The Underlying Pathology of Chronic Disease

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FINANCIAL DISCLOSURE: MEDICAL DIRECTOR OF RESEARCHED NUTRITIONALS
MORE THAN 50% OF THE WORLD LIVES WITH CHRONIC DISEASE
At least 300,000 people are infected with Lyme disease each year in the US.
Autoimmune Diseases

Brain
- Multiple Sclerosis
- Guillain-Barre Syndrome
- Autism

Thyroid
- Thyroiditis
- Hashimoto's Disease
- Graves' Disease

Blood
- Leukemia
- Lupus Erythematosus
- Hemolytic Dysglycemia

GI Tract
- Celiac's Disease
- Crohn's Disease
- Ulcerative Colitis
- Diabetes Type I

Bones
- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Polymyalgia Rheumatica

Muscles
- Muscular Dystrophy
- Fibromyalgia

Nerves
- Peripheral Neuropathy
- Diabetic Neuropathy

Skin
- Psoriasis
- Vitiligo
- Eczema
- Scleroderma

Lung
- Fibromyalgia
- Wegener's Granulomatosis

>100 Autoimmune Diseases

THE AUTOIMMUNE EPIDEMIC

More Americas — 1 in 12 — suffer from autoimmune disorders than cancer or heart disease

Environmental triggers have helped to triple disease rates in the last three decades

Learn to protect your immune system while exploring possible causes and potential cures for nearly 100 autoimmune diseases including multiple sclerosis, lupus, Crohn's disease, type 1 diabetes, rheumatoid arthritis, and autoimmune-related diseases like fibromyalgia and chronic fatigue syndrome.

Donna Jackson Nakazawa

Foreword by Dr. Douglas Kerr, director, Johns Hopkins Transverse Myelitis Center
How we learned to practice medicine

Symptom Based Diagnosis: An Evidence-Based Guide
Differential diagnosis - the distinguishing of a disease or condition from others presenting with similar signs and symptoms.

Treatment by cause of symptoms

Symptoms → Biologic Cause → Treatment Plan
Common Symptoms in Chronic Disease
Fatigue
Poor recovery from exercise
Poor endurance
Fatigue in children
ADHD, Chronic Fatigue Syndrome, and Autism – What Do They Have in Common?
Mitochondrial Dysfunction

- Gastrointestinal Disorders
- Lack of Endurance
- Swallowing Difficulties
- Diabetes
- Respiratory Complications
- Poor Balance
- Lactic Acidosis / Lactate Build-up
- Developmental Delays
- Skeletal Muscle Abnormalities
- Nervous System Impairment
- Fatigue
- Muscle Weakness / Pain
- Seizures
- Cardiac Disease
- Poor Growth
- Susceptible to infections
- Atypical Autism
- Diminished / Loss of Motor Control
- Liver Disease
- Visual / Hearing Problems
Mitochondrial Function

1. ATP production—produce energy for the cell
2. Initiating and performing apoptosis and cell death
3. Calcium homeostasis
4. Iron homeostasis
Children with autism were more likely to have mitochondrial dysfunction, mtDNA over replication, and mtDNA deletions than typically developing children.

Mitochondrial dysfunction in FMS/FMD

Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease

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Abstract

Introduction: Fibromyalgia is a chronic pain syndrome with unknown etiology. Recent studies have shown some evidence demonstrating that oxidative stress may have a role in the pathophysiology of fibromyalgia. However, it is still not clear whether oxidative stress is the cause or the effect of the abnormalities documented in fibromyalgia. Furthermore, the role of mitophagy in the redox imbalance reported in fibromyalgia is also controversial. We undertook this study to investigate the role of mitochondrial dysfunction, oxidative stress, and mitophagy in fibromyalgia.

