CHRONIC FATIGUE –DYSHOMEOSTASIS-MITOCHONDRIAL DYSFUNCTION

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CHRONIC FATIGUE

There are multiple core criteria to diagnose Chronic fatigue

- First, impairment of normal ability to function due to fatigue
- Post-exertional malaise (PEM) - worsening of illness after physical, mental and cognitive effort,
- poor unrefreshing sleep
- cognitive impairment
- Dizziness-orthostatic intolerance- moderate to severe, 50% of the time. Dx -HRV
- Post six months of medical investigations and supportive treatment no change in symptoms

Most of the patients remain undiagnosed and unable to access expert medical interventions, despite evidence of significant debilitation and chronicity as seen in our patient

CHRONIC FATIGUE - DYSHOMEOSTASIS

Chronically ill patients are always in the state of constant dyshomeostasis

CHRONIC FATIGUE = DYSHOMEOSTASIS

Chronic Fatigue

Atypical manifestations in Chronically ill patients result from:

- Increase in the Environmental Total Toxic burden and Increase in the Total Body Burden results in Dyshomeostasis
- Mitochondrial dysfunction
- Impaired microcirculation
- Immune deficiency
- Immune dysfunction – Allergies;
- Autoimmune activation

HOMEOSTATSIS
Role of GRS

HOMEOSTASIS-GRS

GRS HOMEOSTASIS:

GRS is a Communication system between **external and internal environment, required for the maintenance** of **homeostasis**

- Rapid, dynamic, harmonic, energy efficient automatic response part of every **defense mechanism**
- It enables body to adapt to changing environment and maintain internal environment within the physiologic range.
- Everchanging Dynamic Response of GRS is essential for obtaining and maintaining optimal physical and mental energy
- It is a information network that controls: **influx of nutrients,02, and efflux of cellular waste.**
- **Ingressing & outgressing of nerve impulses**
- **Maintenance of Isotonia & Isoosmia**

Pain, fatigue and weakness are the early manifestations of homeo-dynamic dysfunction.

HOMEOSTASIS-GRS

Functional unit consists of

- **Connective tissue matrix**

  CT cells: Fibroblast, macrophage, mast cells & leukocyte

  Loose areolar tissue containing GAGS, PGS, Collagen fibers & elastin produced by the fibroblast

  End vascular pathways-Capillary network, lymphatics, autonomic & Somatic nerve nerve endings

  All of these make up GRS's communication network for local, regional-spinal reflexes and central functions and feed back from-reticular formation, hypothalamus, limbic system.

The total response of this system results in the generalized homeostatic response

GRS-Matrix

Connective Tissue Matrix:

- CTM **makes up 40% of** body's tissue surrounding every cell and organ –amounts vary from organ to organ, it makes up **87% of the dermis and submucosa.**

  CTM mesh is the interphase **between the blood vessels, lymphatics and nerve endings** on one side and

  cell parenchyma of the end organ on the other side,

- Primarily involved in **communication of the disturbances** of other tissues
- It completely **regulates** nutrition and waste disposal

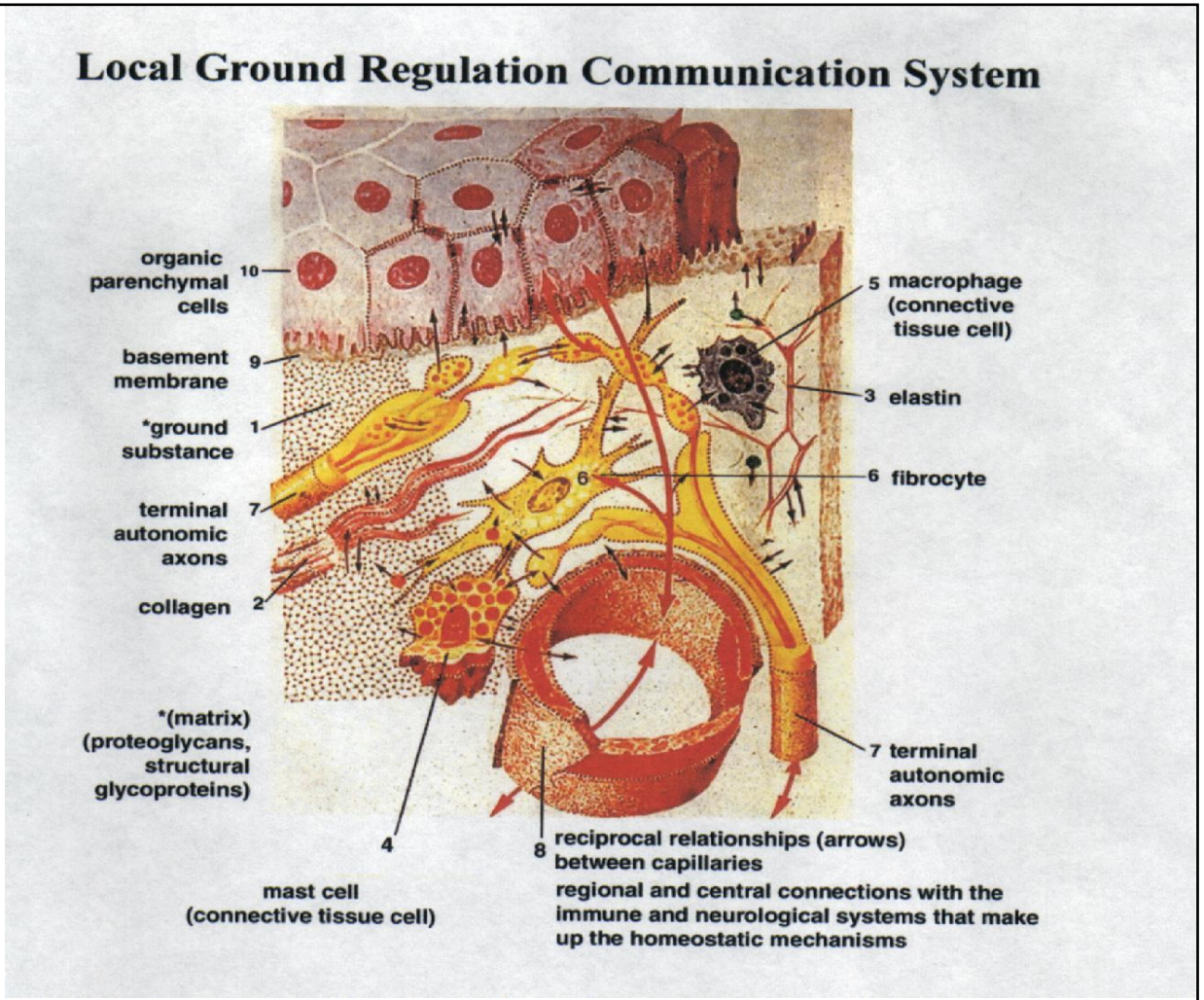
HOMEOSTATSIS-LOCAL GROUND REGULATION SYSTEM

GRS-CTM makes up 40% of the body's tissue surrounding every organ including fascia, tendons and ligaments.
CTM makes 87 % of the dermis and submucosal area

- **It has 3 types of cells-**
  Mast cells, Macrophages, Fibroblasts
- **PG-GAG-HA**
- **Collagen-elastin- Capillaries**
- **Sensory-autonomic nerve endings**
- **Basement membrane**

85% of the Sub-epithelial mast cells are in contact within 0.2 micron of sensory nerve fibers containing substance P, which constantly triggers neuro-immune response in many toxic-Chronic infection pt.

