on 319 Systemic Lupus Erythematosus patients using a structural model to characterize a severity construct of 17 variables. In addition, the model analyzed possible associations of the severity latent trait with other patient covariates including cardiovascular disease, age at onset of disease, and exposure factors. A total of 11 symptoms were included in the item response theory model showing three levels of disease severity. The only covariate registered that reached an association with severity was coffee consumption. (Molano-González 2016).
- (5) Interestingly, a connective tissue disease bearing features of Systemic Lupus Erythematosus and Periungual Telangiectasia (an autoimmune connective tissue disease that is a form of dermatomyositis) has been reported among coffee plantation workers in India. (Narahari 1990).

8. Fibrocystic Breast Disease.

- a. Fibrocystic breast disease is a condition of breast tissue affecting an estimated 30-60% of women and at least 50% of women of childbearing age.
- b. In 1981, American researchers reported that complete abstinence from methylxanthine consumption resulted in resolution of Fibrocystic Breast Disease in 82.5% of women and significant improvement in 15% of women studied. Since 97.5% showed clinical benefit from methylxanthine abstinence, the researchers concluded that methylxanthine intake is etiologically associated with Fibrocystic Breast Disease. (Minton 1981).
- c. In 1984, American researchers published a hospital-based case-control study of 634 women with Fibrocystic Breast Disease and 1,066 controls. Women who consumed 31-250 mg caffeine/day had a 1.5-fold increased risk of Fibrocystic Breast Disease; women who consumed >500 mg/day had a 2.3-fold increased risk. The association with caffeine consumption was especially high among women with atypical lobular hyperplasia and with sclerosing adenosis with concomitant papillomatosis or papillary hyperplasia, both of which have been associated with increased breast cancer risk. The association was specific to Fibrocystic Breast Disease; there was no association of caffeine with fibroadenoma or other forms of benign breast disease. (Boyle 1984).
- d. In 1984, Kaiser Permanente physicians published a study of female twins, only one of whom had Fibrocystic Breast Disease. They found a positive association between coffee consumption and risk of Fibrocystic Breast Disease. (Odenheimer 1984).
- e. In 1985, researchers from Buffalo, New York investigated the effect of theophylline therapy on fibrocystic breast disease in asthmatic women. They found clear evidence that total methylxanthines was a contributing factor in fibrocystic breast disease severity. (Hindi-Alexander 1985).
- f. In 1985, Italian researchers published a case-control study of 288 women with histologically confirmed benign breast lumps. The relative risk of fibrocystic disease for women who drank 1-2 or ≥ 3 cups of coffee/day were 4.1 and 6.4 based on hospital controls, and 2.0 and 3.7 based on outpatient controls. (La Vecchia 1985).
- g. In 1989, Australian researchers published a study of 383 cases of Benign Proliferative Epithelial Disorders (BPED) of the breast. They found a positive association with theobromine intake when cases were compared with biopsy controls. Total methylxanthine

intake was associated with risk of BPED showing severe atypia, with a significant trend, using community controls. (Rohan 1989).

- h. In 2004, a study evaluating dietary factors found that high caffeine consumption increased risk of Benign Breast Disease (RR 2.46, 95% CI 1.11-5.49) for the highest quartile). (Webb 2004).
- i. There are, however, also some negative and null studies.

9. **Gastrointestinal Disorders**

- a. “Gastrointestinal disorders affect an estimated 60 to 70 million Americans annual. In 2004, there were an estimated 4.6 million hospitalizations, 72 million ambulatory care visits, and 236,000 deaths attributable to gastrointestinal disease. Spending on gastrointestinal diseases in the United States has been estimated at \$142 billion per year in direct and indirect costs.” (Peery 2012).
- b. “Coffee has been shown to have profound effects on the gastrointestinal system.” (Brown 1990). Coffee reduces lower esophageal sphincter pressure (Dennish 1972) and stimulates secretion from the stomach (Debas 1971) and the small intestine. (Wald 1976). Coffee increases interdigestive exocrine pancreatic trypsin secretion. (Coffey 1986).
- c. In a recent study of 3,426 subjects from three rural villages in India, consumption of coffee and tea significantly increased the risk of functional gastrointestinal disorders. (Ghoshal 2016).
- d. In a study of hospitalized Medicare beneficiaries, among those who died within 30 days of hospitalization, risk of death from gastrointestinal disorders other than gastroenteritis was increased for those hospitalized with dehydration (RR 1.79, 95% CI 1.68 – 1.91). Among those who died within one month to one year of hospitalization, risk of death from such gastrointestinal disorders was likewise increased among those hospitalized with dehydration (RR 1.78, 95% CI 1.70 - 1.86). (Warren 1994).
- e. **Constipation.**
 - (1) “Constipation is a significant problem in the United States with over 330 million dollars spent each year on over-the-counter laxatives.” (Sandler 1990). In a prospective study of 1,064,004 men and women, 18.5% of men and 33.7% of women reported “constipation.” (Hammond 1964).
 - (2) In a study using data regarding 15,014 participants in the first Health and Nutrition Examination Survey, constipated

individuals reported higher consumption of coffee and tea and lower consumption of other beverages. In the logistic regression model, the increased risk of constipation from coffee and tea was highly significant, as were decreased risks from other beverages ($p < 0.001$). (Sandler 1990).

- (3) In the Nurses' Health Study, a total of 62,036 women responses to questionnaires which assessed bowel movement frequency, dietary, and lifestyle choices. Constipation was defined as two or fewer bowel movements weekly. A total of 3,327 were classified as constipated. On multivariate analysis, the prevalence ratio of constipation was significantly increased among women who drank the most coffee (≥ 6 cups per day) (PR 1.17, 95% CI 1.02 - 1.34, p-trend < 0.0001). (Dukas 2003).
- (4) Studies have reported decreased risks of constipation in children with high total daily fluid intake (Bae 2010, Chan 2010) and increased risks of constipation for children with low total daily fluid intake or constipation (Leung 1996).
- (5) In a study of 8 healthy male volunteers in their twenties, low fluid intake increased the risk of constipation and was considered to be an etiologic factor. (Klauser 1990).
- (6) Studies of constipated adults have shown that increased fluid intake reduces constipation. (Lazebnik 2011, Mazlyn 2013, Ayaz 2014).
- (7) In studies of constipated adults and nursing home residents, interventions and educational programs that included adequate fluid intake were found to improve constipation. (Schnelle 2010, Ayaz 2014, Nour-Eldein 2014).
- (8) Increasing fluid intake in constipated patients has also been shown to significantly enhance the beneficial effect on constipation of adequate daily fiber intake. (Anti 1998).
- (9) Increasing fluid intake is recommended for constipated children, adults and the elderly. (Waggner 1966, Tasman-Jones 1973, Hyams 1974, Bank 1977, Klein 1982, Read 1986, Fitzgerald 1987, Tremaine 1990, Clayden 1992, Squires 1993, Dardaine 1994, Johanson 2007, Bove 2012).
- (10) Based on these studies, it appears that consumption of coffee likely increases the risk of constipation, whereas adequate water intake likely reduces constipation risk.

f. Gallstones

- (1) “Gallstones affect 10%-15% of adults in the Western world and, although often asymptomatic, can cause serious health complications.” (El-Sharkawy 2015).
- (2) A meta-analysis of epidemiologic studies regarding coffee consumption and gallstone disease, based on 1 case-control study and five prospective cohort studies (with 7 cohorts) was published by Chinese researchers in 2015. A significant nonlinear dose-response association was identified (p for nonlinearity = 0.106). Compared with the lowest level of consumption, risk of gallstone disease was decreased for consumption of 2 cups per day (RR 0.89, 95% CI 0.79 - 0.99), 4 cups per day (RR 0.81, 95% CI 0.72 - 0.92) and 6 cups per day (RR 0.75, 95% CI 0.64 - 0.88). (Zhang 2015)
- (3) A study in seven healthy volunteers 24 to 32 years of age demonstrated that consumption of water induces gallbladder contraction and emptying. (Svenberg 1985).
- (4) “Impaired gall-bladder emptying could contribute to gallstone formation by providing time for crystallization of cholesterol from supersaturated gall-bladder bile and their subsequent aggregation into macroscopic stones.” (van Erpecum 2005, van Erpecum 1999).
- (5) “Water is a major component of bile, and modulation of the water content can have major effects on cholesterol crystallization. Significant net water absorption occurs during bile transfer through the bile ducts and during prolonged storage in the gall-bladder. As a result, bile water content decreases from 97 weight percentage in the bile ducts to 90 weight percentage in the gall-bladder. This 3- to 4-fold concentration of bile enhances cholesterol crystallization and gallstone formation considerably.” (van Erpecum 2005, van Erpecum 1999).
- (6) In 1982 the journal Gastroenterology published a letter stating: “By drinking sufficient quantity of water at regular intervals throughout the day and some quantity late at night dilution of bile and decreased stay time of bile in the gallbladder can be achieved. Dilute solutions nucleate probably less easily than more concentration ones. Drinking water may be advised as a physiologic prophylactic measure to prevent gallstone formation” (Math 1982).

- (7) In 1988 Japanese investigators published a study regarding the mechanisms controlling human gallbladder contraction in eight healthy volunteers. They found that 400 mL of water resulted in a gallbladder ejection fraction of $33.5 \pm 4.2\%$ 20 minutes after ingestion. (Yamamura 1988).
- (8) In 2010 Chinese investigators published a case-control study of gallstone disease among women in Taicang. Through univariate and multivariate analysis, drinking water from a deep well was inversely associated with gallstone disease (OR 0.54). (Zhuang 2000).
- (9) In 2012 Italian investigators published a study that investigated the effect of consumption of sulphate-bicarbonate-calcium thermal water on gallstone disease. Forty postmenopausal women with functional dyspepsia and/or constipation underwent a 12 day cycle of water consumption - 20 drank thermal water; 20 drank tap water. They found that sulphate-bicarbonate-calcium thermal water consumption in the postmenopausal women had a positive effect on lithogenic risk. (Corradini 2012).

g. Gastroesophageal Reflux Disease.

- (1) A meta-analysis of epidemiologic studies regarding coffee consumption and gastroesophageal reflux disease reported an increased risk of gastroesophageal reflux disease for studies where esophagitis was diagnosed by endoscopy (OR 1.17, 95% CI 1.08 - 1.26), but not in studies that only used symptoms to define GERD (OR 0.99, 95% CI 0.84 - 1.16). (Kim 2013)
- (2) In a multi-center cross-sectional study, coffee consumption was found to increase the risk of atrophic chronic gastritis more than two-fold. (Eurohepygast Study Group 2002).
- (3) Risks greater than four-fold have been reported for gastroesophageal reflux symptoms from consumption of coffee. (Castelo Vega 2003).
- (4) One researcher reported: "Coffee ... commences the risk of gastroesophageal reflux, which may lead to gastric ulcers and increase the risk of gastric cancer." (Fiebich 2006).
- (5) In a study of 8 healthy volunteers, Japanese researchers investigated the effects of postprandial water intake on the gastrointestinal tract. At 4 minutes after water intake, there

was a significant decrease in gastric antral motility and significant, transitory increases in plasma cholecystokinin level and gastroesophageal reflux. (Kusano 2005).