Methods: We studied 20 patients (12 male, 8 female patients) and 10 healthy controls. We evaluated mitochondrial function in fibromyalgia patients measuring: coenzyme Q10 levels; mitochondrial membrane potential with flow-cytometry; superoxide production with MitoSOX™ and flow cytometry in fibromyalgia patients. Autophagy activation was evaluated by electron microscopy examination of blood mononuclear cells. Mitophagy was defined as the engulfment of mito-chondria by autophagosomes.

results: We found reduced levels of coenzyme Q10, decreased mitochondrial membrane potential, increased levels of mitochondrial superoxide in blood mononuclear cells, and increased levels of lipid peroxidation in both blood mononuclear cells and plasma from fibromyalgia patients. Mitochondrial dysfunction was also associated with increased expression of autophagic genes and the elimination of dysfunctional mitochondria with mitophagy.

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Oxidative Stress

Definition

- Imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects through neutralization by antioxidants
Causes of Mitochondrial Dysfunction and Oxidative Stress

- **Mitochondrial Dysfunction**
  - Medicines
  - Poor Nutrition
  - Stress
  - Pesticides (Glyphosate)
  - Heavy Metals
  - Environmental toxins

- **Oxidative Stress**
  - Medicines
  - Poor Nutrition
  - Stress
  - Pesticides (Glyphosate)
  - Heavy Metals
  - Environmental Toxins
Research comparing anti-oxidant markers and markers of lipid peroxidation to assess oxidative stress

Study population: 20 children with ASD
- 25 matched healthy controls

Results: Positive in ASD children younger than 6 yrs
- Decreased anti-oxidant markers with SOD and GSH-PX
- Increase in lipid peroxidation marker MDA

Increased oxidative stress

Then:

Increased need for glutathione
What are the functions of Glutathione?

1. Master Antioxidant
2. Reduces Free Radicals
3. Detoxifies Chemicals
4. Chelates Heavy Metals
5. Protects Mitochondrial DNA
6. Cellular Anti-inflammatory compound
7. Storage and transport of cysteine
8. Enhances immune function
Environmental Chemicals: Depletion of glutathione

- Tylenol
- Acetone/solvents
- Fuel/gasoline
- Heavy Metals
- Pesticides/Herbicides
- Nitrates: Food preservatives
- Artificial sweeteners
- Synthetic food dyes
- Benzopyrenes: tobacco
- Industrial pollutants
- Ethanol
- Household chemicals: detergents, cleaners, bleach
- Plastics
- Non-stick cookware
- Chlorine treated water
- Formaldehydes
- X-rays
- EMF’s
- UV radiation
Alzheimer’s disease dependent reduction of GSH was observed in both Hippocampus and Frontal C (p < 0.001).

GSH reduction in these regions correlated with decline in cognitive functions.

Hippocampal GSH discriminates between mild cognitive impairment and healthy controls.
PAIN IN AMERICA

More people live with chronic pain than cancer, heart disease, and diabetes, combined.

More than 30% of Americans are living with some form of chronic or severe pain.

Sources: National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), Institute of Medicine
Inflammation

Tissue injury caused by physical or chemical agent or pathogenic microorganism

- Capillary widening
- Increased capillary permeability
- Attraction of white blood cells
- Systemic response

- Increased blood flow
- Release of fluid
- Migration of white blood cells to injury
- Fever and proliferation of white blood cells

Heat, Redness, Tenderness, Swelling, Pain
Inflammation

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Fever and proliferation of white blood cells

Heat

Redness

Tenderness

Swelling

Pain
Inflammation

- **Acute Inflammation**
  - Normal immune response to injury or infection

- **Chronic Inflammation**
  - Prolonged abnormal immune response

- **Oxidative Stress**
  - Normal part of metabolism and immune response

- **Chronic Oxidative Stress**
  - Destructive process that damages DNA and cell membranes
Inflammation

- Lyme
- Cardiovascular \[^1\] \[^2\]
- Osteoarthritis
- Obesity
- Autism
- Depression
- Autoimmune Disorders
  - rheumatoid arthritis
  - lupus
  - asthma
  - inflammatory bowel diseases (ulcerative colitis, Crohn’s)