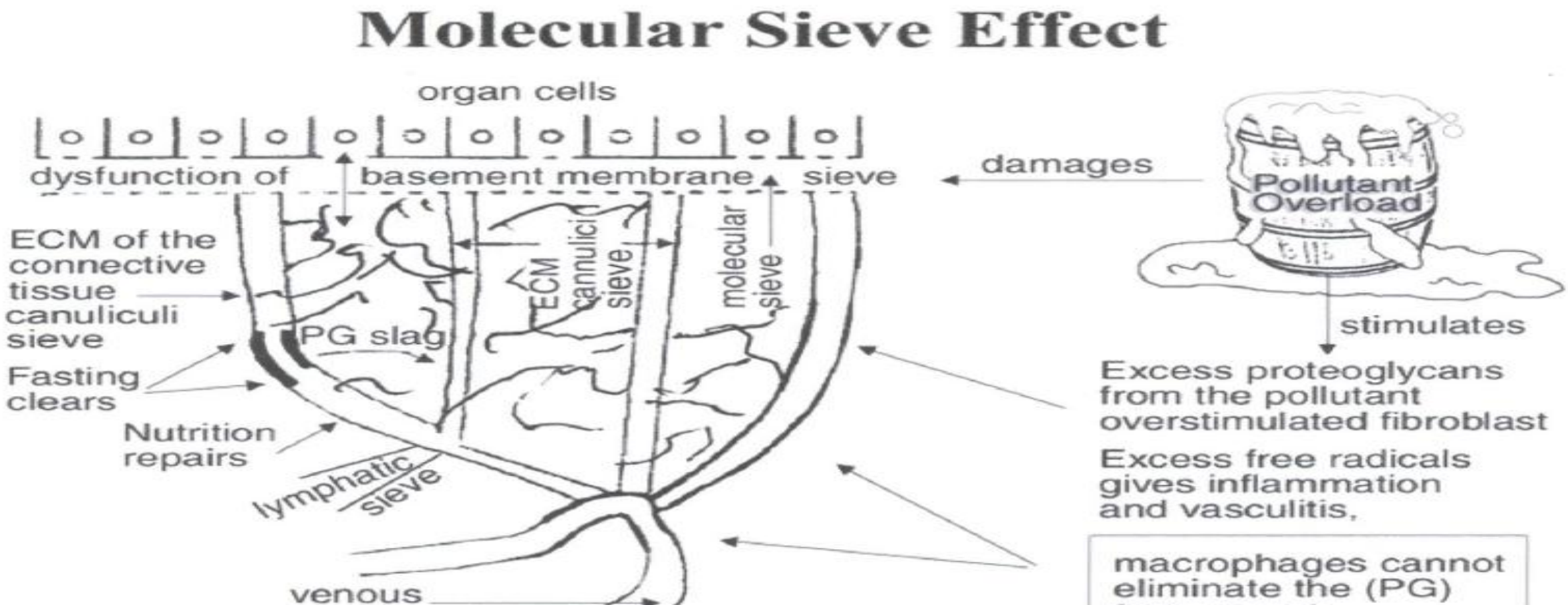
Thus Mast cell activation syndrome is not an isolated new syndrome but is body's response to increase in Total body burden. It does not need drug management in most cases



HOMEOSTASIS

Connective tissue matrix

Basement memb is rich in Vit C and Ca, quenches free radicals .Nutrients enter through BM but when pollutant damage BM organ malfunctions .Pollutant overload stimulates excessive formation of PGS, oxidative Free radicals that trigger Inflammation



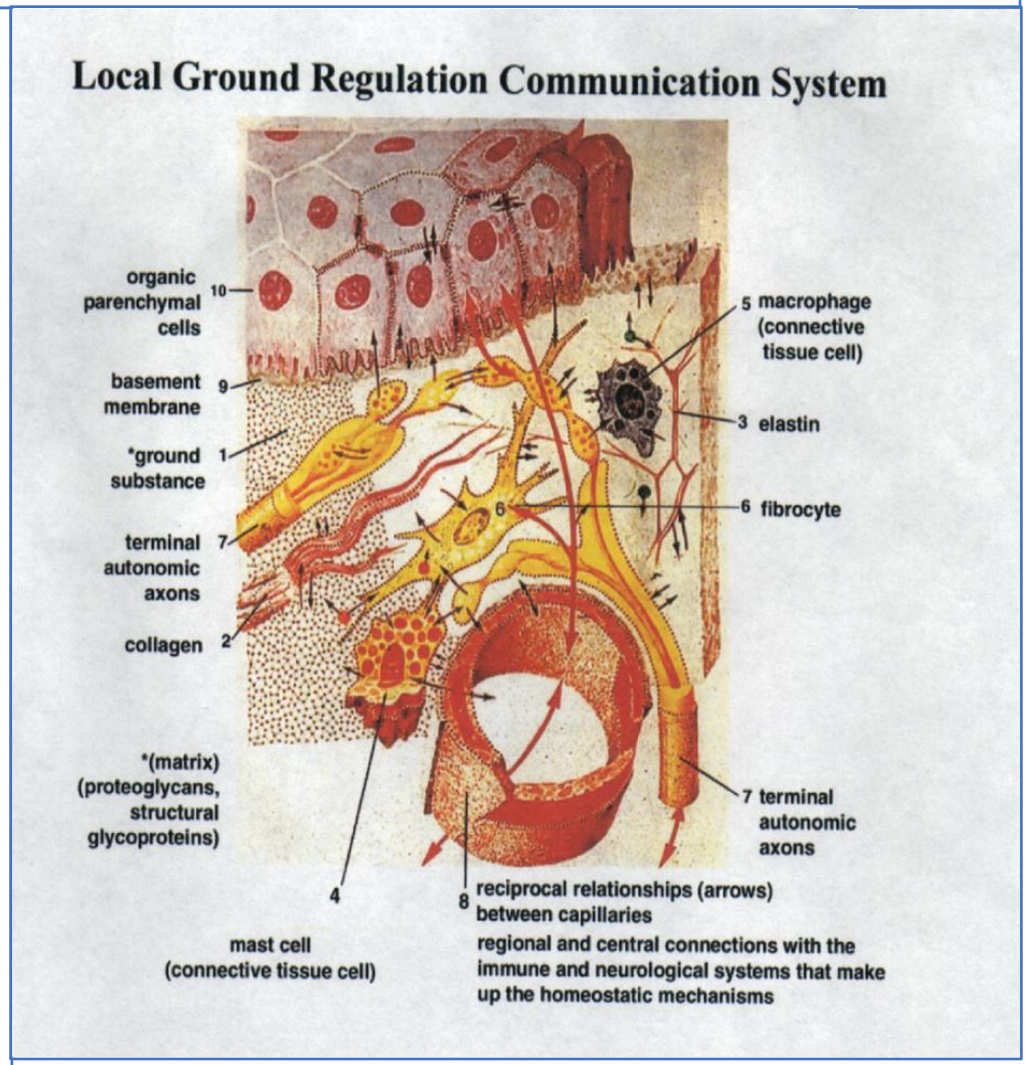
GRS-MATRIX-NEURO-VASCULAR-IMMUNE RESPONSE

- **Autonomic nerve ending share < .2 micron from the capillary & mast cells when stimulated massive**

release of histamine acetylcholine, norepinephrine, serotonin occurs

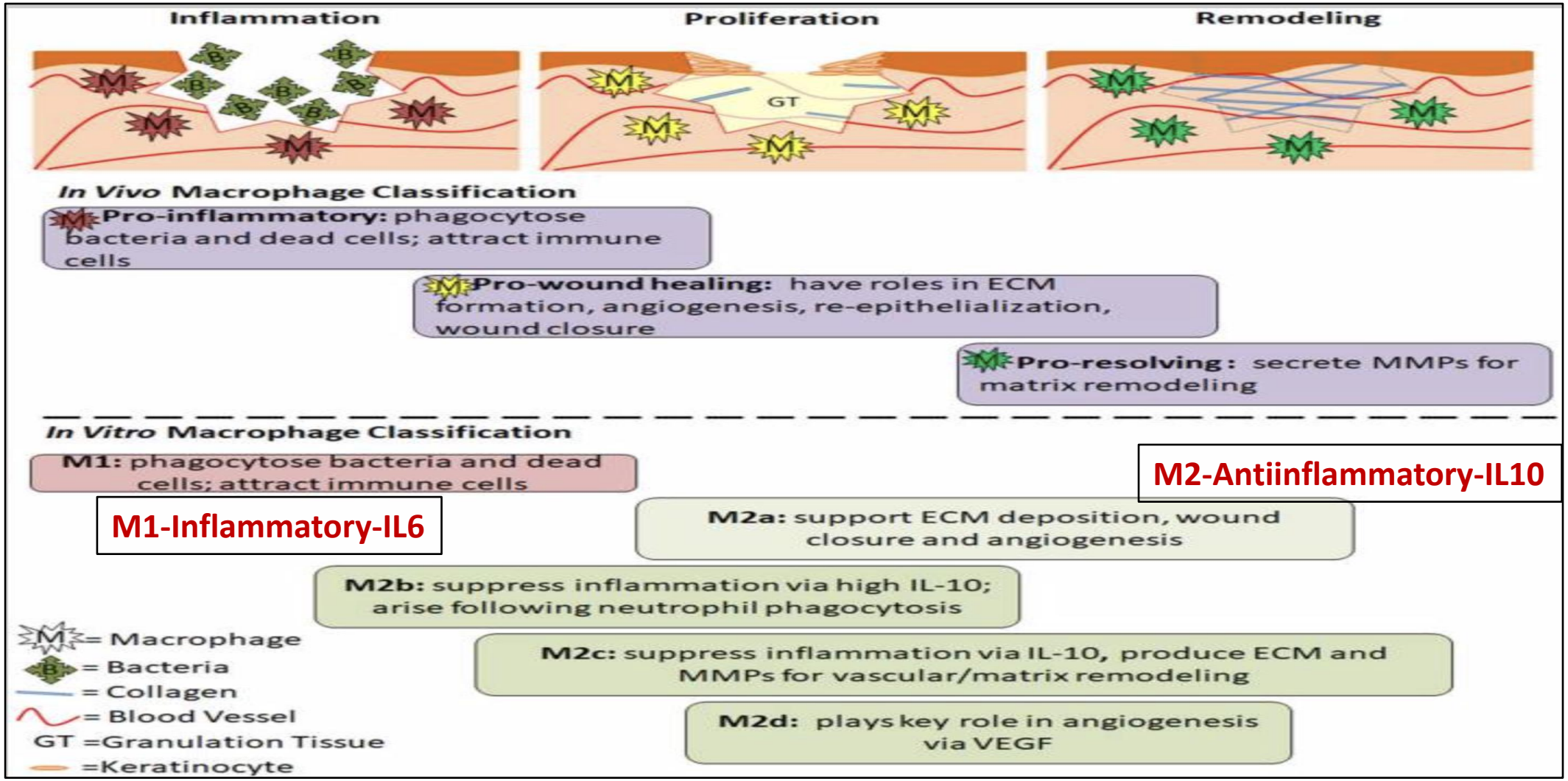
- sensory nerve fibers containing substance P are in contact within 0.2 micron of 85% of the Subepithelial mast cells. On activation of mast cells there is massive triggering of neuro, immune vascular system in C/S Pt.