- (6) Greek researchers observed that many patients with heartburn report immediate relief after drug administration and that the majority of patients take acid-suppressive drugs with tap water, which usually has an alkaline pH. They hypothesized that the water could be the putative factor of the early post-administration effect, whereas the active drug results in the later and prolonged action. To test this hypothesis, they conducted a cross-over study in 12 subjects without *H. pylori* infection in which gastric pH was recorded for 6 hours after consuming acid-inhibiting drugs or water. They found that water increased gastric pH above 4 in 10/12 subjects after just 1 minute, comparable to the effect observed after antacids intake. They concluded that in healthy subjects a glass of water increases gastric pH immediately and recommended that heartburn patients swallow an antacid pill with at least a glass of water to immediately relieve GERD symptoms. (Karamanolis 2008)
- (7) In a study of 50 healthy volunteers and 29 patients with gastroesophageal reflux disease, Brazilian researchers evaluated the ingestion dynamics of 100 mL of acidic liquid (concentrated lemon juice, pH 3.0) and 100 mL of water (pH 6.8). In both the volunteers and the patients, the acidic liquid took longer to be ingested, a higher number of swallows, a slower flux of ingestion, and a smaller volume in each swallow than water. (Gomes 2014).
- (8) While consumption of contaminated water increases the risk of gastrointestinal infections (Kaushal 2012) and the risk of gastroesophageal reflux disease (Nourai 2007), therapeutic effects on gastroesophageal reflux disease may be achieved by consumption of uncontaminated water (Mederos 2010), alkaline water (Koufman 2012), and mineral water (Gasbarrini 2006, Gasbarrini 2010).
- (9) Apparently only one study has compared the effects of coffee and water on gastroesophageal reflux. In 1994, German researchers published a study in which they evaluated gastroesophageal reflux induced by coffee and tea before and after a decaffeination process, and compared it with water and water-containing caffeine. Three-hour ambulatory pH-metry was performed in 16 healthy volunteers, who received 300 ml of coffee, decaffeinated coffee, tea, decaffeinated tea, and tap water. Regular

coffee, but not decaffeinated coffee, induced significant gastroesophageal reflux compared to tap water and tea. Median pH during the three postprandial hours in the 16 subjects after intake of a standard breakfast with fluid intake was highest for regular coffee (pH 3.7, range 0-14.4), lower for decaffeinated coffee (pH 2.7, range 0-10.7), and lowest for water (pH 1.6, range 0 - 9.8). The researchers concluded that consumption of coffee increases gastroesophageal reflux, whereas consumption of water reduces gastroesophageal reflux. (Wendl 1994).

10. Metabolic Disorders

a. Type 1 Diabetes

- (1) “Type 1 diabetes mellitus is a chronic disease resulting from autoimmune destruction of pancreatic beta cells responsible for insulin secretion and glucose homeostasis. The incidence of [Type 1 diabetes] is double-peaked, with the first peak being around the age of 57 years, and the second peak occurring near puberty. . . . [Type 1 diabetes] incidence has increased substantially during the last two decades, a phenomenon that could not be entirely explained by genetic factors alone.” (Sharif 2017).
- (2) In a Finnish case-control study of 600 children under age 15 with Type 1 diabetes, children who drank more than 2 cups of coffee per day had almost double the risk of the disease (OR 1.94, 95% CI 1.08 - 3.47). (Virtanen 1994).
- (3) In a Swedish case-control study a slight nonsignificant risk of latent autoimmune diabetes in adults was found for coffee intake (OR 1.04, 95% CI 0.96 - 1.13), but stratifying according to the levels of autoantibody (glutamic acid decarboxylase), a significant association was found (OR 1.11, 95% CI 1.00 - 2.34) for consumption of 1 cup of coffee per day. Additionally, levels of glutamic acid decarboxylase showed a significant proportional increase with additional coffee consumption (> 6 cups per day), a result that was found to be significant after adjustment for multiple other factors. (Lofvenberg 2014).
- (4) In a prospective randomized placebo-controlled double-blind study of 34 patients with type 1 diabetes, hypoglycemic episodes during the day were found to increase with higher consumption of caffeine ($p < 0.003$) and patients with higher coffee consumption had more severe warning symptoms ($p < 0.05$). Thus, disease development

- seems to increase with coffee consumption. (Watson 2000).
- (5) Thus, coffee intake has been shown to increase the risk of Type 1 diabetes mellitus. (Sharif 2017).

b. Type 2 Diabetes

- (1) “More than 29 million Americans are living with diabetes, and 86 million are living with prediabetes, a serious health condition that increases a person’s risk of type 2 diabetes and other chronic diseases. Type 2 diabetes accounts for about 90% to 95% of all diagnosed cases of diabetes, and type 1 diabetes accounts for about 5%. The health and economic costs for both are enormous: Diabetes was the seventh leading cause of death in the United States in 2013 (and may be underreported). Diabetes is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness. More than 20% of health care spending is for people with diagnosed diabetes.” (CDC 2014)
- (2) A meta-analysis of prospective cohort studies regarding coffee consumption and Type 2 Diabetes reported an overall 29% reduction in risk of Type 2 Diabetes in association with coffee consumption. (Jiang 2013).
- (3) In a study of hospitalized Medicare beneficiaries, among those who died within 30 days of hospitalization, risk of death from diabetes was increased for those hospitalized with dehydration (RR 1.73, 95% CI 1.50 – 1.99). Among those who died within one month to one year of hospitalization, risk of death from diabetes was also increased among those hospitalized with dehydration (RR 1.32, 95% CI 1.20 – 1.45). (Warren 1994).
- (4) In 2011 French researchers published a study in which 3,615 middle-aged men and women with normal baseline fasting glycemia were followed for 9 years. The incidence of hyperglycemia was calculated according to daily water intake classess based on a self-administered questionnaire. There were 565 incident cases of hyperglyemia. After adjustment for confounding factors, self-reported water intake was inversely and independently associated with the risk of developing hyperglycemia. Risk of hyperglycemia among those consuming 0.5 to < 1 liter per day was reduced by 32% (OR 0.68, 95% CI 0.52 - 0.89); among those consuming more than 1 liter per day, the risk was also reduced (OR 0.79, 95% CI 0.59 - 1.05). A dose-response relationship was found ($p=0.016$). (Roussel 2011).

- (5) A recent study reported that plain water intake was significantly negatively correlated with Type 2 Diabetes risk score ($\tau = -0.180$, $P = 0.005$). For every 240-mL cup of water consumed per day, Type 2 Diabetes risk score was reduced by 0.72 points (range, 0-47) ($\tau = -0.03$, 95% CI -0.06 to -0.01). (Carroll 2015).
- (6) Another recent study showed that the risk of Type 2 Diabetes was reduced by substituting one serving per day of water for sweetened-milk beverages (HR 0.80, 95% CI 0.67 - 0.94), artificially sweetened beverages (HR 0.96, 95% CI 0.81 - 1.11), soft drinks (HR 0.86, 95% CI 0.74 - 0.99), fruit juice (HR 0.98, 95% CI 0.82 - 1.13), and sweetened tea or coffee (HR 0.99, 95% CI 0.91 - 1.08). The researchers concluded that water or unsweetened tea/ coffee appear to be suitable alternatives to sugar-sweetened beverages for diabetes prevention. (O'Connor 2015).
- (7) In a study published this very year, researchers from Purdue University assessed the effects of consuming common breakfast beverages (water, sugar-sweetened coffee, reduced-energy orange juice, and low-fat milk) on postprandial plasma glucose and insulin responses in adults who were overweight or obese. Forty-six subjects (33F/13M, body mass index: 32.5 ± 0.7 kg/m², age: 50 ± 1 years, mean \pm SEMs) consumed a standard sandwich with one of the six beverages on separate mornings in randomized order. The test beverages (except water) each contained 12 g digestible carbohydrate. Plasma glucose and insulin concentrations were measured from blood obtained pre- and post-meal at 30-min intervals for 4 h and incremental areas under the curve (AUC) were computed. The researchers found that among different beverage types, glucose AUC was higher for coffee versus water, orange juice, and low-fat milk, and that insulin AUC was higher for coffee and low-fat milk versus orange juice and water. They concluded that consumption of water, reduced-energy orange juice, or milk with a meal may be preferable to consuming sugar-sweetened coffee for glucose control in middle-aged overweight and obese adults. (Li 2017).
- (8) These studies suggest that reduction in risk of Type 2 Diabetes by coffee consumption is either comparable or inferior to that of water consumption. The apparent protective effect of coffee consumption on Type 2 Diabetes risk may therefore be due to increased water intake among coffee drinkers, rather than any effect of coffee itself.

11. Neurodegenerative Diseases

a. Alzheimer's Disease/Dementia

- (1) “Alzheimer’s disease accounts for more than 70% of all cases of dementia, so it is important to identify modifiable risk factors for the disease.” (Gharibzadeh 2007).
- (2) While some meta-analyses of epidemiologic studies regarding coffee consumption and Alzheimer’s disease/dementia reflect an approximate 20% reduction in the risk of such cognitive disorders in association with coffee consumption, (Barranco Quintana 2007, Kim 2015, Wu 2016, Liu 2016) a recent meta-analysis of nine prospective cohort studies concluded that a “J-shaped” association was presented between coffee intake and incident cognitive disorders. While the risk of Alzheimer’s disease was decreased comparing consumption of 1-2 cups of coffee per day with less than 1 cup per day (RR 0.71, 95% CI 0.54 - 0.94), the risk of Alzheimer’s disease was increased comparing more than 3 cups of coffee per day with less than 1 cup of coffee per day (RR 1.07, 95% CI 0.63 - 1.82). (Wu 2017).
- (3) Investigators from Hong Kong reported that fluid intake greater than five cups per day was associated with a reduced risk of dementia (OR 0.40, 95% CI 0.20 – 0.79, $p = 0.008$). (Lee 2010).
- (4) Since fluid intake has been reported to reduce the risk of dementia to an extent greater than that reported for coffee, it is unclear whether reduced risks of Alzheimer’s disease/dementia associated with low (but not medium or high) coffee consumption are attributable to coffee or to water.

b. Parkinson's Disease

- (1) Parkinson’s Disease is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta and its projections.
- (2) The epidemiology of Parkinson’s Disease is unusual, as alcohol consumption and smoking reduce disease risk.
- (3) Meta-analyses of coffee consumption and Parkinson’s disease have been published, each showing reductions in risk of about 25%. (Hernán 2002, Costa 2010, Qi 2013).

- (4) A 2004 Japanese investigators published a study in which they assessed constipation and nutritional status in 94 Parkinson's Disease patients and controls. Nutritional status was assessed using a diet history questionnaire and total water intake was calculated from the consumption of coffee, green tea, and tea. Assessment was also made of water drinking in early life. The nutritional status of the patients did not differ significantly from those of controls though several studies have shown excess intake of animal fats or reduced consumption of coffee are risks in Parkinson's Disease. In contrast, water intake was significantly lower in Parkinson's Disease patients than controls (604.0 ± 377.2 ml/g vs 909.5 ± 531.6 ml/d; $p < 0.0001$). Amount of water intake correlated inversely with severity of constipation and the depletion of water intake preceded constipation in most cases. The investigators concluded that their results support previous findings that constipation precedes the onset of motor dysfunction in Parkinson's Disease. The investigators commented that it was uncertain "whether coffee or caffeine themselves are the protective factor for Parkinson's Disease or alternatively the amount of water in coffee drinking is more essential." (Ueki 2004).
- (5) Two case-control studies of uncontaminated water have reported reductions in the risk of Parkinson's Disease. In 1993, researchers from Tianjin, China published a case-control study of environmental risk factors of Parkinson's Disease, reporting a 41% reduction in the risk of Parkinson's Disease in association with consumption of well water – OR 0.59, 95% CI 0.36 - 0.95; $p < 0.05$. (Wang 1993). A few years later, researchers from Boston University reported a highly significant 7% reduction in risk of Parkinson's Disease in association with years of well water consumption in the fully-adjusted logistic regression analysis – OR 0.93, 95% CI 0.88 - 0.98, $p = 0.003$. (Taylor 1999). It should be noted that other studies have reported increased risks of Parkinson's Disease in association with consumption of well water, but most of these increases were attributable to contaminated water.
- (6) The reductions in risk of Parkinson's Disease reported in meta-analyses regarding coffee consumption are comparable to reductions in risk of Parkinson's Disease reported in case-control studies regarding consumption of well water and increased risk of Parkinson's Disease in association with decreased water intake and constipation, indicating that increased coffee consumption and water

consumption reduce the risk of Parkinson's Disease, whereas decreased water intake increases disease risk.