Cytokines

- Proinflammatory
  - IL-1
  - IL-6
  - IL-8
  - TNF-alpha
Brain Fog

OUT OF ORDER!
Depression
Signs and symptoms of depression in children

- Irritability or anger
- Continuous feelings of sadness, hopelessness
- Social withdrawal
- Increased sensitivity to rejection
- A major change in eating (increased or decreased) and/or sleeping patterns (usually sleeplessness)
- Vocal outbursts or crying
- Difficulty concentrating
- Fatigue and low energy
- Physical complaints (such as stomach aches, headaches) that do not respond to treatment
- Low self-esteem and guilt
- Thoughts or expressions of suicide or self-destructive behavior

Sources:
1. Dr Adnan Omar
   www.aacap.org/cs/root/facts_for_families/the_depressed_child

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Neuroinflammation: The Brain on Fire
Pathology of Depression

- A: normal cerebellum in control patient
- B-C: atrophic cerebellum in a patient with autism with loss of Purkinje and granular cells
- D-K: activated microglial and inflammatory cells
Digestive Symptoms
1 in 5 people suffer from IBS
Disrupted Gut-Brain-Microbiome:

Leaky Gut Affects the Whole Body

Leaky Gut Leads to Leaky Gut

- Sinus and Mouth: Frequent Colds, Food Sensitivities
- Brain: Depression, Anxiety, ADHD
- Skin: Acne, Rosacea, Eczema, Psoriasis
- Joints: Rheumatoid Arthritis, Fibromyalgia, Headaches
- Adrenals: Fatigue
- Colon: Constipation, Diarrhea, IBD
- Thyroid: Hashimotos, Hypothyroidism, Graves
40 autistic subjects (36 out of 40 autistic subjects were classified as severe ASDs, Childhood Autism Rating Scale (CARS) value >37) and 40 neurotypical controls

Analysis of gut microbiota

Results:

- *Candida* was more than double in the autistic than neurotypical subjects
- Significant increase in the *Firmicutes/Bacteroidetes* ratio in autistic subjects due to a reduction of the *Bacteroidetes* relative abundance

Effect of Probiotics on Alzheimer’s disease

- 60 Patients with Alzheimer’s disease randomized to 30 patients taking probiotics versus 30 patients on placebo for 12 weeks

- Results: Patients on probiotics
  - Significant improvement in Mini-mental state exam (p<0.0001)
  - Decreased plasma malondialdehyde levels
  - Decreased CRP
  - Decreased TG’s

The Gut-Brain Axis: The Missing Link in Depression

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The gut microbiota is essential to human health and the immune system and plays a major role in the bidirectional communication between the gut and the brain. Based on evidence, the gut microbiota is associated with metabolic disorders such as obesity, diabetes mellitus and neuropsychiatric disorders such as schizophrenia, autistic disorders, anxiety disorders and major depressive disorders. In the past few years, neuroscientific research has shown the importance of the microbiota in the development of brain systems. Recent studies showed that the microbiota could activate the immune and central nervous systems, including comorbid and pathogenic microorganisms in the gastrointestinal tract. Gut microorganisms are capable of producing and delivering neuromodulatory substances such as serotonin and gamma-aminobutyric acid, which act on the gut-brain axis. Preclinical research in rodents suggested that certain probiotics have antidepressant and anxiolytic activities. Effects may be mediated via the immune system or neuroendocrine systems. Herein, we present the latest literature examining the effects of the gut microbiota on depression.

KEY WORDS: Depression, Probiotics, Microbiota.

INTRODUCTION

The effects of the gut microbiota on the immune system, brain development and behavior have attracted attention in recent years. Over 90% of the more than 4,000 articles on microbiota were published in PubMed in the last 5 years. Presumably, microorganisms living in the intestine are in contact with the gut epithelial and immune systems, and through this contact are involved in the development of many neuropsychiatric and metabolic disorders, particularly autoimmune diseases. Clinical observations and animal trials have revealed much evidence of a strong link between the gut and the brain, which is established during the intrauterine period and the influence of which continues throughout the life of an individual.