- Vascular tree has only sympathetic innervation, has dual response, adrenergic & cholinergic.



Reversibility of CHR Degenerative Disease and Hypersensitivity
Volume 1 -WJ Rea-K Patel

THE MANY FACES OF MACROPHAGES



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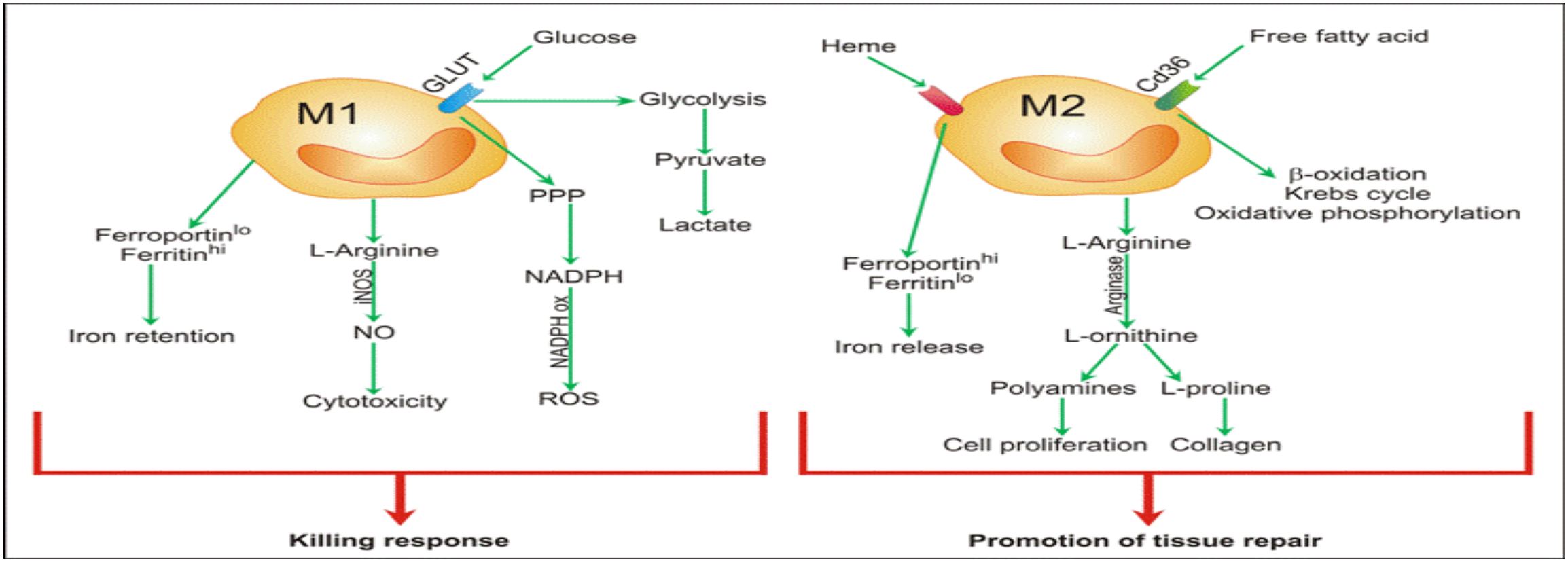
Macrophage-M1- M2



Left: classically activated macrophages **(M1) induce an aerobic glycolytic program that results in lactate production.** The **pentose phosphate pathway (PPP) provides ROS** for killing response. L-arginine is a substrate for **iNOS which produces NO, the major effector molecule in M1 macrophage-mediated cytotoxicity**.
Right: alternatively activated macrophages **(M2) trigger a metabolic program including β- oxidation, Krebs cycle and oxidative phosphorylation.**

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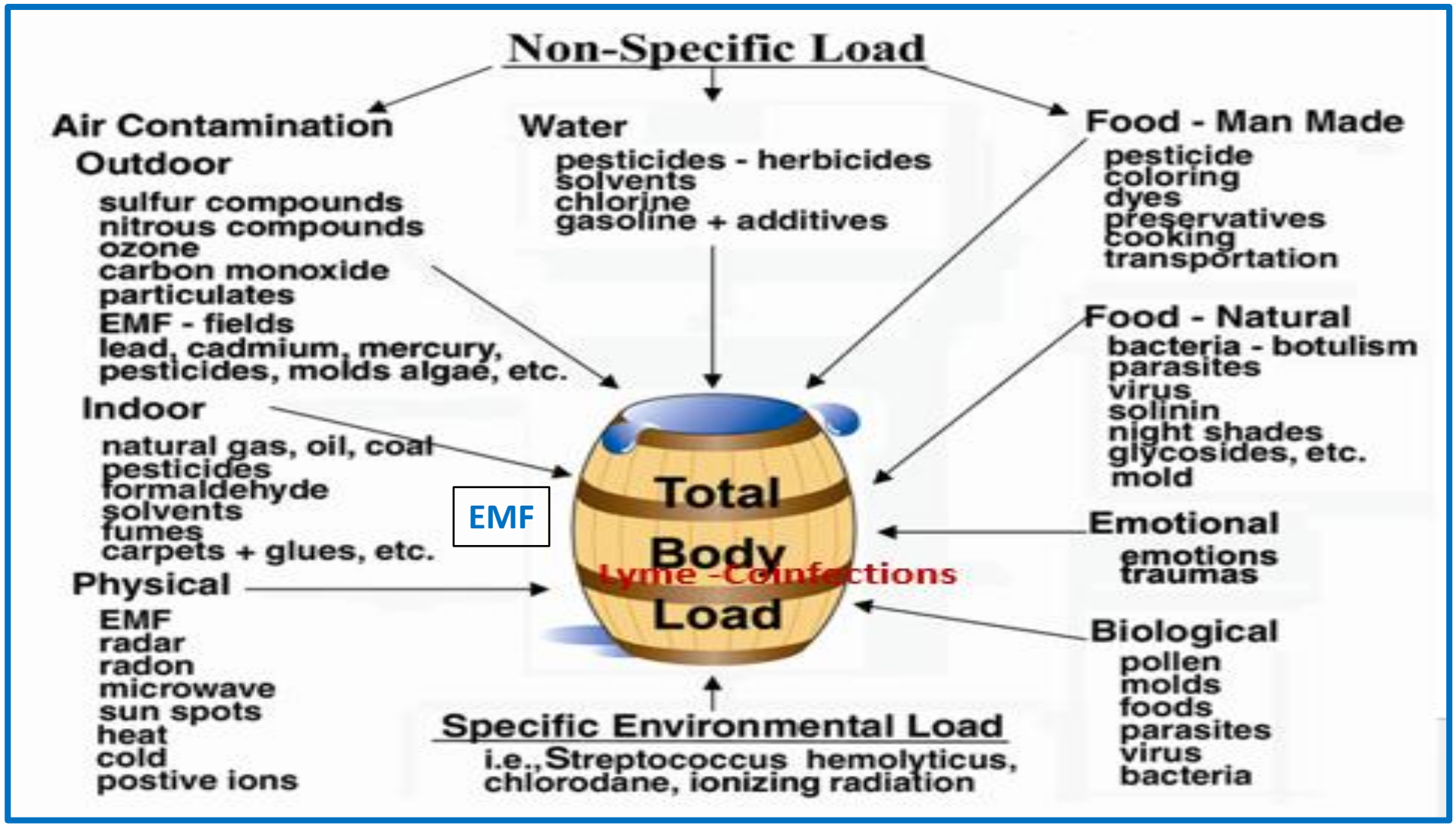
HOMEOSTASIS