12. Urological Conditions

a. Urological conditions include chronic kidney disease, urolithiasis, urinary tract infections, urinary incontinence, and lower urinary tract symptoms.

b. Chronic Kidney Disease

- (1) Chronic kidney disease, which has historically also been called chronic kidney failure, is a progressive condition that leads to fibrosis and scarring of the kidney.
- (2) “In several experimental disease models, chronic caffeine administration has been found to exacerbate the development of hypertension and renal disease, perhaps through the effect of caffeine on renin secretion.” (Osswald 2011). Caffeine-induced renal disease is characterized by increased proliferation, inflammation, and fibrosis. (Tofovic 2002, Tofovic 2007, Osswald 2011).
- (3) Nevertheless, a few epidemiologic studies have reported decreased risks of chronic kidney disease with increased consumption of coffee. (Kim 2013, Hsu 2014).
- (4) A recent meta-analysis of four observational studies with 14,898 individuals assessed the association between coffee consumption and chronic kidney disease. The pooled relative risk of chronic kidney disease in individuals consuming 1 or more cups of coffee per day was 0.71 (95% CI 0.47 - 1.08). In the subgroup analyses, the risk of chronic kidney disease from coffee consumption was nonsignificantly increased in men (RR 1.10, 95% CI 0.94 - 1.29) and nonsignificantly decreased in women (RR 0.81, 95% CI 0.58 - 1.13). (Wijarnpreecha 2016)
- (5) Several observational studies have examined the role of water intake in the progression of chronic kidney disease. (Clark 2011, Strippoli 2011, Sontrop 2013, Clark 2013).
- (6) In 2011 researchers from Ontario published a prospective cohort study in which they followed a Canadian cohort of 2,148 apparently normal participants for 6 years. They found that the rate of estimated glomerular filtration rate (eGFR) decline was inversely related to increased 24-hour urine volume. For each liter increase in 24-hour urine

volume from <1 liter to > 3 liters (stratified by quartile), the annual percentage decline in eGFR decreased by 1.3, 1.0, 0.8, and 0.5%, respectively. The risk of developing mild to moderate renal decline, defined as eGFR decline from baseline between 1% and 4.9%, was significant (OR 0.66, 95% CI 0.46 - 0.94). The risk of developing rapid renal decline, defined as eGFR loss > 5%, was less than 50% for individuals with urine volume > 3 liters/day compared with the reference group (urine volume 1-1.9 liters/day (OR 0.46, 95% CI 0.23 - 0.92). (Clark 2011)

- (7) In 2011, researchers from Italy and Australia published two cross-sectional population based studies in Australia. The proportion of participants who completed food frequency questionnaires and had GFR measures was 75% for the first study and 70.6% for the second study. Chronic kidney disease was present in 12.4-23.5% of men and 14.9-28.7% of women. Participants who had the highest quintile of fluid intake (3.21 liters/day) had a significantly lower risk of chronic kidney disease (OR 0.5, 95% CI 0.32 - 0.77, *p*-for trend = 0.003). There was a significant inverse linear association between self-reported daily fluid intake volume and chronic kidney disease prevalence. The investigators concluded that higher fluid intake appears to protect against chronic kidney disease and the disease may be prevented with low-cost increased fluid intake. (Strippoli 2011).
- (8) In 2013, Canadian researchers published a cross-sectional analysis of the U.S. National Health and Nutrition Examination Survey, in which they assessed water intake and chronic kidney disease. They categorized total water intake from foods and beverages as low (< 2.0 liters/day), moderate (2.0 - 4.3 liters/day) and high (> 4.3 liters/day) and found higher chronic kidney disease prevalence among those with the lowest water intake versus highest water intake (OR 2.52, 95% CI 0.91 - 6.96). When stratified by intake of plain water and other beverages, chronic kidney disease was associated with low intake of plain water (OR 2.36, 95% CI 1.10 - 5.06), but not other beverages (OR 0.87, 95% CI 0.30 - 2.50). These results provided evidence of a protective effect of higher total water intake, particularly plain water, on the kidney. (Sontrop 2013)
- (9) In 2013 the same research group conducted a six-week pilot study to examine the safety and feasibility of asking adults with chronic kidney disease to increase their water intake. They randomly assigned 29 patients to either a hydration or a control group. The hydration group was

asked to increase water intake by 1 to 1.5 liters per day relative to their weight, gender, and 24 hour urine osmolality, in addition to usual consumed beverages. The control group was asked to continue with usual fluid intake. After six weeks, the change in urine volume was significantly different between groups (0.9 liters/day, $p = 0.002$ with no change in serum sodium and no serious adverse effects. This study provided clear evidence of efficacy, safety and the absence of a negative impact on the quality of life of the hydration intervention relative to the control chronic kidney disease population. (Clark 2013)

- (10) In 2016 two critical reviews were published regarding increased water intake and risk of chronic kidney disease. One review by Canadian researchers concluded that “increasing water intake appears to have a beneficial effect on renal function in patients with all forms of chronic kidney disease and in those at risk of CKD.” (Clark 2016). The other review, by researchers from Kansas, concluded that “recent observational studies suggest a strong, direct association between preservation of renal function and fluid intake” and that “water has promising therapeutic roles in nephrology.” (Wu 2016).
- (11) These studies indicate that if increased coffee consumption reduces the risk of chronic kidney disease, the reduction in disease risk is likely attributable to increased water intake from coffee consumption rather than any effect of coffee.

c. Urolithiasis

- (1) Urolithiasis is the formation of calculi or stones in the urinary tract, usually in the kidneys or ureters, but also in the bladder and the urethra. Urolithiasis occurs in up to 10% of the population with a lifetime recurrence rate of up to 80%. (de la Guéronnière 2011).
- (2) In 2014, Chinese researchers published a meta-analysis of coffee intake and the risk of urolithiasis. A total of 6 studies (2 cohort studies and 4 case-control studies) on coffee intake were included in the meta-analysis. The pooled odds ratio showed a significant reduction of the risk of urolithiasis for the highest consumption of coffee (OR 0.70, 95% CI 0.60 - 0.82). (Wang 2014).
- (3) Epidemiologic studies have reported an adverse effect of dehydration on the risk of urolithiasis (Embon 1990, Pin 1992, Olapade-Olaopa 2004), and a beneficial effect of

increased water consumption on the risk of urolithiasis. (Borghini 1996, de la Guéronnière 2011, Sorensen 2012).

- (4) Epidemiologic studies have observed an association between dehydration and urolithiasis, with a higher incidence being reported in hot climates and during summer months. (Baker 1993, Al-Hadramy 1997).
- (5) In 2011 Brazilian researchers published a retrospective cohort study of steelworkers in which they compared the incidence of urolithiasis in hot-area workers with those working at room temperature. They demonstrated an increased prevalence of urolithiasis in those working in hot areas, with those working at high temperatures having a 9-fold increased risk of urolithiasis. (Atan 2005).
- (6) A study published in 1992 by researchers from Singapore compared the prevalence of urinary stone disease quarry drilling and crusher workers, quarry truck and loader drivers, postal clerks and hospital maintenance workers. The prevalence of urinary stone disease was found to be five times higher in the outdoor workers compared to the indoor workers ($p < 0.05$). The investigators concluded that chronic dehydration is likely to be the most important risk factor for increased risk of urolithiasis. (Pin 1992).
- (7) A large population-based study published by Harvard researchers in 2004 demonstrated a significant decreased risk of kidney stones with increasing fluid intake, the highest quintile of fluid intake (> 2517 ml/day) having an almost 30% decreased risk of incident kidney stones (RR 0.71, 95% CI 0.59 - 0.85, p -trend < 0.001). (Taylor 2004).
- (8) The strongest evidence that increased water intake reduces the risk of urolithiasis is a randomized intervention study by Italian researchers published in 1996. They randomized patients following development of their first kidney stone to receive a higher intake of water targeting a urine output of more than 2 liters per day (intervention group), or to receive no intervention (control group). They reported a significant reduction in the recurrence rates of urolithiasis (12.1% in the intervention group versus 27.0% in the control group) and increased time to recurrence (38.7 ± 13.2 months in the intervention group versus 25.1 ± 16.4 months in the control group). (Borghini 1996).
- (9) Given the strength of the evidence, international practice guidelines recommend increased water intake to produce 2-

3 liters of urine per day as a preventive measure for recurrence of urolithiasis. (EAU 2015, NIHCE 2014).

- (10) In light of the strong evidence that increased water intake substantially reduces the risk of urolithiasis, the 30% reduction in risk from increased coffee consumption reported in the Wang meta-analysis is likely due to increased water intake among coffee drinkers rather than any constituent of coffee. This is especially true, because about 70-80% of kidney stones are calcium oxalate stones and about 80-85% of oxalate in the human diet derives from consumption of coffee and tea. (Gasińska 2007).

d. Lower Urinary Tract Symptoms.

- (1) The term “lower urinary tract symptoms” or LUTS, has been used as a general term to refer to any combination of urinary symptoms or as a more specific term to refer to those symptoms primarily associated with overactive bladder (frequency, urgency, and nocturia).
- (2) Consumption of caffeinated beverages has been reported to significantly increase risk of lower urinary tract symptoms.
- (3) In 2002 British researchers published a randomized controlled trial in which the experimental group received caffeine reduction education and the control group continued existing caffeine intake. The results were indicative of a trend for urgency, with a 37% reduction in symptoms among low users (101-200 mg caffeine), 15% reduction among medium users (201-300 mg), and a 4% increase in symptoms among the high users (> 301 mg). The investigators concluded that the decrease in caffeine intake in the experimental group established that an intervention that encourages caffeine reduction was successful in its aim. Outcome comparisons between the two groups showed a substantial beneficial effect among those who received the intervention. Significant improvements in occasions of urgency per day and number of voids per day were found and a beneficial non-significant trend was evidence in occasions of leakage a day. On the basis of this evidence, the investigators concluded that they could advise their patients that caffeine reduction to < 100 mg a day is likely to reduce their symptoms of urgency and frequency. (Bryant 2002).
- (4) In 2010, Chinese researchers investigated risk factors for lower urinary tract symptoms in Chinese men without

urinary tract infection or benign prostatic hyperplasia who satisfied criteria for painful bladder syndrome based on the O'Leary-Sant interstitial cystitis symptom and problem indices. The risk of lower urinary tract symptoms in men who met these criteria was increased more than four-fold for consumption of caffeinated beverages (OR 4.29, 95% CI 1.86 - 9.86). In the multivariate analysis, the risk among men decreased to slightly less than four-fold (OR 3.54, 95% CI 1.54 - 8.12, $p = 0.003$). Caffeinated beverage intake was the only modifiable association noted in the multivariate analysis in men. (Li 2010).

- (5) In 2013, researchers from the New England Research Institute reported that consumption of more than two eight-ounce servings of caffeinated coffee per day doubled the risk of lower urinary tract symptoms in men (OR 2.09, 95% CI 1.29 - 3.40, $p < 0.01$). (Maserejian 2013).
- (6) In 2014, British researchers published a double-blind randomized cross-over study of 14 community-dwelling women newly diagnosed with overactive bladder and a history of caffeine consumption. They were assigned to two groups - one which consumed caffeinated beverages for 14 days followed by decaffeinated beverages for 14 days, the other which consumed decaffeinated beverages for 14 days followed by caffeinated beverages. In the 11 women who completed the study, a significant reduction in urgency ($p < 0.01$) and frequency ($p < 0.05$) of urinary voids on day 3 of the diary, and total ICIQ-OAB score ($p < 0.01$) was found for the period of decaffeinated compared to caffeinated drink intake. (Wells 2014).
- (7) In 2016 researchers from Michigan published a study that sought to determine whether lower urinary tract symptoms improves after elimination of potentially irritating beverages – coffee, tea, alcohol, and carbonated and/or artificially sweetened beverages. Thirty community-dwelling women were in three phases: (1) baseline, (2) eliminate the potentially irritating beverages, and (3) reintroduce the irritating beverages at 50% of baseline volume. Despite incomplete adherence to study protocols, the women reported reduction in symptoms of urge, inability to delay voiding, and bother during both phases ($p \leq 0.01$). The number of voids per day decreased on average by 1.3 and 0.9 voids during Phases 2 and 3 respectively ($p = 0.002$ and $p = 0.035$). The investigators concluded the findings of their study support instructing women to reduced intake of potentially irritating beverages

to improve lower urinary tract symptoms. (Miller 2016).