The term microbiome refers to all microorganisms and their genetic material living in the body, and the term microbiota refers to populations of microorganisms present in the body’s various ecosystems (for example, the gut microbiota and skin microbiota). There are 10^{14} microorganisms in the gut, which is 10-fold greater than the number of human cells. These microorganisms also contain 150-fold more genes than the human genome.

Similar to the Human Genome Project, another study, the Human Microbiome Project (HMP), is being conducted. The aim of this project is to understand the diversity of the microbiome and microbiota in various anatomical regions and determine the roles of microorganisms in health and disease. HMP is supported by the National Institutes of Health (NIH); in 2014, more than one million US dollars (USD) in resources was transferred to the project.

Improvements in modern life such as antimicrobial treatments, vaccinations, intensive use of disinfecting and cleaning products and dietary changes exert a deep and lasting impact on the microbiome. Changes in the gut microbiota may cause Clostridium difficile infection, irritable bowel syndrome (IBS), pathogen colonization (e.g., vancomycin-resistant Enterococcus), autoimmune and allergic diseases, obesity and metabolic disorders, and neuropsychiatric disorders such as autism.

In this review we explain the pathophysiological mechanisms of the gut-brain axis, show the possible impact of the gut microbiota on depression, and inform clinicians of the latest scientific developments in this field.
Genetic Influences
Chronic Pathology

Chronic Disease
Recent studies have shown some evidence demonstrating that oxidative stress, mitochondrial dysfunction and inflammation may have a role in the pathophysiology of fibromyalgia.

Skin biopsies from patients showed a significant mitochondrial dysfunction with reduced mitochondrial chain activities and bioenergetics levels and increased levels of oxidative stress.

OS, mitochondrial dysfunction and inflammation as interdependent events in the pathophysiology of FM.
Neurodegeneration

- ROS/RNS are both harmful and beneficial (signaling) molecules
- Neurons have different levels of needs for ROS/RNS as signaling molecules

High demand for ROS/RNS as signaling molecules

High intrinsic OS

Low ATP production & mitochondrial dysfunction

Chronic inflammatory response

Deficient DNA repair

Calcium dysregulation & glutamate hyperactivity

Selective neuronal death
Diabetes and Cardiac Disease

Type 2 Diabetes Mellitus

- Hyperglycemia Glucotoxicity
  - Oxidative stress: Impaired antioxidant defenses, Increased ROS generation, AGES formation
- Hyperinsulinemia Insulin Resistance
  - Mitochondrial dysfunction: Impaired autophagy and mitophagy, Fusion-fission imbalance, Abnormal Ca2+ handling
- Hyperlipidemia Lipotoxicity
  - Inflammation: Activation of NF-kB pathway and inflammatory mediators, Activation of TLRs and of the inflammasome
  - Other mechanisms: RAAS overactivation, Endothelial dysfunction, Substrate shift towards increased FFAs oxidation

Cardiac Dysfunction

- Functional Changes
  - Diastolic Dysfunction
  - Systolic Dysfunction
- Structural Changes
  - Ventricular Hypertrophy
  - Cardiac Fibrosis

Diabetic Cardiomyopathy
Treatment for chronic disease

1. **Repair and support mitochondria**
   - Membrane repair
   - Support nutrients in ATP production from breakdown of macronutrients to Krebs cycle to oxidative phosphorylation

2. **Decrease causes of oxidative stress and inflammation**

3. **Increase anti-oxidants to counteract oxidative stress including activating Nrf2**

4. **Decrease inflammation through down regulating inflammatory mediators and improving microbiome**
Diagnosis of Mitochondrial Dysfunction

- **Urine organic acids (OAT)**
- Blood Lactate and pyruvate
- Plasma Acyl-carnitine profile
- CoQ10 levels
- Liver enzymes and ammonia
- Quantitative amino acids
- Creatinine kinase

- Mitochondrial Disease: additional testing
  - muscle biopsy, genetic profiles, echocardiogram, analysis of cerebral spinal fluid
Note: Compounds Reported in the ION™ Profile are Printed in Colors.
Vitamin & mineral requirements for enzyme cofactors are shown in light blue boxes.
Elevations of metabolites before these steps indicate functional deficiency of the nutrients.
Amino acids are shown in white oval boxes.
Mitochondrial Dysfunction