TOTAL ENVIRONMENTAL POLLUTANT LOAD



TOTAL ENVIRONMENTAL POLLUTANT LOAD

"sandpile model" to demonstrate the cumulative impact
of environmental stressors on our bodies over time .
It is an elegant visual metaphor for how we are continuously refashioning ourselves at ever-higher levels of resilience and adaptive capacity –

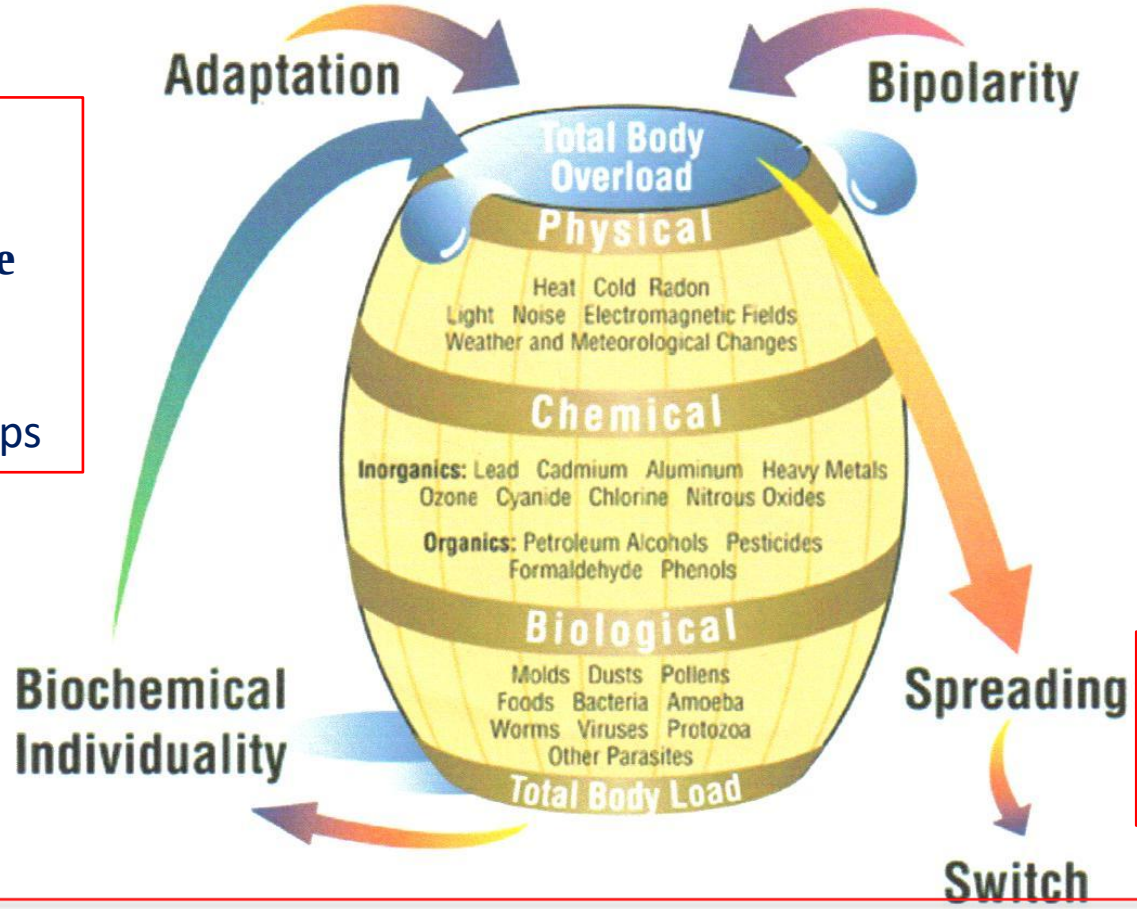
grains of sand being added to a gradually evolving sandpile are the occasion for both its disruption and its repair.

Not only do the grains of sand being added to precipitate partial collapse of the sandpile but also by the means sandpile will be repaired then be able to build itself back up – each time at a new level of homeostasis.

The system will therefore have been able not only to manage the impact of the stress but also to benefit from that stress.

Total Environmental Load-Body response

Adaptation is an **acute survival mechanism, get used to acute exposure Maladaptation-Masking** nutrient depletion and fixed name Disease develops



Bipolarity response Stimulatory and withdrawal response occurs in the different organs –system in response to noxious stimuli

Spreading occurs with increase in the Total Load,I nvolvement of one or more organs

Each individual is biochemically diff-Immune Detox Vit/MIN/Ao/Protein/CHO/fats

Specific Environmental Load i.e. Streptococcus hemolyticus, Borrelia Burgdorferi, chlorodane, ionizing radiation

Homeostasis -Dyshomeostasis

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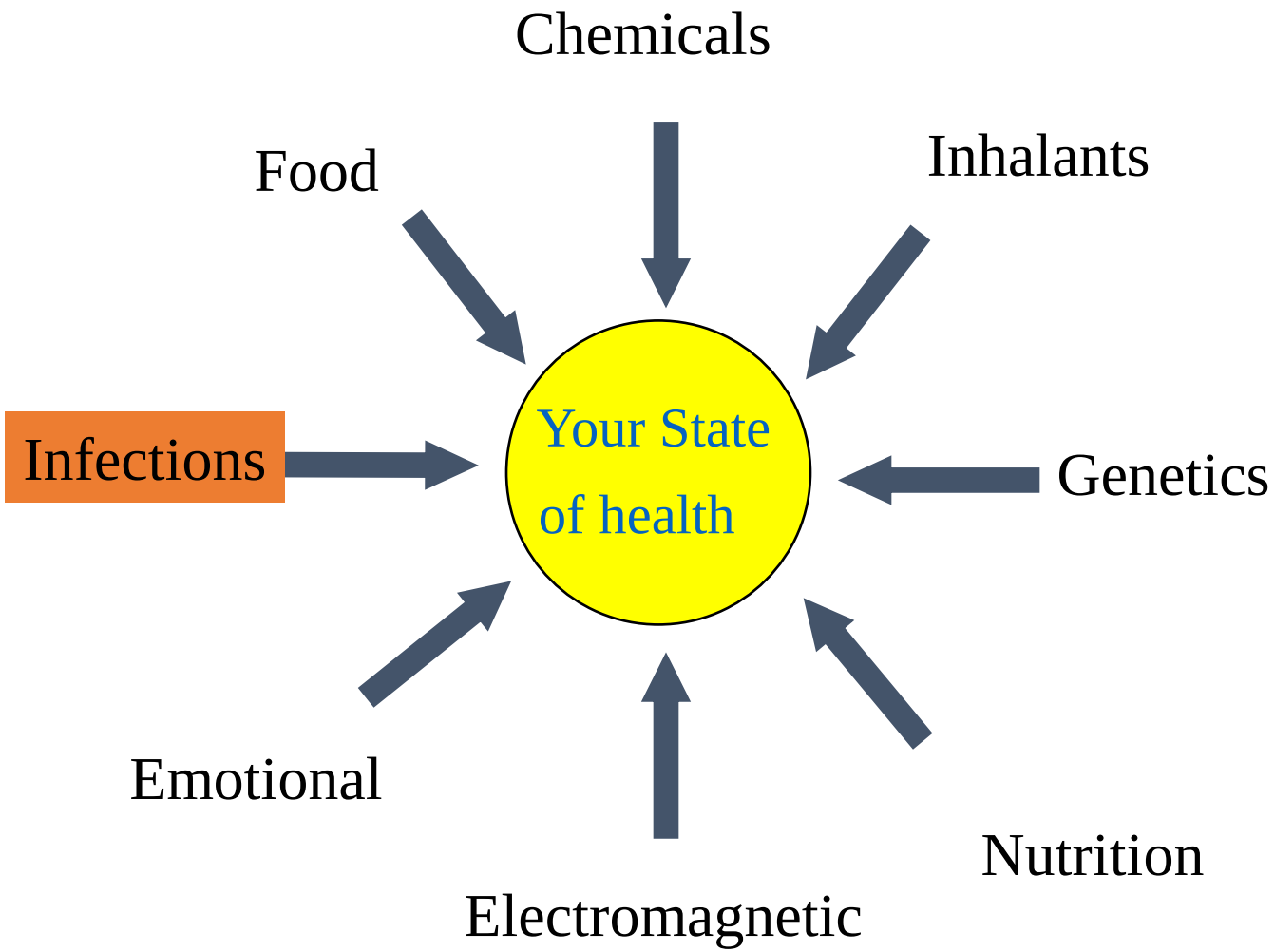
CHRONIC FATIGUE- TOTAL BODY BURDEN