- (8) In 2006, researchers from the Netherlands published a randomized placebo-controlled trial of 141 men to determine the effect of increased water intake on lower urinary tract function. The experimental group drank 1.5 liters of extra water daily; the control group consumed one tablespoon of placebo syrup daily. After 6 months, the subjects were evaluated for bladder contractility, voided volumes, and the severity of lower urinary tract symptoms. Water consumption in the intervention group increased by 359 mL per 24 hours compared with the control group. At 6 months, a significant effect was found for bladder pressure, bladder wall stress, and average voided volumes per urination. The investigators concluded that drinking more water improves some aspects of male bladder function, though the effects were small. (Spigt 2006).

e. Urinary Incontinence

- (1) A recent meta-analysis found no association between coffee consumption and urinary incontinence. (Sun 2016).
- (2) In 2013 researchers from the Department of Veterans Affairs published two cross-sectional studies evaluating the caffeine intake and the risk of urinary incontinence - one in men (Davis 2013), the other in women. (Gleason 2013). Both of the studies used data collected from the National Health and Nutrition Examination Surveys (NHANES).
- (3) In the study of U.S. men, urinary incontinence was defined using a standard questionnaire with Incontinence Severity Index scores 3 or greater categorized as moderate to severe. Structured dietary recall was used to determine caffeine consumption (mg per day), water intake (gm per day) and total dietary moisture (gm per day). Of the 5297 men, 3960 (75%) were 20 years old or older with complete data. Mean caffeine intake was 169 mg per day. Using stepwise multivariable logistic regression models, caffeine intake at the upper 75th percentile (≥ 234 mg per day) significantly increased the risk of moderate to severe urinary incontinence (RR 1.72, 95% CI 1.18 - 2.49), and caffeine intake at the upper 90th percentile (≥ 392 mg per day) doubled the risk of moderate to severe urinary incontinence (RR 2.08, 95% CI 1.15 - 3.77). In addition, after adjusting for prostate conditions, the effect size for the association between caffeine intake and moderate to severe urinary incontinence remained. The investigators concluded that

caffeine consumption equivalent to approximately 2 cups of coffee per day is significantly associated with moderate to severe urinary incontinence in U.S. men. (Davis 2013).

- (4) In the study of U.S. women, risk of urinary incontinence from caffeine consumption was assessed for 4309 non-pregnant women age 20 or older who had complete urinary incontinence and dietary data. After adjusting for multiple factors, caffeine intake in the highest quartile (≥ 204 mg/day) was associated with any urinary incontinence. The prevalence odds ratio was significantly increased for any urinary incontinence (POR 1.47, 95% CI 1.07 - 2.01), but the increased risk did not quite achieve statistical significance for moderate/severe urinary incontinence (POR 1.42, 95% CI 0.98 - 2.07). (Gleason 2013).
- (5) In 2011 researchers from Massachusetts published a study investigating urinary incontinence in 65,176 women without incontinence in the Nurses' Health Study. Incident incontinence was identified from questionnaires, during 4 years of follow-up. Caffeine intake was measured using food frequency questionnaires administered prior to incontinence development. They report a significantly increased risk of incontinence at least weekly among women with the highest versus lowest (>450 vs. <150 mg/day) intake of caffeine (RR 1.19, 95% CI 1.06 - 1.34) and a significant trend of increasing risk with increasing intake (p -for trend = 0.01). This risk was higher for incident urgency incontinence comparing highest versus lowest intake (RR 1.34, 95% CI 1.00 - 1.80, p -for trend = 0.05). (Jura 2011).
- (6) In 2016 Chinese investigators published a meta-analysis of coffee and caffeine intake and risk of urinary incontinence based on 7 observational studies (1 case-control, 2 cohort, and 4 cross-sectional studies). The summary odds ratios for any versus non-consumption were 0.75 (95% CI 0.54 - 1.04) for coffee consumption and 1.29 (95% CI 0.94 - 1.76) for caffeine consumption. Compared with individuals who never drink coffee, the pooled odds ratio of urinary incontinence was 0.99 (95% CI 0.83 - 1.18) for regular coffee/caffeine drinkers. The risk of moderate to severe urinary incontinence was nonsignificantly increased (OR 1.18, 95% CI 0.88 - 1.58). The investigators concluded that their meta-analysis found no evidence for an association between coffee/caffeine consumption and the risk of urinary incontinence. (Sun 2016).

- (7) The meta-analysis by the Chinese researchers should not be interpreted to negate the significant positive findings of the NHANES studies, because the exposure assessment of the two NHANES studies is superior to exposure assessments of all the other studies included in the meta-analysis.
- (8) A few studies have observed an association between dehydration or low daily water intake and urinary incontinence. (Spangler 1984, Colling 1994, Van Laecke 2009, Flanagan 2014, Ge 2015).
- (9) In 2010 American researchers published a randomized controlled trial of an intervention to improve urinary incontinence. An intervention of toileting assistance, exercise, and choice of food/fluid snacks every 2 hours for 8 hours per day over three months was provided to 112 nursing home residents with fecal incontinence. Urinary incontinence significantly improved with the intervention, even when adjusting for other variables. (Schnelle 2010).
- (10) Clinical practice guidelines for urinary incontinence recommend decreasing consumption of caffeinated beverages that irritate the bladder, and maintaining adequate fluid intake during the day, but reducing fluid intake before bed to minimize nocturia. (Wyman 2009)
- (11) The studies regarding caffeine and fluid intake and urinary incontinence indicate that caffeine consumption increases urinary incontinence, as does dehydration, and that increased water consumption reduces urinary incontinence.

f. Urinary Tract Infections

- (1) Urinary tract infections are the most common bacterial infection. According to the 1997 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, UTI accounted for nearly 7 million office visits and 1 million emergency department visits, resulting in 100,000 hospitalizations.” (Foxman 2002)
- (2) There is no evidence that consumption of coffee reduces the risk of urinary tract infections; the few published studies either report increased risks of urinary tract infections from consumption of coffee or caffeinated beverages (Vincent 2013) or no significant effect. (Kontiokari 2003).

- (3) Experimental studies conducted in the 1960s and 1970s showed that increased water intake reduced urinary tract infections. (Andriole 1965, Andriole 1968, Andriole 1970, Furtado 1970, Danzig 1972, Levison 1972).
- (4) Most clinical studies have shown a reduction in urinary tract infections with increased water intake, (Roberts 1967, Ervin 1980, Pitt 1989, Eckford 1995, Nygaard 1997, Lin 2013), although some studies have showed no significant effect. (Adatto 1979, Remis 1987). Likewise, studies have reported significantly increased urinary tract infections from inadequate water intake/dehydration. (Warren 1994, Rudaitis 2009, Hossain 2015, Saleh 2016).
- (5) Results of experimental and clinical studies concerning urinary hydrodynamics are the basis for advice given by expert committees to patients with urinary tract infections to drink large volumes of water, to void frequently, and to completely empty the bladder. (Beetz 2003).

III. Mortality

A. Coffee Consumption

1. Some recent meta-analyses have reported decreased risks of total (all-cause) mortality in association with increased consumption of coffee. (Malerba 2013, Je 2014, Crippa 2014, Zhao 2015, Grosso 2016).
2. The studies do not consistently report decreased mortality risks; some studies report significantly increased risks of all-cause mortality with increased coffee consumption.
3. In a one-year follow-up study of 27,350 adult Seventh Day Adventists, increased risks of all-cause mortality were observed for consumption of 1-2 cups of coffee per day (RR 1.21, 95% CI 1.06 - 1.39) and ≥ 3 cups of coffee per day (RR 1.26, 95% CI 1.05 - 1.51), upon adjustment for age, history of cardiovascular disease, hypertension, diabetes, cancer, and smoking status. (Kahn 1984).
4. In a study of 60,000 Finnish men and women followed for over 23 years, a significant increase in all-cause mortality was found in men who drank 8 or more cups of coffee per day (HR 1.20, 95% CI 1.01 - 1.41), following adjustment for age, smoking status, alcohol intake, study year and 4 pre-existing chronic diseases. (Laaksonen 2008).
5. In the Aerobics Center Longitudinal Study, all-cause mortality was investigated in 43,727 participants with a median of 17 years of follow-up. In multivariate analyses, coffee consumption was positively associated

with all-cause mortality. Increased all-cause mortality for consumption of more than 28 cups of coffee per week was observed in men (RR 1.21, 95% CI 1.04 - 1.40) and women (RR 1.21, 95% CI 0.78 - 1.88) after adjusting for age, baseline examination year, decaffeinated coffee use, regular tea use, decaffeinated or herbal tea use, physical inactivity, BMI, smoking status, alcohol intake, diabetes, hypertension, hypercholesterolemia, family history of cardiovascular disease and fitness. Among participants less than 55 years of age who drank more than 28 cups of coffee per week, higher risks were found for both men (RR 1.56, 95% CI 1.30 - 1.87) and women (RR 2.13, 95% CI 1.26 - 3.59). (Liu 2013).

6. Dehydration.

- a. Several studies have reported increased risks of mortality in association with dehydration.
- b. In 1994, government researchers used data from 1991 Medicare files to analyze the contribution of dehydration to mortality. They found that Medicare beneficiaries hospitalized with dehydration had significantly increased risks of death compared to those without dehydration. Among those hospitalized with a principal diagnosis of dehydration, almost half died within a year of admission, with 17.4% dying within 30 days of admission and an additional 30.6% dying in the remaining months of the year. The researchers concluded that dehydration is a significant cause of mortality in the elderly. (Warren 1994).
- c. In 2009, American researchers published a study using a case-control design, in which they estimated the incidence, risk factors, and outcomes of dehydration in hospitalized adults. They observed significantly increased rates of mortality at 30 and 180 days postdischarge among dehydrated patients. (Wakefield 2009).
- d. In 2013, researchers from Texas estimated the risk of death associated with documented unintentional falls and acute care hospitalization among older adults in the US using data from the 2005 Nationwide Inpatient Sample. They observed an increased risk of mortality for dehydration (OR 1.14, 95% CI 1.05 - 1.25). (Moudouni 2013).
- e. In 2015 researchers from the United Kingdom published a prospective cohort study of adults admitted acutely to a large UK teaching hospital. Of the 200 patients recruited, 37% were dehydrated at admission, 62% of whom were still dehydrated 48 hours after admission. Overall, 7% of the participants died in the hospital 79% of whom were dehydrated at admission ($p = 0.001$). Cox regression analysis adjusted for age, gender, the Chilson

comorbidity index, national early warning score, the Canadian Study of Health and Aging clinical frailty scale, and the Unnutrition Risk Screening Tool showed that participants dehydrated at admission were 6 times more likely to die in the hospital than those euhydrated (HR 6.04, 95% CI 1.64 - 22.25, $p = 0.007$). (El-Sharkawy 2015).

- f. In 2015 Swedish researchers published a study in which they evaluated 30-day mortality in 256 elderly patients (mean age 82 years) using urine color, specific gravity and osmolality as a composite index of fluid retention, an early sign for dehydration. Concentrated urine consistent with dehydration was present in 16% of the patients. Patients with such fluid retention had a significantly higher 30-day mortality compared to those patients who were euhydrated ($p = 0.03$). (Johnson 2015).
- g. In 2015, researchers from the United Kingdom published a retrospective study in which they compared the risk of hypernatremia and mortality of patients admitted from nursing homes with those who lived at home. They found 5-fold increased risk of hypernatremia among patients admitted from nursing homes compared to those living at home. Compared with own-home residents, nursing home residents had about a two-fold increased risk of in-hospital mortality compared with own-home residents (OR 1.97, 95% CI 1.59 - 2.45). The researchers concluded that patients admitted to hospital from nursing homes are commonly dehydrated on admission and, as a result, appear to experience significantly greater risks of in-hospital mortality. (Wolff 2015).

7. Water Intake

- a. Few studies have evaluated consumption of water intake and the risk of all-cause mortality.
- b. In a study using data from 7,666 patients in the Third National Health and Nutrition Examination Survey (NHANES III), all-cause mortality was nonsignificantly increased on multivariate analysis in patients who reported drinking no “pure water” (i.e., water consumed from drinking water not including from food) compared to those who reported drinking 6 to 8 glasses of water per day (RR 1.93, 95% CI 0.80 - 4.63). (Aggarwal 2012).
- c. In a prospective cohort study of 1,558 nursing home residents (1,044 in the U.S. and 513 in Netherlands) with lower respiratory infection, insufficient water intake was related to increased 14-day mortality with antibiotics (HR 1.90, 95% CI 1.38 - 2.60) or without antibiotics (HR 7.12, 95% CI 4.83 - 10.5). After 14 days,

relative mortality worsened for antibiotic-treated residents with insufficient water intake. (Szafara 2012).