- Repair mitochondrial membrane
  - Phospholipids
Repair mitochondrial membrane
Phospholipids
Support mitochondrial function
CoQ10/Ubiquinol
Carnitine
NADH
Alpha-lipoic acid
B vitamins
Vitamin E
Support for oxidative stress

- Anti-oxidants to combat oxidative stress
  - Glutathione
  - Molecular Hydrogen (H₂: Hydrogen gas)
  - Vitamin E: mixed tocopherols and tocotrienols
  - Curcumin
  - Tea: EGCG
  - Resveratrol
  - N-acetyl-cysteine
Diagnosis: Oxidative Stress

- Test for DNA/RNA damage: 8-hydroxydeoxyguanosine (8-OHdG)
  - Urine and blood
- Test for lipid peroxidation: 8-isoprostane
  - Urine and blood
- Anti-oxidant Reserves and enzyme function: Total antioxidant capacity, glutathione peroxidase, superoxide dismutase (SOD)
  - Blood tests
- Glutathione blood level (Need to draw and put on ice immediately to be accurate)
Molecular Hydrogen: $H_2$

- **Hydrogen gas is very stable molecule**
- **Neutralizes harmful free radicals, including the hydroxyl radical**
  - Hydrogen electron donation turns hydroxyl into water
- **Diffuses across membranes, including mitochondria, due to its small size**
  - Most antioxidant supplements are limited in their cellular distributions and are poorly taken up by organelles like mitochondria
  - Hydrogen has the ability to effectively penetrate biomembranes and infiltrate into organelles, such as mitochondria and the nucleus
  - In contrast to many antioxidants, H2 also has the advantage of being able to penetrate the blood-brain barrier


2 Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine, Ohta S., Pharmacology & Therapeutics, Volume 144, Issue 1, October 2014, Pages 1–11

3 Clinical Effects of Hydrogen Administration: From Animal and Human Diseases to Exercise Medicine, Nicolson G. et al., International Journal of Clinical Medicine, 2016, 7, 32-76
Summary

- Anti-oxidant for dangerous hydroxyl radical without destroying free radicals needed for metabolism
- Activates Nrf2 anti-oxidant cascade including glutathione peroxidase, catalase, and superoxide dismutase (SOD)
- Decreases pro-inflammatory cytokines through cell signaling
- Promotes mitochondrial ATP energy function

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Neuroinflammation: Molecular Hydrogen

Research: animal study with hydrogen rich saline

- 3 groups: control, induced amyloid-beta neural inflammation, and induced amyloid inflammation plus hydrogen saline

Results:

- Hydrogen-saline prevented amyloid-beta induced neuroinflammation and oxidative stress

Molecular Hydrogen: Parkinson’s Disease

- Randomized placebo controlled trial
  - 48 weeks consuming either 1000 ml of molecular hydrogen water or placebo

- Results
  - Statistically significant improvement in the molecular hydrogen group: Unified Parkinson’s Disease Rating Scale (UPDRS)
  - Worsening disease rating in the placebo group

Support for Inflammation and Abnormal Cytokines

- Glutathione
- Molecular Hydrogen ($H_2$: Hydrogen gas)
- Vitamin E: mixed tocopherols and tocotrienols
- Curcumin
- Tea: EGCG
- Resveratrol
- N-acetyl-cysteine
- Probiotics
- Omega 3 fatty acids
- Boswellia
- White willow bark
Goal: Activate Nrf2: Nuclear Factor 2

- Master regulator of the antioxidant system
- Mechanism: A Nrf2 activator releases protein into the cell nucleus where it binds to DNA and activates anti-oxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase and these enzymes can neutralize up to 1 million free radicals
Goal: Block NFKB
References for Glutathione


References for Molecular Hydrogen

- Molecular hydrogen foundation: [www.molecularhydrogenfoundation.com](http://www.molecularhydrogenfoundation.com)