GRS-Homeostasis-Total load

Total Body Pollutant Burden increases in the CT Matrix

When **local Matrix** and their cells

can not contain ++Total body burden

Regionalization of incitant occurs in the spinal cord and adjacent muscle mass, regional nerve, injury occurs –if not contained,

Secondary Amplification System is triggered:

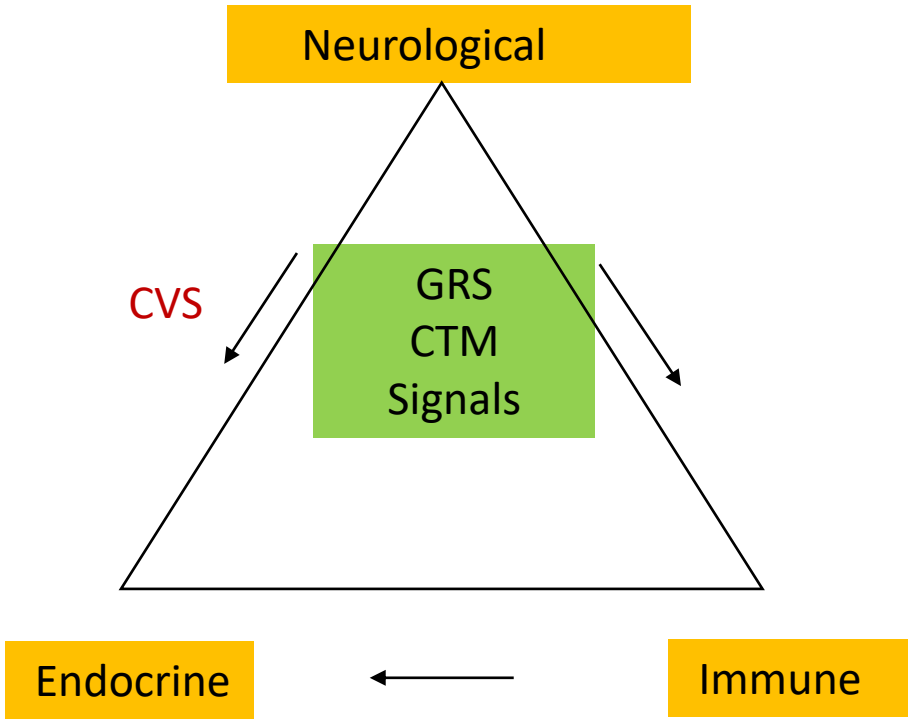
central alarm system in the brain gets activated

CNS activation involves

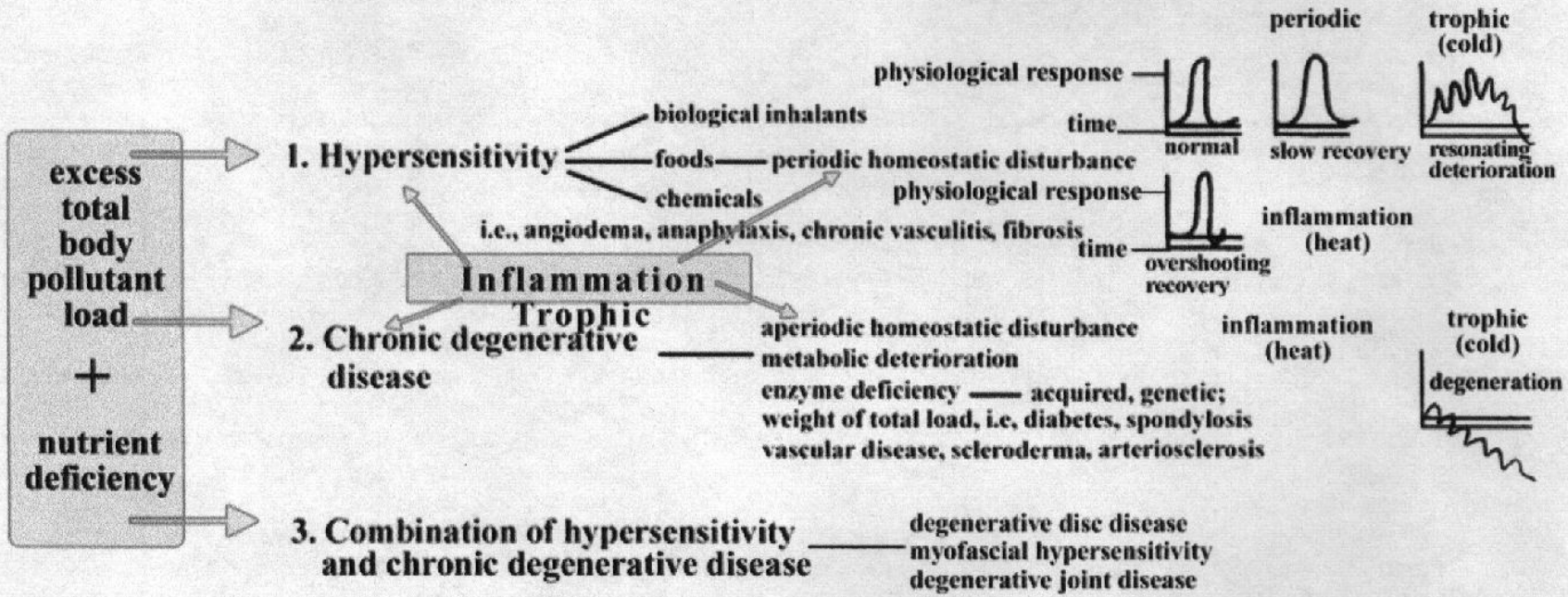
1. **reticular formation,**
2. **hypothalamus,**
3. **limbic system including Amygdala**
4. **Area postrema of fourth ventricle**
5. **Pineal gland**

All of these activate the rest of the body by alarm reaction through ANS and Adrenal gland

Secondary Amplification System Neuro- Immune- Endocrine axis



Types of Normal Physiologic Changes from the Dynamics of Homeostasis to the Pathological Changes of Dyshomeostasis