- d. In a population-based cohort study of 1055 Australian women aged ≥ 70 , all-cause mortality was slightly but nonsignificantly increased for consumption of coffee (HR 1.02, 95% CI 0.94 - 1.10), but slightly and nonsignificantly decreased for consumption of water (HR 0.99, 95% CI 0.95 - 1.04). (Lim 2017).

IV. Acute Cardiovascular Effects

A. Overview.

1. “In the past two decades, experimental studies have shown that caffeine induces various acute cardiovascular effects, including effects on blood pressure, circulating catecholamines, arterial stiffness, and endothelium dependent vasodilation.” (Rixsen 2009).
2. “The large number and diversity of relevant studies provide unassailable evidence of adverse acute effects of caffeine on cardiovascular function, especially blood pressure.” (James 2007).
3. Experimental studies in healthy subjects have shown that drinking 2 cups of coffee acutely raises systolic and diastolic blood pressure and lowers heart rate. (Nurminen 1999). Caffeine appears to be responsible for this pressor effect, because the same response is observed after administration of caffeine (Robertson 1978k, Smits 1987), but not of decaffeinated coffee. (Smits 1985, Smits 1985).
4. At levels from coffee consumption, caffeine antagonizes the adenosine A_1 and A_{2A} receptor. (Fredholm 1999). Caffeine prevents systemic and local hemodynamic effects of adenosine, which is compatible with effective adenosine receptor antagonism, especially for adenosine A_2 receptor-induced actions which are largely cAMP-dependent. (Smits 1987, Smits 1990). Since adenosine receptor stimulation induces vasodilation in vascular beds (Ronben 1997), caffeine may induce vasoconstriction. (Rixsen 2009). Acute administration of caffeine increases systemic vascular resistance in healthy people. (Pincomb 1985, Casiglia 1991, Farag 2005).
5. Administering coffee or caffeine increases the circulating concentration of epinephrine and norepinephrine. (Robertson 1978, Smits 1985). The increase in epinephrine may contribute to the acute pressor effect of coffee. (Smits 1986).
6. Coffee also adversely affects arterial stiffness (Echeverri 2017, Karatzis 2005, Vlachopoulos 2003, Mahmud 2001), and endothelium dependent vasodilation. (Papamichael 2005). Consumption of caffeinated coffee

acutely increased pulse wave velocity in healthy subjects. (Mahmud 2001). Coffee drinking also resulted in an increased augmentation index of the aortic pressure waveform, indicating increased wave reflection. (Karatzis 2005, Mahmud 2001).

7. Intake of 250 mg caffeine induces similar effects on arterial stiffness and augmentation index (Papamichael 2005), indicating that caffeine is responsible for the effects.
8. Lastly, consumption of one cup of coffee acutely impaired flow-mediated dilation in the brachial artery in healthy people without affecting nitroglycerin-induced vasodilation, indicating impaired endothelium dependent vasodilation. (Papamichael 2005).

B. Events Within One Hour of Consumption

1. Serious cardiovascular events have been reported to occur within 1 hour of drinking coffee in case-crossover studies, prompting some to refer to coffee as a “trigger” for acute cardiac death.
2. In one study, the risk of acute cardiac death was significantly increased about 75% in the hour after drinking coffee (RR 1.73, 95% CI 1.14 - 2.96). (Šemerl 2004).
3. In another study, the overall risk of myocardial infarction in the hour after drinking coffee was significantly increased by about half (RR 1.49, 95% CI 1.17 - 1.89), the risk being greatest among those drinking ≤ 1 cup of coffee per day (RR 4.14, 95% CI 2.03 - 8.42) and decreasing with increasing coffee consumption. (Baylin 2006)
4. In another study, the risk of stroke in the hour after consuming coffee was found to be double (RR 2.0, 95% CI 1.4 - 2.8; $p < 0.001$). (Mostofsky 2010).
5. In yet another study, the population-attributable risk for rupture of intracranial aneurysms was found to be 10.6%, which was the highest population-attributable risk for any factor. (Vlak 2011).
6. The association of coffee consumption in the hour preceding fatal or almost fatal cardiac emergencies has been attributed to the acute effects of caffeine on the cardiovascular system. (Logroscino 2010, Siscovick 2006).

EXHIBIT “B”

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Board Certified, Internal Medicine, Nephrology, Forensic Medicine

Fellow, Collegium Ramazzini

American College of Toxicology

American College of Occupational, Environmental Medicine

Internal Medicine

Toxicology & Chemical Exposure

Kidney Disease & Hypertension

Pharmacology

Pension Disability Evaluation

Impairment Evaluation

Revised 6/22/2016

Curriculum Vitae Nachman Brautbar, M.D.

Date and Place of Birth:

October 22, 1943

Haifa, Israel

Education and Academic Appointments:

Medical School:

Hebrew University - Hadassah Medical School, Jerusalem, Israel, 1961-1968, M.D., 1969.

Internship:

Rotating Internship: Ramban Hospital, Haifa University, Israel, 1968-1969 (12 months).

Residencies:

Resident in Internal Medicine, Rothschild Medical Center, Haifa, Israel, 1971-1973 (18 months).

Chief Resident: Department of Medicine "D", Hadassah University Hospital, Jerusalem, Israel, 1974-1975 (12 months).

Total Residency in Internal Medicine (30 months).

California Licensure Examination, 1975

U.S.A. Internship: Wadsworth V.A. Medical Center, Los Angeles, October 1975-June 1976.

Nephrology Fellowship: Wadsworth V.A. Medical Center, Los Angeles, March 1975 to June 1977.

Assistant Professor of Medicine, UCLA, 1977-1978.

Assistant Chief, Hemodialysis Unit, Wadsworth V.A. Hospital, April 1977-1978.

Assistant Professor of Medicine, U.S.C., July 1, 1978.

Assistant Professor of Pharmacology, U.S.C., July 1981.

Tenured Associate Professor of Medicine and Pharmacology, U.S.C., January 1982-1988.

Clinical Professor of Medicine and Pharmacology, U.S.C., April 1988 - 1993.

Clinical Professor of Medicine, U.S.C., 1994 - December 2007.

Clinical Professor Emeritus of Medicine, U.S.C., January 1, 2008.

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Private Practice of Medicine: 1980 - present; Internal Medicine, Nephrology, and Toxicology.

Past and Present Professional Activities:

A. Utilization Review Consultation

American Insurance Administrators, Los Angeles, California.
Hollywood Presbyterian Medical Center, Los Angeles, California, Utilization Review.

B. Societies:

European Dialysis and Transplantation Association, 1975
American Federation for Clinical Research, 1975
International Society for Nephrology, 1975
Israel Nephrology Society, 1975
American Society for Nephrology, 1976
American Society of Artificial Internal Organs, 1978
American College of Emergency Medicine, 1979
American Society of Bone and Mineral Metabolism, 1979
Western Society for Clinical Investigation, 1980
American Physiological Society, 1981
American Endocrine Society, 1981
Biophysical Society, 1982
Biochemical Society, 1982
American Chemical Society, 1982
American College of Nutrition, 1983
American Society of Neuroscience, 1984
American Society of Experimental Biology & Medicine, 1984
American Society for Renal Biochemistry, 1984
International Society for Alcohol Research, 1984
American Society of Parenteral and Enteral Nutrition, 1984
California Society of Industrial Medicine & Surgery, 1985
American Society of Industrial Medicine, 1985
Society of Toxicology - Southern California Chapter, 1986
American College of Occupational & Environmental Medicine, 1992
American Association for the Advancement of Science, 1993
American College of Toxicology, 1993
American Academy of Environmental Medicine, 1993
American Board of Forensic Examiners, 1994
American College of Legal Medicine, 1994
American College of Physicians, 1994
International Society for Environmental Epidemiology, 1994
American College of Physician's Executives, 1995
Council of Fellows of the Collegium Ramazzini, 1995
International Society for the Study of Xenobiotics, 1996
Society of Toxicology, 1996
Society of Toxicology, Neurotoxicology Specialty Section, 1996
Society of Toxicology, Immunotoxicology Specialty Section, 1996
Renal Physicians Association, 1996

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American Academy of Experts in Traumatic Stress, 1997
American Academy of Preventive Medicine
Environmental Assessment Association, 1997
American Academy of Disability Evaluating Physicians, 1998
British Toxicology Society, 1998
Environmental Assessment Association, 1998
Society of Toxicology, Risk Assessment Specialty Section, 1999
California Society of Industrial Medicine and Surgery, Board of Directors, 2001
California Society of Industrial Medicine and Surgery, Member, Education Committee, 2001

C. **Awards:**

M.D. Thesis, "Prize for Excellence," Hadassah Medical School, Jerusalem, Israel, 1970.
Fellow in Nephrology, V.A. Wadsworth Medical Center, J.W. Coburn, M.D., Los Angeles, California, October, 1975 to September 1977.

"Prize for Excellence", American Student Medical Association, Western Branch: Meritorious research paper, Carmel, California, 1977.

Traveling Scholarship, American Society of Nephrology, 1978.

Cedars-Sinai Hypertension Research Clinic, U.C.L.A., July 1976 to February 1977.

Award for "Outstanding Organization of the 2nd International Congress on Myocardial and Cellular Bioenergetics," 1984, U.S.C.

Award for Excellence in Teaching and Community Involvement, The City of Los Angeles Council, December 1984.

Award for Voluntary Work for the Hispanic Community, Los Angeles, City of L.A., Councilman A. Schneider, 9/85.

Award for 15 Years of Service, Queen of Angels/Hollywood Presbyterian Medical Center, 12/95.

Fellow of the Collegium Ramazzini, 1995 to present

Fellow of the American College of Physicians, 1998

Resolution of Appreciation, Santa Clara Valley Water District, 09/07/99

Certificate of Recognition, California State Senate, Senator Richard G. Polanco, 09/21/99

Resolution Relative to Commending, Senator Richard J. Mountjoy, 29th Senatorial District, 11/15/00

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Board of Internal Medicine: Diplomate in Internal Medicine, January 1979
Board of Nephrology: Diplomate in Nephrology, June 1980
Board of Forensic Examiners: Diplomate in Forensic Medicine, January 1996
Medical Board of California: Expert Medical Reviewer, December 2005
Citizenship: American, Naturalized, July 1980

D. Specific Teaching Responsibilities: (Past and Present)

Internal Medicine Weekly Seminars for House Staff, 1974 – 1975, Hadassah, Jerusalem, Israel.
Lectures in Physical Examination and Diagnostics for Medical Students: U.C.L.A., 1977-1978.
Lectures and Seminars in Renal Physiology to Residents, U.C.L.A., 1977-1978.
Mechanism of Diseases, U.S.C., Medical School, 1978-1987.
Pathophysiology Course, U.S.C., Medical School, 1978-1987.
Student Ward Attending, U.S.C., Medical School, 1978-1987.
Attending on Nephrology Ward, U.S.C., Medical School, 1978-1987.
Attending on Medicine Ward, U.S.C., Medical School, 1978-present
Residents Seminars in Nephrology, U.S.C. Medical School, 1978-1987.
Senior Advisor, Ph.D. Program, Department of Pharmacology, U.S.C., Medical School, 1978-1987.
Department of Medicine - Attending in Internal Medicine 1-2 Months Per Year. Direct Daily Teaching To Residents, Interns, and Students. University of Southern California, School of Medicine, Department of Medicine 1978, Presently Emeritus.

E. Medical Scientific Committees: (Past and Present)

Assistant Chief Hemodialysis Unit, Wadsworth, V.A. Hospital and U.C.L.A., June 1977-June 1978, Center, January 1980-1983.
Director, Renal Research Laboratory, U.S.C./L.A.C. Medical Center, January 1980-1983.
Advisor to the Scientific Council, Kidney Foundation of Southern California.
Chairman, Nephrology Section, Hollywood Presbyterian Medical Center, Los Angeles, California.
Member, Research Committee, Kidney Foundation of Southern California, August 1979.
Chairman, Public Relations Committee, Kidney Foundation of Southern California, August, 1980.
Member, Research Committee, Kidney Foundation of Southern California, 1983.
Chairman, Research Council, Kidney Foundation of Southern California, 1983.
Chairman, Annual Scientific Symposium, Kidney Foundation of Southern California.
Chairman, Organizing Committee 2nd International Congress on Myocardial and Cellular

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Bioenergetics, 1984.

Member, Organizing Committee and Vice Chairman, Program Committee, American Society for Magnesium Research, Los Angeles, 1985.

Director, Center for Internal Occupational and Toxicological Medicine, March, 1986.

Director, Osteoporosis Center, March, 1986.

Chairman, Department of Medicine, Hollywood Presbyterian Medical Center, 1985-1987.

Chairman, Utilization Review Committee, Hollywood Presbyterian Med Center, 1987-89

Member, Quality Utilization Council, Queen of Angels Medical Center, 1996.

Member, Medical Records Committee, Queen of Angels Medical Center, 1996.

Chairman, Subacute Care Committee SNF, Queen of Angels Medical Center, 1996.

Member, Clinical Nutrition Committee, Queen of Angels Medical Center, 1996.

Member, Executive Committee, California Society of Industrial Medicine and Surgery

Chairman Task Force Environmental Health, City of Los Angeles, City Attorney.

Chairman, Skilled Nursing Services, Queen of Angels Medical Center, 1996

Chairman, Allied Services Committee, Queen of Angels Medical Center, 1997

Vice-Chairman, Dept of Medicine, Queen of Angels Medical Center, 1999, 2000, 2001

Chairman, Pharmacy & Therapeutics Committee, Queen of Angels Medical Center, 1999, 2000

Member, CSIMS Education Committee, California Society of Industrial Medicine & Surgery, 2000

Chairman, Panel Discussion, New York Academy of Sciences. Carcinogenesis Bioassays and Protecting Public Health: Commemorating the Lifework of Cesare Maltoni. April, 2002.

Chairman, Education Committee, California Society of Industrial Medicine & Surgery, 2002

F. **Grants:**

Recipient of a Kidney Foundation Fellowship Grant, 1977

Recipient of an American Heart Association, Clinical Investigation Grant, 1980

Recipient of an NIH Grant, \$240,000 for Investigation Into Myopathy of Phosphate Depletion, 1985-1987.

G. **Editorial Boards, Consultants & Peer Review:** (Past and Present)

Editorial Board, Journal of Clean Technology and Environmental Sciences.

Editor-in-Chief, International Journal of Occupational Medicine and Toxicology.

Assistant Editor to Mineral and Electrolyte Metabolism.

Consultant to the Editor of Archives of Internal Medicine.

Consultant to the Editor of Biochemical Medicine.

Consultant to the Editor of Kidney International.

Consultant to the Editor of Journal of Clinical Investigation.

Editorial Board, Biochemical Medicine.

Editorial Board, Nephron.

Consultant to the Journal of Clinical Investigation.

Consultant to Kidney International.

Assistant Editor, American Journal of Nephrology.
Consultant to "Magnesium", Journal of the American Society for Magnesium Research.
Consultant to the Journal of the American College of Nutrition.
Consultant to the American Journal of Physiology.
Consultant to the Editor of Renal Physiology.
Consultant to the Editor of Advances of Modern Environmental Toxicology.
Editorial Board, Toxicology and Industrial Health.
Consultant to the Archives of Environmental Health
Consultant to the Journal of Exposure Analysis
Consultant for the Life Sciences Research Office, Federation of American Society for
Experimental Biology
Consultant for the Scientific Advisory Committee and Study Section, American Heart
Association, Los Angeles, California.
Editor-in-Chief, Journal of Clean Technology, Environmental Toxicology, and
Occupational Medicine.
Coeditor, Toxicology and Industrial Health
Peer Reviewer, Department of Health & Human Services/ATSDR, A Follow-Up
Investigation of the Stability and Predictive Value of Kidney Biomarkers Among
Participants in Three Earlier ATSDR Health Investigations, 2000
Peer Reviewer, Federal Judicial Center, Reference Manual on Scientific Evidence,
Second Edition, 2000
Peer Reviewer, Eastern Research Group/ATSDR, Malathion Chemical Technical
Summary for Public Health and Public Safety Professionals, 2000
Editorial Board, International Journal of Occupational medicine and Environmental
Health
Editorial Board, Archives of Environmental & Occupational Health
Peer Reviewer, A Medical-Legal Companion to the AMA Guide Fifth, Chapter on
pulmonary medicine.

Publications:

1. Better, O.S., N. Brautbar, S. Branstater, et al. Obstruction of the inferior vena cava. Harefuah (Journal of the Israel Society of Medicine) 73:83-5, 1967.
2. Brautbar, N., Lead poisoning in a family of immigrants from Iran. Department of Public Health, Israel, 1967.
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157. Jones, K., N. Brautbar. Toxicity to the lung in patients with prolonged exposure to organic solvents. *Thirty-Fifth Annual Meeting of the Society of Toxicology*, 12/1995.

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162. Jones, R. Kathleen, N. Brautbar. Reactive airway disease in patients with prolonged exposure to industrial solvents. *Toxicology and Industrial Health*, Vol. 13, No. 6, pp 743-750, 1997.
163. Vojdani, A., H. Kalhor, N. Brautbar. Expression of CYP1A1 gene in peripheral lymphocytes as a marker of exposure to petroleum products in service stations. American Chemical Society, Submitted.
164. Altura, M.B., A. Gebrewold, B. Altura, N. Brautbar. Magnesium depletion impairs myocardial carbohydrate and lipid metabolism and cardiac bioenergetics and raises, myocardial calcium content in vivo: relationship to etiology of cardiac diseases. *Biochem Mol Biol Int.* 40(6):1183-90, December 1996.
165. Vojdani, A., G. Namatalla, N. Brautbar. Methyl tertiary-butyl ether antibodies among gasoline service station attendants. *Ann NY Acad Sci.* 837:96-104, 1997.
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168. Brautbar, N., K. Jones. Abstract. Neurotoxic effects of industrial solvents (IS). American College of Toxicology, Eighteenth Annual Meeting, 1997.
169. Lin, R., N. Brautbar. Abstract. Industrial solvents exposure and human immune response. Society of Toxicology, Annual Meeting, 1998.
170. Brautbar, N., R. Lin, A. Vojdani. Abstract. Mixed solvents exposure, autoimmunity and connective tissue disease. Society of Toxicology, Annual Meeting, 1998.

171. Joyner, L.R., A. Desai, N. Brautbar. Abstract. Reactive airway disease syndrome (RADS) in patients exposed to nitrogen tetroxide (N₂O₄). Society of Toxicology, Annual Meeting, 1998.
172. Joyner, L.R., P. Harch, A. Desai, N. Brautbar. Chronic neurological symptomatology and abnormal SPECT tomographic analysis of the brain after nitrogen tetroxide exposure. Society of Toxicology, Annual Meeting, 1998.
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174. Brautbar, N., A. Vojdani. Effects of drinking water contaminated with MTBE on human cell cycles and specifically apoptosis. Annual Ramazzini Days, Collegium Ramazzini, Carpi (Italy), 1997.
175. Brautbar, N, K. Jones. Industrial solvents exposure and reactive airway disease. Annual Ramazzini Days, Collegium Ramazzini, Carpi (Italy), 1997.
176. Brautbar, N., K. Jones. Occupational exposure to industrial solvents (IS) and neurotoxicity. ISEE/ISEA Joint Conference 1998, Accepted for presentation (08/17/1998).
177. Brautbar, N. K. Jones. Prolonged exposure to volatile industrial solvents and the development of reactive airway disease: role of methacholine stimulation test. *Eur J Oncol*. 3(4):395-398, 1998.
178. Vojdani, A., N. Brautbar. Contaminated drinking water with MTBE and gasoline: immunological and cellular effects. *Euro J Oncol*. 3(3):191-199, 1998.
179. Vojdani, A., N. Brautbar, C. Tagle, P. Choppa. Polymorphisms in chemical metabolizing enzymes as a mechanism responsible for altered immune functions in patients with chemical sensitivities. American Chemical Society, National Meeting, 1998.
180. Brautbar, N, N. Navizadeh. Sewer workers: occupational risk for hepatitis C – report of two cases and review of literature. *Archives of Environmental Health*. Volume 54, No. 5, pages 328-330, September/October 1999.
181. Brautbar, N, R. Lin, A. Vojdani. Solvent exposure, autoimmunity and connective tissue diseases. 2nd International Congress for Autoimmunity, Israel, 1999.
182. Joyner, LR, N. Brautbar. Accidental release of nitrogen tetroxide (N₂O₄) causing reactive airway disease in exposed patients. Annual Ramazzini Days, Collegium Ramazzini, 1998.

183. Brautbar, N., A. Vojdani. White blood cell DNA adducts and immunological abnormalities in humans exposed to contaminated drinking water containing gasoline and MTBE. Annual Ramazzini Days, Collegium Ramazzini, 1998.
184. Brautbar, N. Ammonia exposure: a common cause for sinusitis – a case report and review of the literature. *Toxicology & Industrial Health*, Vol. 14, No. 6, pages 891-895, 1998.
185. Brautbar, N. Science and the law: scientific evidence, causation, admissibility, reliability. “Daubert” decision revisited. *Toxicology and Industrial Health*. 15, pages 532-551, 1999.
186. Brautbar, N., A. Barnett. Hydrocarbon exposure & chronic renal disease. *Environmental Epidemiology and Toxicology*, 1999, 1, 163-166, 1999.
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191. Brautbar, N., R. Lin, A. Vojdani. Solvent exposure, autoimmunity and connective tissue diseases. *Journal of Autoimmunity*. Annual Ramazzini Days, Collegium Ramazzini, 1999.
192. Brautbar, N., R. Lin, G. Gaines, A. Vojdani. Occupational solvent exposure, autoimmunity and connective tissue disease. *Eur J Oncol*. Volume 5, Suppl 2, pages 17-20, 2000.
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Book Chapters and Reviews:

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2. Lee, D., N. Brautbar, M. Walling, et. al. Mineral Balance And Gut Sac Transport Studies In Phosphorus Depletion Intact And Hypophysectomized Rats. 3rd International Workshop on Phosphate, Madrid, June 1977.
3. Coburn, J., N. Brautbar. Disease States In Man Related to Vitamin D. In: Vitamin D - Molecular Biology and Clinical Nutrition. A. Normal (Ed). Marcel Deker, New York, 515-77, 1980.
4. Brautbar, N., C.R. Kleeman. Osteodystrophy and Renal Handling of Divalent Ions in Chronic Renal Failure. *Advances in Nephrology*. 8:170-205, 1979.
5. Massry, S.G., N. Brautbar. Renal Handling of Phosphate in Renal Failure. Renal Handling of Phosphate. S.G. Massry, H. Fleisch (Eds). Plenum Press, New York, 307-19, 1980.
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7. Brautbar, N., M.W. Walling, J.W. Coburn. The Role of Phosphorus in the Intestinal Transport of Calcium: Studies in Vitamin D and Deficient Rats. Phosphate and Minerals in Health and Disease. S.G. Massry, E. Ritz, H. Jahn (Eds). Plenum Press, New York, 391-9, 1980.
8. Levine, B.S., D.B. Lee, N. Brautbar, M.W. Walling, C.R. Kleeman, J.W. Coburn. Effects on Mineral Homeostasis of 1,25 (OH) 2D3 and 23, 25 (OH) 2D3 Alone in Combination, In Rats. Vitamin D: Basic Research and its Clinical Application. A. Norman, K. Schaefer, D. Herrath, H. Grigoeit, J.W. Coburn, H.F. DeLuca, E.B. Mawer, T. Suda, W. DeGruyter (Eds). Berlin, New York. 429-31, 1979.
9. Levine, B.S., N. Brautbar, D.B.N. Lee, M.W. Walling, C. Kurokaw, C.R. Kleeman, J.W. Coburn. The Effect of Vitamin D3 and its Metabolism on Magnesium Metabolism. Vitamin D: Basic Research and its Clinical Application. A. Norman, K. Schaefer, D. Herrath, H. Grigoleit, J. Coburn, H. DeLuca, E. Mower, T. Suda (Eds). 1979.
10. Lee D.B., B.S. Levine, M.W. Walling, N. Brautbar, C.R. Kleeman, W. Millis, J.W. Coburn. Regulation of Serum Phosphorus by 1,25 (OH) D23 Vitamin D: Basic Research and its Clinical Application, op cit. 939-41, 1979.
11. Nortman, D.F., J.W. Coburn, N. Brautbar, D. Sherrard, M.R. Haussler, F.R. Singer, A.S. Erickman, R.T. Sarton. Treatment of Mesenchymal Tumor Associated Osteomalacia with 1,25 (OH) 2D3: Report of a Case. Vitamin D: Basic Research and its Clinical Application, op cit. 1167-9, 1979.
12. Massry, S.G., N. Brautbar. The Inter-Relationship Between Phosphate and Magnesium Metabolism. Phosphate and Minerals in Health and Disease. S.G. Massry, E. Ritz, H. Jahn (Eds). Plenum Press, New York, 51-66, 1980.