CHRONIC FATIGUE-MITOCHONDRIAL DYSFUNCTION

CHRONIC FATIGUE

=

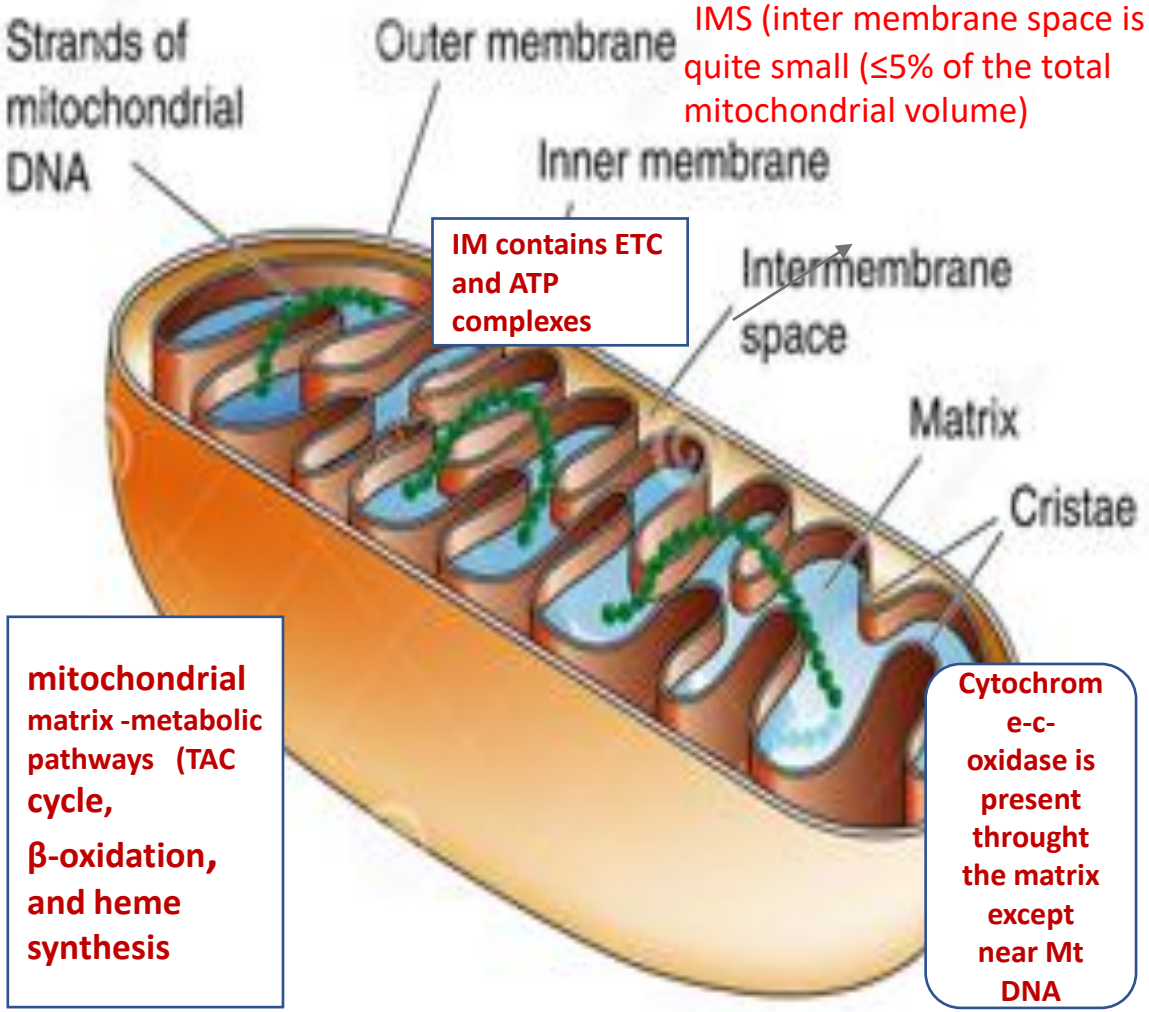
MITOCHONDRIAL DYSFUNCTION

MITOCHONDRIA

Mitochondria (MT) are

- **Dynamic double-membrane-bound organelles present in cytoplasm of every cell of the human body** except Red blood cells and skin(from few to none)
- Most cells have one to 2,500 MT **making up 1/5 th of the cell volume** germ cells have 100,000 and platelets have 2-5 MT
- semi-autonomous,
- **possess their own genome and**
- **the machinery for replication, transcription, and protein synthesis** ,
- contains ~30% of the cellular pool of *S*-adenosyl methionine (SAM) necessary for methylation

It produces energy, powers every cell in the body which is very critical to cell function

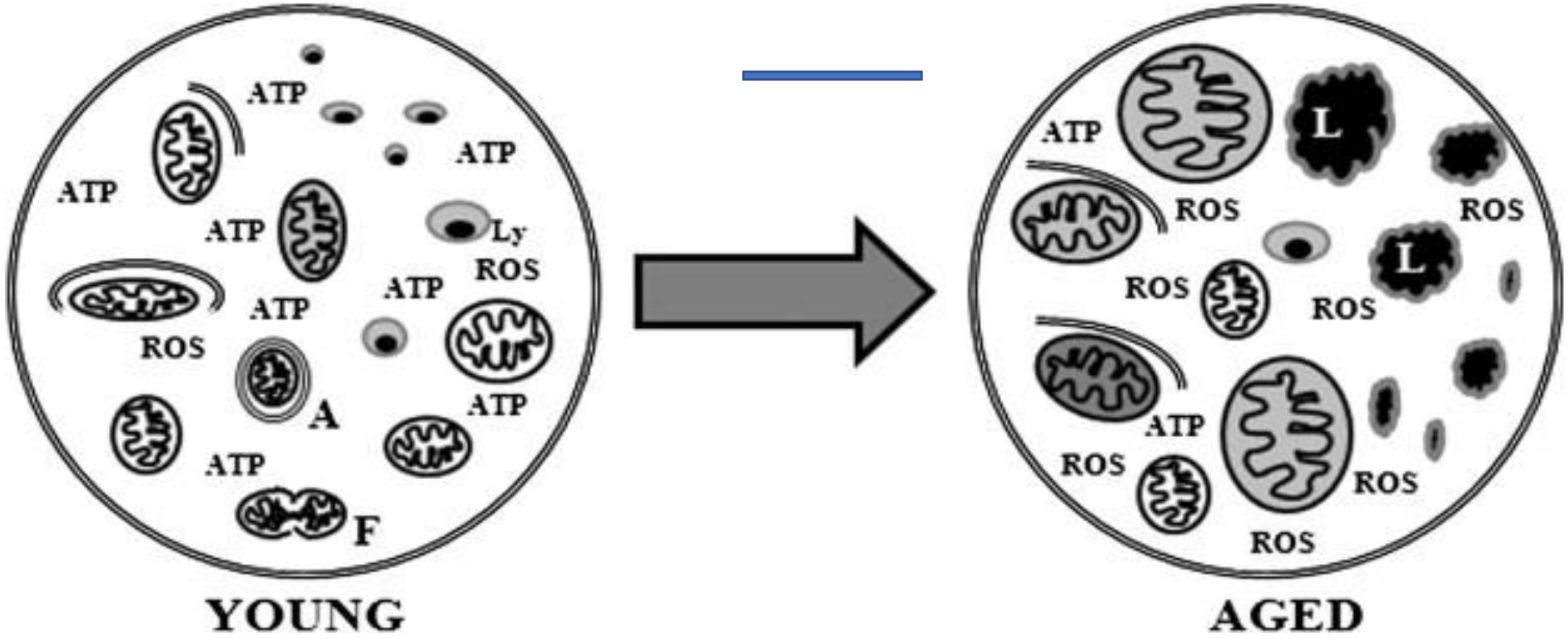


Wallace DC, Brown MD, and Lott MT. (1997) Mitochondrial genetics. In: Rimoin DI, Connor JM, et al. (eds.). Emory and Rimoin's Principles and Practice of Medical Genetics. London: Churchill Livingstone, 277–332; (Arch Biochem Biophys **343**: 201–206)

MITOCHONDRIA-YOUNG-OLD-Lyme

Mitochondria in young
8 ATP and 2 ROS

Mitochondria in aged-
M-Pneumoniae–
Chr Borrelliosis
2 ATP and 6 ROS



Large mitochondria are likely to be poorly phagocytosed, leading to further damage and enlargement

Damaged mitochondria and lipofuscin inclusions during Chronic persistent Lyme/chronic Infection