13. Massry, S.G., N. Brautbar, D. Goldstein. Renal Handling of Calcium Magnesium, and Phosphorus in Renal Failure. *Nephrology*. W. Flamenbrawn, R. Hamburger (Eds.) Lippincott, 159-93, 1982.
14. Brautbar, N. Extrarenal Factors in Acid Base Balance. *Seminars in Nephrology*. 1:232-50, 1981.
15. Brautbar, N., D.B.N. Lee, C.R. Kleeman. Divalent Ion Metabolism. *Contemporary Metabolism*. N. Freinkel (Ed) Plenum Press, New York. 441-509, 1982.
16. Lee, D.B.N., N. Brautbar, S.G. Massry. Renal Production and Metabolites. *Seminars in Nephrology* 1:335-55, 1981.
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20. Brautbar, N., G. Gruber, D.B.N. Lee. Disorders of Calcium, Phosphorus and Magnesium. G. Gonick (Ed). Current Nephrology 7:371-487, 1984.
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23. Nakhoul, F., G. Yu, N. Brautbar, D. Lee. Hypophosphatemia and Phosphorus Depletion. R.J. Glasscock (Ed). Current Therapy in Nephrology and Hypertension, 3rd Edition, BC Decker, Inc., 1991.
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 33. Brautbar, N. Industrial Solvents and Kidney Disease, Chapter 20.4, In: Handbook of Solvents, George Wypych (ed), William Andrew Publishing/ChemTec Publishing, 2001.
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 35. Brautbar, N. Chromosomal aberrations and sister chromatoid exchanges, Chapter 20.6, In: Handbook of Solvents, George Wypych (ed), William Andrew Publishing/ChemTec Publishing, 2001.
 36. Brautbar, N. Hepatotoxicity, Chapter 20.7, In: Handbook of Solvents, George Wypych (ed), William Andrew Publishing/ChemTec Publishing, 2001.
 37. Brautbar, N., J. J.A. Williams II, M.P. Wu. Chapter 12. Cardiotoxicity of industrial chemicals and environmental pollution. Cardiovascular Toxicology, Fourth Edition. D. Acosta Jr. (Ed). Informa Healthcare USA, Inc. 2008:429-545.

Service Record and Professional Leadership: (Past and Present)

A. **Academic Administration, Departmental, School and University Committee Membership:**

1. Committee for the course in Physiology-Renal and Electrolyte for Year I.
2. Committee for the course in Nephrology for Year II.
3. Committee for the Mechanism of Diseases for Years II and III.
4. Director of Renal Research Laboratory.
5. Member, Radiation Safety Committee.
6. Director, Renal and Electrolyte Outpatient Services, LAC/USC Medical Center.

B. **Chairmanships and Organizing Committees:**

1. Chairman of the Public Relation Committee for the Scientific Advisory Committee of the Kidney Foundation of Southern California.
2. Chairman, Annual Scientific Symposium, Kidney Foundation of Southern California.
3. Organizing Committee, Int'l. Nephrology Congress, 1984.
4. Program Chairman, 2nd Int'l. Congress on Myocardial Metabolism and Compartmentation, 1983.
5. Member, Research Committee, Scientific Advisory Committee of the Kidney Foundation of Southern California.
6. Consultant and Reviewer for multiple journals (see bibliography).
7. Chairman, Organizing Committee, American Society for Magnesium Research, 1984.
8. Chairman, Organizing Committee, 2nd Int'l. Congress on Myocardial and Cellular Bioenergetics and Compartmentation, 1984.
9. Chairman, Nephrology Section, Hollywood Presbyterian Medical Center, 1980 to present.
10. Member, Acute Utilization Review Committee, Hollywood Presbyterian Medical Center, 1983 to 1985.
11. Member, Medical Records Committee, Queen of Angels/Hollywood Presbyterian Medical Center, 1983 to 1985.
12. Chairman, Department of Medicine, Hollywood Presbyterian Medical Center. (2 years).

13. Member, Clinical Nutrition Committee, Queen of Angels/ Hollywood Presbyterian Medical Center, 1994-present.
14. Member, Quality Management Committee, Queen of Angels /Hollywood Presbyterian Medical Center, 1996.
15. Member, Emergency Room Services Committee, Queen of Angels/Hollywood Presbyterian Medical Center, 1996.
16. Chairman, Subacute Care Committee, Queen of Angels/ Hollywood Presbyterian Medical Center, 1996.
17. Member, Medicine Supervisory Committee, Queen of Angels/Hollywood Presbyterian Medical Center, 1997
18. Member, Quality Management Committee, Queen of Angels/Hollywood Presbyterian Medical Center, 1997
19. Member, Emergency Room Services Committee, Queen of Angels/Hollywood Presbyterian Medical Center, 1997
20. Member, Medicine Supervisory Committee, Queen of Angels/Hollywood Presbyterian Medical Center, 1998
21. Member, Quality Management Committee, Queen of Angels/Hollywood Presbyterian Medical Center, 1998
22. Member, Emergency Room Services Committee, Queen of Angels/Hollywood Presbyterian Medical Center, 1998
23. Vice Chairman, Department of Medicine, Queen of Angels/Hollywood Presbyterian Medical Center, 1999, 2000, 2001
24. Chairman, Pharmacy & Therapeutics Committee, Queen of Angels/Hollywood Presbyterian Medical Center, 1999.
25. Chairman of By-Laws Committee, Queen of Angel/Hollywood Presbyterian Medical Center, 2000.
26. Member, Credentialing Committee, Queen of Angels/Hollywood Presbyterian Medical Center, 2001.
27. Vice Chairman, Department of Medicine, Queen of Angles/Hollywood Presbyterian Medical Center, 2001, 2002.

C. **Chairing Scientific Sessions in National and International Meetings:**

1. American Society of Nephrology, 1979.
2. International Society for Phosphate and Mineral Metabolism, 1978.
3. International Society for Phosphate and Mineral Metabolism, 1981.

D. **Invited Speaker, Professorship or Visiting Scientist:**

1. Annual Gordon Conference on Magnesium, 1980.
2. Visiting Scientist, Max Plank National Institute; Heidelberg, Germany, Department of Biochemistry, 1980.
3. International Society for Phosphate and Mineral Metabolism, 1981.
4. National Institute of Health, Renal and Electrolyte Laboratory, 1981.
5. Yale University and Medical School, Department of Medicine and Physiology, 1981.
6. Downstate University and V.A. Hospital, New York Medical School, 1981.
7. University of Virginia, Richmond, Department of Medicine and Nephrology, 1981.
8. International Congress for Nutrition in Uremia, 1982.
9. Harvard Medical School, Peter Brent Brigham and Women's Hospital, Division of Medicine, Department of Nephrology, 1982.
10. Mayo Clinic, Mayo Medical School, Department of Nephrology and Physiology, 1982.
11. International Society for Phosphate and Mineral Metabolism, 1983.
12. Annual Gordon Conference on Magnesium, 1984.
13. International Congress of Nephrology, 1984.
14. National Institute of Health, Renal and Electrolyte Laboratory, 1984.
15. Weitzman Institute for Sciences, Rehovot Israel, Visiting Professor, Department of Agriculture, 1988.
16. Beilinson Hospital, Tel Aviv University, Visiting Professor, Department of Medicine, 1988.
17. Collegium Ramazzini, Experimental Cancer Center, Bologna, Italy, 1995.

18. Hadassah Medical Center, Hebrew University, Department of Environmental Medicine, Israel, 1995.
19. Hadassah Medical Center, Hebrew University, Department of Immunogenetics and Tissue Typing, Israel, 1996.
20. National Institute of Public Health, Czech Republic, 1996.
21. Hebrew University-Hadassah School of Medicine, Jerusalem, Lautenberg Center for General & Tumor Immunology, Israel, 1996.
22. Autoimmune Research Institute and Department of Medicine, Sheba, Tel Hashomer Hospital, and University of Tel-Aviv, 1996.
23. Lautenberg Center for General and Tumor Immunology, Hebrew University, Hadassah Medical School, Israel, 1997.
24. Hadassah Medical Center, Hebrew University, Department of Environmental Medicine, Israel, 1997.
25. Institute of Biochemistry, Food Science and Nutrition, Hebrew University of Jerusalem, Faculty of Agriculture, Rehovot Israel, 1997.
26. Technion-Israel Institute of Technology, Department of Nephrology, Israel, 1997.
27. Hadassah Medical Center, Hebrew University, Department of Environmental Medicine, Israel, 1998.
28. Joseph H & Bell R Braun Hebrew University – Hadassah School of Public Health & Community Medicine, Department of Occupational & Environmental Medicine, Israel, 1998.
29. Baylor College of Medicine, Houston, Texas, 1998.
30. Hebrew University-Hadassah School of Medicine, Jerusalem, Lautenberg Center for General & Tumor Immunology, Israel, 1998.
31. Technion – Israel Institute of Technology, Israel, 1998
32. Bnai Zion – Medical Center, Department of Emergency Medicine, Israel, 1998
33. National Judicial College, “Science and the Courtroom”, Reno, Nevada, 1998
34. 2nd International Autoimmunity Congress, Tel Aviv, Israel, 1999
35. Israel Association for Occupational Medicine, Israel, 1999

36. Hebrew University-Hadassah School of Medicine, Jerusalem, Lautenberg Center for General & Tumor Immunology, Israel, 1999
37. Joseph H & Bell R Braun Hebrew University – Hadassah School of Public Health & Community Medicine, Department of Occupational & Environmental Medicine, Israel, 1999
38. Technion – Israel Institute of Technology, Israel, 2001
39. Joseph H & Bell R Braun Hebrew University – Hadassah School of Public Health & Community Medicine, Department of Occupational & Environmental Medicine, Israel, 2001
39. Israel Society of Occupational Medicine, First International Symposium on "The Use of Induced Sputum in Medicine", 2001
40. Department of Epidemiology, Tel Aviv University, School of Public Health, Israel, October, 2003. Visiting Professor
41. Technion Medical School Research Institute, Haifa, Israel, October, 2003. Visiting Professor
42. Department of Environmental Health, Hebrew University, Hadassa Medical Center, Israel, October 2003. Visiting Professor
43. Collegium Ramazzini, Carpi, Italy, October, 2003.
44. Attended Recent Advances in Benzene Toxicity, International Conference, October 9-12, 2004, Munich, Germany.
45. Technion Israel Institute of Technology, Ruth and Bruce Rappaport Faculty of Medicine, October, 2004 Industrial Toxic Hazards and Solvent Neuropathy.
46. Visiting Professor of Epidemiology, Hebrew University School of Public Health and Community Medicine, Occupational and Environmental Medicine, October, 2004.
47. Visiting Professor Tel Aviv University, School of Public Health, Israel, October, 2004.
48. Collegium Ramazzini, Carpi, Italy, October 2004.
49. Visiting Professor, Faculty of Medicine, Hebrew University of Jerusalem, May 13-May 19, 2009
50. Visiting Professor, Department of Epidemiology, Public Health Program, Tel Aviv University, Sackler Faculty of Medicine, May 13-25, 2009.