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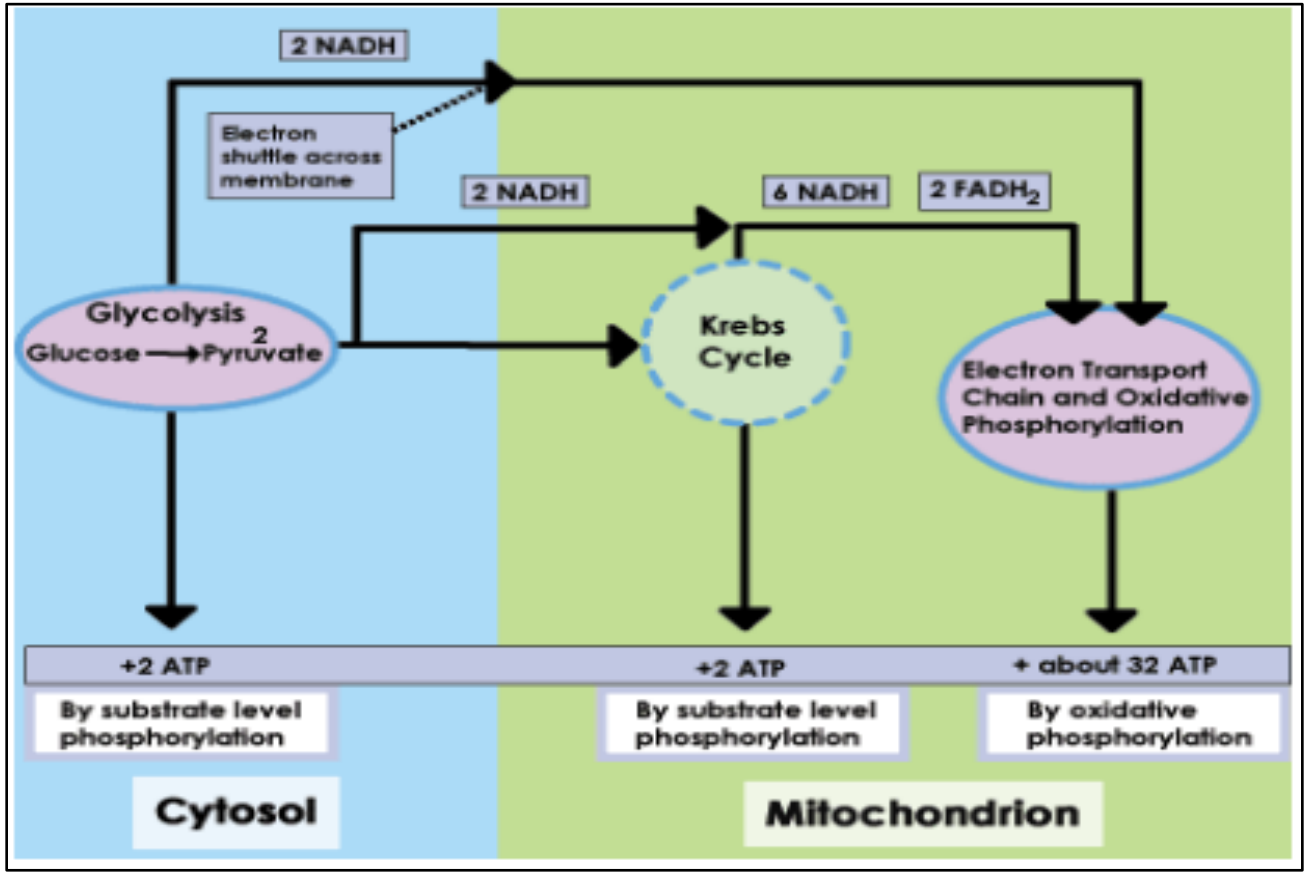
Mitochondria - Oxidative phosphorylation

Oxidative phosphorylation is very essential for more ATP formation



Oxidative phosphorylation occurs **in the matrix of mitochondria**

- MT Generates ATP by using O2 as a final electron acceptor.
- There are two main steps of oxidative phosphorylation electron Transfer Chemosmosis

Both of these processes use the movement of charged particles to transfer energy.

Glycolysis only produces 2 ATPs while oxidative phosphorylation produces 32 ATP when electrons are shuttled through the electron transfer chain by using oxygen as a final electron acceptor

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Int J Clin Exp Med. 2009; 2(1): 1–16.; Published online 2009 Jan 15., PMCID: PMC2680051, PMID: 19436827
Chronic fatigue syndrome and mitochondrial dysfunction Sarah Myhill,[1] Norman E. Booth,[2] and John McLaren-Howard[3]

Mitochondria- Electron Transport Chain

In Electron transport chain

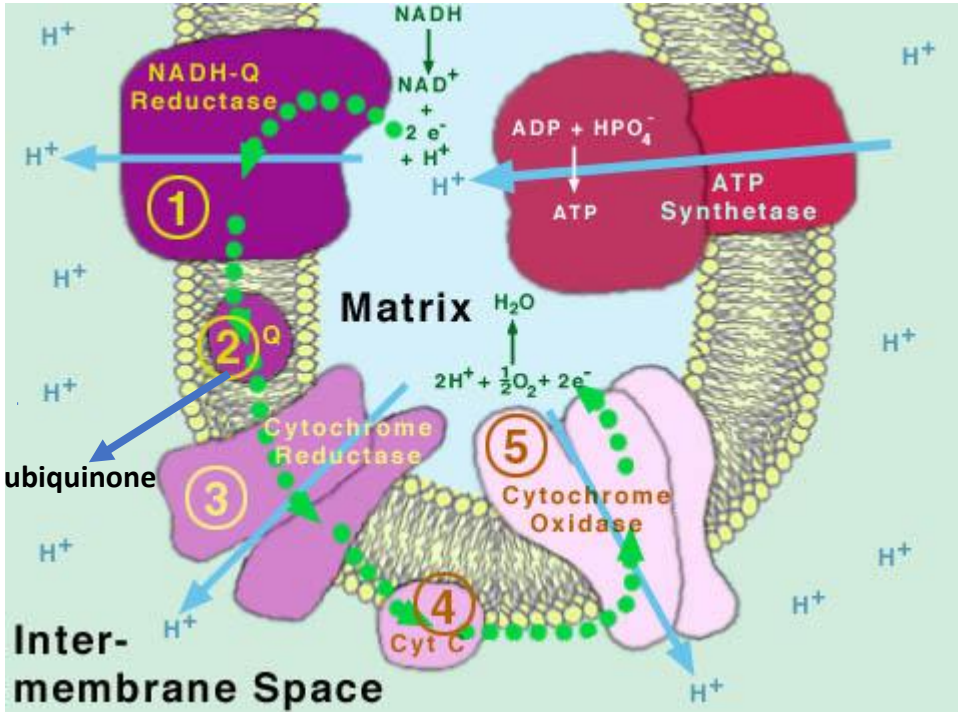
electrons move from Complex 1-NAD to O_2.

(path of the moving electrons is shown with the green dotted line)

Enzymes **involved in oxidative phosphorylation are NADH-Q reductase** (1), **cytochrome reductase** (3) , and **cytochrome oxidase** (5) **are electron carriers as well as proton pumps,** using the energy gained from each electron-transfer step to move protons (H^+) against a concentration gradient, from the Mitomatrix to the intermembrane space.

Ubiquinone (Q) (2) and **cytochrome c (Cyt C)** (4) are **mobile electron carriers.** All of the electron carriers are shown in purple, with lighter shades representing increasingly higher reduction potentials. **Ubiquinone, Q, is an organic molecule (not a protein) dissolved in the hydrophobic region of the inner membrane of the mitochondrion, moves freely within the inner membrane, by diffusion**. [Note that ubiquinone diffuses *from one region of the membrane to another (i.e.,within the walls of the membrane),* whereas polar molecules can diffuse *from one side of the membrane to the other side (i.e., across the membrane)* through channels.]

Enzymes involved in electron transport chain oxidative phosphorylation



PBM has direct effect at this level and increases ATP production

The electrons move from position 1-5 in an electron-transport chain- electrons move from one carrier to another until they are finally transferred to electron acceptor O_2

MITOCHONDRIAL Function

Function:

- **ATP generation occurs** by oxidation of food -releases chemical energy and free radicals as a byproduct

  (**only 4% of O2 we breath is used for M-Oxidation** and **90% of free radicals are generated by the process of oxidation in Mitochondria**)
- **cell metabolism, heat production**
- **calcium homeostasis-helps** to maintain proper concentration of Ca ions within the various compartments of the cell and stores Ca, **regulation of membrane potential**
- **Formation of steroids**, Testosterone, Estrogen and other hormones
- **Detoxify** Ammonia in Liver
- **Apoptosis- programmed cell death**
- **caloric restriction, increases MT efficiency**
- **High caloric** intake produces dysfunction and **increase in apoptosis**

A. Tzagoloff **Mitochondria** Plenum Press, New York (1982)

MITOCHONDRIAL-FUNCTION –PBM Rx

Photobiomodulation by monochromatic LED laser light 660-810Frequency-promotes normalization of MT-ETC

Mitochondria are principle photoreceptors of cell which accepts light and are activated by light

- PBM Increases mitochondria ATP production
- **PBM modulates the chronic stress,**
- **promote normalization of dysfunctional state,**
- **then upgrades normal function by having direct effect on CCO-Cytochrome-c-oxidase system of ETChain**
- Several transcription factors are regulated by LLLT-PBM
- Modulates Reactive Oxygen Species (ROS)

Timon Cheng-Yi Lin, South china Normal univ; International Journal of Photoenergy, Volume 2012,

CHRONIC FATIGUE - NAD

MITOCHONDRIA
&
SIRTUINS - NAD

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Timon Cheng-Yi Lin, South china Normal univ; International Journal of Photoenergy, Volume 2012,

CHRONIC FATIGUE–MT – SIRTUINS -NAD

- **Harvard studies – described close association between Sirtuin genes-Mitochondria and NAD (*nicotine adenine dinucleotide-Aminoacid*)**

  Sirtuin genes are found in every cell- cytoplasm, nucleus & mitochondria

  SIRT1 genes are responsible for critical biological functions like DNA expression, reduce aging process.