51. Visiting Professor, Environmental Toxicology Graduate Program, University of California, Riverside, California, February 15, 2012.
52. Visiting Professorship, Department of Immunology, Hebrew University, October 15-17, 2012.
53. Visiting Professor, Department of Epidemiology, Tel Aviv University, October 18-23, 2012.
54. Visiting Professor, National Cancer Institute “Regina Elena”, Istituti Fisioterapici Ospitalieri, Istituto Regina Elena – Istituto San Gallicano, Istituti di Ricerca e Cura a Carattere Scientifico, Rome, Italy, October 23-26, 2012.
55. Visiting Professor, Department of Epidemiology, Tel Aviv University, October 15-22, 2013.
56. Visiting Professor, Hebrew University-Hadassah Medical School, Jerusalem, Israel, October 9-14, 2015.
57. Visiting Professor, Tel Aviv University, School of Public Health, Department of Epidemiology, October 10-14, 2015.

Teaching Record:

1. Full-time responsibility as an Attending Staff Physician in Renal Ward for 2 months per year. This includes daily teaching rounds and consult rounds, 1977-1987.
2. Residents and Students seminars in Nephrology, 1977-1987.
3. Attending on the Student Ward for 6-8 weeks per year. This includes teaching rounds and case discussions, 1977-1987.
4. Attending on General Medicine Ward for 2-3 months per year. This includes presentation of cases, intake rounds and daily teaching rounds, 1977-1987.
5. Course in Renal Physiology - Fluids and Electrolytes, for Year I students, 1977-1987.
6. Course in Nephrology for Year II students, 1977-1987.
7. Mechanism of Disease for Years II and IV, 1977-1987.

Past and Present Teaching:

1. Clinical Professor of Medicine, University of Southern California School of Medicine, Department of Medicine. 1-2 months per year. Daily rounds, teaching rounds, patient care, student seminars.

2. Advisor, Collegium Salerni USC. Advisor for 1st year medical students.
3. In-office teaching (medical students), University of Southern California School of Medicine, Department of Medicine

Civic Activity Past and Present:

1. Member, Bereavement Committee, Sinai Temple, Los Angeles, California.
2. Member, Board of Directors, Sinai Temple, Los Angeles, 1994-1996.

Testimony in State & U.S. Government Committees:

1. California State Senate Transportation Committee, 04/15/97
(Regarding Gasoline & MTBE Toxicity)
2. California State Senate Environmental Quality Committee, 05/12/97
(Regarding Gasoline & MTBE Toxicity)
3. U.S. Senate Committee on Environment & Public Works, 12/02/97
(Regarding Gasoline & MTBE Toxicity)
4. California State Senate Environmental Quality Committee, 04/15/98
(Regarding Gasoline & MTBE Toxicity)

Most recent speaking engagements:

1. United States Senate Environment and Public Works Committee. Statement of Nachman Brautbar, MTBE Water Pollution, in front of the United States Senate Environment and Public Works Committee. Los Angeles, California. December 9, 1997.
2. American College of Toxicology, 25th Annual Meeting. Palm Springs, California. November 7-10, 2004. Invited Speaker.
3. Mealey's Bextra and Celebrex Litigation Conference. Chicago, Illinois. May 11, 2005. Presented on the topic of Bextra, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis.
4. California Society of Industrial Medicine and Surgery (CSIMS) 20th Annual Mid-Summer Seminar. Anaheim, California. June 10-12, 2005. Presented on the topic of cancer presumption.
5. 3rd International Scientific Conference of the Collegium Ramazzini, Framing the Future in Light of the Past: Living in a Chemical World. Bologna, Italy. September 18-21, 2005. Presented two manuscripts: 1) Brautbar N, Wu MP, Gabel E, Regev L. Industrial, non-chlorinated solvent exposure and kidney cancer. Collegium Ramazzini, 2005. Abstract for Framing the Future in the Light of the Past Living in a Chemical World, The 3rd International Scientific

- Conference Bologna, September 18-21, 2005; 2) Brautbar N, Wu MP. Medical monitoring to early detect and cure from a latent disease. Collegium Ramazzini, 2005. Abstract for Framing the Future in the Light of the Past Living in a Chemical World, The 3rd International Scientific Conference Bologna, September 18-21, 2005.
6. HarrisMartin's Benzene Litigation Conference. Marina del Rey, California. September 29-30, 2005. Presented on the following topic: "General Causation to Specific Causation."
 7. Los Angeles Valley Applicants' Attorneys Association. Encino, California. March 8, 2006. Presented on the following topic: "AMA 5th Guides Application for Impairment Rating."
 8. Harbor Chapter of the California Applicant's Attorneys Association. Long Beach, California. March 21, 2006. Presented on the following topic: "AMA 5th Guides Application for Impairment Rating."
 9. American Bar Association Toxic Torts & Environmental Law Committee Meeting. "Science and the Law 2006: A Day in the Life of Toxic Torts and Environmental Law." Phoenix, Arizona. April 7, 2006. Presented on the following topic: "Recent News in Benzene and Hematopoietic Malignancies."
 10. California Society of Industrial Medicine and Surgery (CSIMS) 21st Annual Mid-Summer Seminar. Incline Village, Nevada. June 9-11, 2006. Presented on the following topic: "Apportionment 2006."
 11. Mealey's Benzene Litigation Conference. Marina del Rey, California. June 12-13, 2006. Presented on the following topic: "Low Levels of Benzene and Hematopoietic Malignancies."
 12. California Department of Industrial Relations, Division of Occupational Safety and Health (DOSH), better known as Cal/OSHA. First Advisory Meeting on Diacetyl and Chemicals in the Flavor Manufacturing Industry in California. Oakland, California. September 28, 2006.
 13. HarrisMartin's Benzene Litigation Conference. Las Vegas, Nevada. May 17-18, 2007. Presented on the following topic: "Benzene Exposure Levels."
 14. Mealey's Benzene Litigation Conference. Santa Monica, California. June 4-5, 2007. Presented on the following topic: "Benzene Exposure Levels and Leukemia."
 15. Los Angeles Metropolitan Applicants' Attorney Association (LAMAAA). Commerce, CA. August 23, 2007. Presented on the following topic: "Tackling the AMA Guides: Internal Medicine. Impairment Rating. AMA 5th Guides."

16. HarrisMartin's Benzene Litigation Conference: Trial of a Benzene-Leukemia Case from Jury Selection to Verdict Agenda. New York, New York. December 3-4, 2007. Presented on the following topic: "Medical Causation - Examination of Plaintiff and Defense Causation Experts. Benzene and Acute Myeloid Leukemia."
17. Southern California Applicant's Attorneys Association (SCAAA). Los Angeles, California. February 18, 2009. Presented on the following topic: "Handling Sleep Impairment and the Compensable Consequences."
18. Latino Association of Workers' Compensation Professionals. Monterey Park, California. March 19, 2009. Presented on the following topic: "How to Master the Compensable Internal Consequences of an Orthopedic Injury. Impairment Rating, AMA 5th guides. How to Master the Internal Medicine."
19. HarrisMartin's Benzene Causation Conference. Las Vegas, Nevada. May 24-25, 2010. Presented on the following topic: "Medical Causation in Cases Involving Benzene and Multiple Myeloma."
20. HarrisMartin's Conference-Benzene Litigation and Lymphoid Cancers: New Scientific Evidence. Marina del Rey, California. December 9, 2010. Presented on the following topic: "Medical Causation in Cases Involving Benzene and Acute Lymphocytic Leukemia (ALL)."
21. Hadassah Medical Center/Hebrew University. "Effects of benzene and solvents on the immune system." June 2011.
22. Tel Aviv University, Department of Epidemiology. "Solvent exposure and target organ damage." June 2011.
23. Annual Ramazzini Days Meeting 2011. Collegium Ramazzini. Scientific Committee member and meeting participant. Carpi, Italy. October 28-30, 2011.
24. California Applicants' Attorneys Association (CAAA). CAAA 2012 Winter Convention. Rancho Mirage, California. January 29, 2012. Presented on the following topic: "Protecting Your Client's Medical Care: Medical Treatment Utilization Schedule (MTUS) and Internal Medicine."
25. Environmental Toxicology Graduate Program seminar series. University of California, Riverside, California. February 15, 2012. Presented on the following topic: "Causation Revisited: from Daubert to Milward."
26. Tel Aviv University, Department of Epidemiology. Presented on the following topics: "Benzene exposure", "Benzene Affecting the Immune System", "Benzene and Leukemia", "Benzene and Lymphomas", "Hydroquinone and Hematototoxicity". February - March 2012.

27. California Applicants' Attorneys Association (CAAA). Support Staff Seminar. Los Angeles, California. March 10, 2012. Presented on the following topic: "Compensable Consequences of Industrial Injuries."
28. American Bar Association (ABA), Spring Meeting on Toxic Torts. Mock Trial of a Toxic Tort Case. Phoenix, Arizona. March 31, 2012. Participated in a mock trial on benzene toxicity, solvents toxicity and lymphomas.
29. California Society of Industrial Medicine and Surgery (CSIMS). CSIMS 28th Annual Mid-Summer Seminar. Westin Hotel, San Diego, CA. June 14-16, 2012. Participated on panel: "Surviving and Thriving in a Deposition". Specialty Specific Breakout Session: Internal Medicine, presented on the following topic: "1. Precautionary tale of medication use and consequences of industrial injuries; 2. Medical foods in workers' compensation."
30. Collegium Ramazzini. Mount Sinai School of Medicine, New York. June 28, 2012. Presented on the following topic: "Benzene and multiple myeloma."
31. Hebrew University, Department of Immunology. October 15-17, 2012. Genotoxicity and immunotoxicity of industrial solvents.
32. Tel Aviv University, Department of Epidemiology. October 18-23, 2012. Presented on the following topics: "Solvents, genotoxicity and immunotoxicity".
33. National Cancer Institute "Regina Elena", Istituti Fisioterapici Ospitalieri, Istituto Regina Elena – Istituto San Gallicano, Istituti di Ricerca e Cura a Carattere Scientifico. Rome, Italy, October 23-26, 2012. Presented on the following topics: Carcinogenic effects of chemicals on the gastrointestinal tract.
34. LawWorm.com Seminars. The Queen Mary Grand Salon. January 19, 2013. Presented on the following topic: "New and underutilized PD litigation strategies, new regulations, case law update, and the entire playing field post SB 863."
35. California Society of Industrial Medicine and Surgery (CSIMS). CSIMS 28th Annual Mid-Summer Seminar. Fairmont Hotel, Newport Beach, CA. June 20-23, 2013. Specialty Specific Breakout Session: Internal Medicine, presented on the following topic: "Precautionary tale of medication use, drug interactions and consequences of industrial injuries."
36. Tel Aviv University, Department of Epidemiology. October 15-22, 2013. Presented on the following topics: "Solvents, genotoxicity and immunotoxicity".
37. State of California, Department of Industrial Relations, Division of Workers' Compensation. "Internal Medicine: Improving Outcomes When Red Flags Fly." 22nd Annual Education Conference LAX Marriott Hotel. Los Angeles, CA. February 10, 2015.

38. California Society of Industrial Medicine and Surgery (CSIMS). CSIMS 30th Annual Mid-Summer Seminar. Hyatt Regency, Long Beach, CA. June 19-20, 2015. a) Specialty Specific Breakout Session: Internal Medicine. In small groups, the audience analyzes case studies discussing the intricacies and pitfalls of each, from both a treating and forensic perspective. Each group will then bring back the results of their analysis to the entire group. b) Right reporting: Nachman Brautbar, M.D. (causation), WCJ (ret.) Pamela Foust, Esq., Richard Lieberman, M.D., Peter Mandell, M.D.
39. Hebrew University-Hadassah Medical School, Jerusalem, Israel, October 9-14, 2015. Lecture on the role of topoisomerase in carcinogenesis.
40. Tel Aviv University, School of Public Health, Department of Epidemiology, October 10-14, 2015. Seminars on the mechanisms of benzene carcinogenicity and genetic and epigenetic mechanisms.
41. California Society of Industrial Medicine and Surgery (CSIMS). CSIMS 31st Annual Mid-Summer Seminar. Paradise Point Resort and Spa, San Diego, CA. June 16-18, 2016. Specialty Specific Breakout Session: Internal Medicine. In small groups, the audience analyzes case studies discussing the intricacies and pitfalls of each one, from both a treating and forensic perspective. Each group will then bring back the results of their analysis to the entire group.