  SIRT1 gene induces the formation of new mitochondria only in the presence of NAD+

  NAD controls the health, numbers and function of the mitochondria.

  Mitochondria has a downstream effect on most of the cellular functions

Mitochondrial Biogenesis through Activation of Nuclear Signaling Proteins John E. Dominy and Pere Puigserver; pere puigserver@dfci.harvard.edu

CHRONIC FATIGUE –MT - SIRTUINS-NAD

NAD activates SIRT3, which **keeps mitochondria running smoothly**.

NAD^+, **an essential element of cellular metabolism and DNA damage repair.**

- **Reduced levels of NAD^+**
  - **reduces** sirtuin activities and
  - reduces the communication **between the cell nucleus** and **mitochondria at a cellular level and**
  - **adipose tissue at a systemic level.**
  - Dysfunction in **hypothalamus**- results in dysfunction of endocrine and nervous systems

Hypothalamus plays a big role in many essential functions of the body such as:

body temperature, thirst, appetite, weight control, emotions, sleep cycles, and a host of other functions-sxs common in CFS

Mitochondrial Biogenesis through Activation of Nuclear Signaling Proteins John E. Dominy and Pere Puigserver; pere_puigserver@dfci.harvard.edu

CHRONIC FATIGUE -CNS- ROS INDUCED DAMGE

The central nervous system (CNS) is very susceptible to ROS induced damage

because brain - MT have little resilience to minor illness and

minimal trauma triggers sudden massive- irreversible damage

(1) CNS -high consumption of 02, 20% of body's 02 consumption

(2) It has **high levels of membrane polyunsaturated fatty acids** **susceptible to free radical damage,**

(3) CNS is **relatively deficient in oxidative defenses** **(poor CAT activity and moderate SOD and GPx activities**

(4) some regions of the CNS has higher content of iron and ascorbate, thus through the Fenton/Haber Weiss reaction generates more ROS

Chronic- Lyme patients first develop cognitive dysfunction and

then loss of cognitive function

If ongoing damage is not controlled may develop neurodegenerative disorder-Dementia

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R. Rizzuto, P. Bernardi, T. Pozzan Mitochondria as all-round players of the calcium gameJ. Physiol., 529 (2000), pp. 37-47

MITOCHONDRIA-Oxidative Stress

- **Environmental toxins**, **Viral infections, Bacterial infection-toxins generate** reactive oxygen species **(ROS)** and reactive nitrogen species**(RNS-no/oono)** which **result in oxidative stress and free radical damage**
- Major ROS are byproducts of aerobic metabolism- are superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl free radical ($OH^{\bullet}$), peroxynitrite ($ONOO^-$)
- ROS cause **serious damage to enzyme complexes in** lipid containing inner mito matrix where Oxidative Phosphorylation occurs and outer membranes of MT.
- Oxidation leads to a **loss of their biological properties** and eventually to a cell death
- MT-ROS also act as **signal messengers** and modify operation of many enzymes in different cell compartments
- MT-ROS are important in execution of programmed cell death

Arch Biochem Biophys. 2016 Apr 1;595:68-71. doi: 10.1016/j.abb.2015.11.028

MITOCHONDRIA as a SIGNALING MOLECULE

Many function of MT :

- **ATP production.**
- **MT Act as a signaling molecule directing different cells to do different tasks.**
- **Neurogenesis signaling**
- **stress signaling induces the overproduction of osteoclasts, cells that nibble away the bone- osteoporosis in Lyme-Chr inf patients**

Arch Biochem Biophys. 2016 Apr 1;595:68-71. doi: 10.1016/j.abb.2015.11.028

MITOCHONDRIA AND CHRONIC-LYME DISEASE

During progression of –Chronic fatigue in Chronic Lyme or Chronic infection or chemical sensitivity

MT goes through profound alterations in function that lead to :

- **Reduced generation of adenosine triphosphate (ATP)-Chronic fatigue** and
- **Enhanced production** of reactive oxygen species **(ROS) and nitrogen species.**
- **Loss of calcium (Ca^{2+}) buffering capacity**, initiate cascade of deleterious events within the cell.

Damaged mitochondria release several pro-apoptotic proteins that translocate into the nucleus to induce DNA fragmentation and cell death

These alterations in MT contribute to cell degeneration and death.

some mitochondrial, pro-apoptotic proteins translocate into the nucleus to induce deoxyribonucleic acid (DNA) fragmentation. Altogether, these mitochondrial alterations contribute to cell degeneration and death. AIF, apoptosis-inducing factor; APAF-1, protease-activating factor 1; dATP, 2′-deoxyadenosine 5′-triphosphate; ROS, reactive oxygen species; ADP, adenosine diphosphate; H^+, protons; H_2O, water; Pi, inorganic phosphate; O_2, molecular oxygen; $O_2^{\cdot-}$, superoxide anion radical.

MITOCHONDRIA-Antioxidant system

Mitochondria has First and Second line antioxidant defense systems

- First line defense:

  Enzymatic antioxidant system that directly react with ROS and decrease ROS production

  such as superoxide dismutase(SOD), catalase, glutathione peroxidase(GPX) and glutathione reductase, **SOD1 (Cu-Zn-SOD) is found in the mitochondrial intermembrane space** and when **catalase, SOD1 AND SOD2 as well as GPX occurs Neuro-inflammation in the brain results**

- Second line defense:

  Non-enzymatic antioxidants that **remove ROS** and other oxygen derivatives like **vitamins A, C and E and polyphenol, GSH antioxidants**

- Vitamin E plays an important role in cellular defense against lipid peroxidation of cell membrane by free radicals

MITOCHONDRIA - Glutathione

- Glutathione is the most abundant thiol in cells.
- **MT does not synthesize glutathione**
- Glutathione is transported from the cytoplasm to the mitochondria by a high-affinity, low capacity transporter - the dicarboxylate and 2-oxoglutarate(Alpha ketoglutarate)
- **The MT glutathione pool amounts to approximately 15% of total cellular glutathione** but the MT glutathione pool **plays a critical role in cell protection**.
- **Vitamin D act as catalyst for glutathione production**

Therapeutics; Proc. Natl. Acad. Sci. U. S. A., 82 (1985), pp. 4668–4672J; Pharmacol. Exp. Ther., 285 (1998), pp. 608–618; J. Biol. Chem., 257 (1982), pp. 3747–3753

MITOCHONDRIA - Glutathione

- **Glutathione is primary determinant of the cellular redox environment,**
- **MT Glutathione is an in antioxidant and also antitoxin, augment Detoxification of xenobiotic- Biotoxins**
- **Efficient free radical scavenger**
- **Glutathione is intimately related to the regulation of the nitric oxide cycle.**
- Nitric Oxide is very important in increasing stem cell output from the bone marrow,

  DNA synthesis and repair,

  protein synthesis,

  prostaglandin synthesis,

  amino acid transport, and enzyme activation.
- Thus, every system in the body can be affected by the state of the glutathione system, especially the immune system, the nervous system, the gastrointestinal system and the lungs
- **Overproduction of ROS and oxidized levels of glutathione result in**

  MT dysfunction and diseases

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Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease-Volume 1762, Issue 2, February 2006, Pages 256–265-Mitochondria in Diseases and Therapeutics; Proc. Natl. Acad. Sci. U. S. A., 82 (1985), pp. 4668–4672J; Pharmacol. Exp. Ther., 285 (1998), pp. 608–618; J. Biol. Chem., 257 (1982), pp. 3747–3753Arch Biochem Biophys. 2016 Apr 1;595:68-71. doi: 10.1016/j.abb.2015.11.028

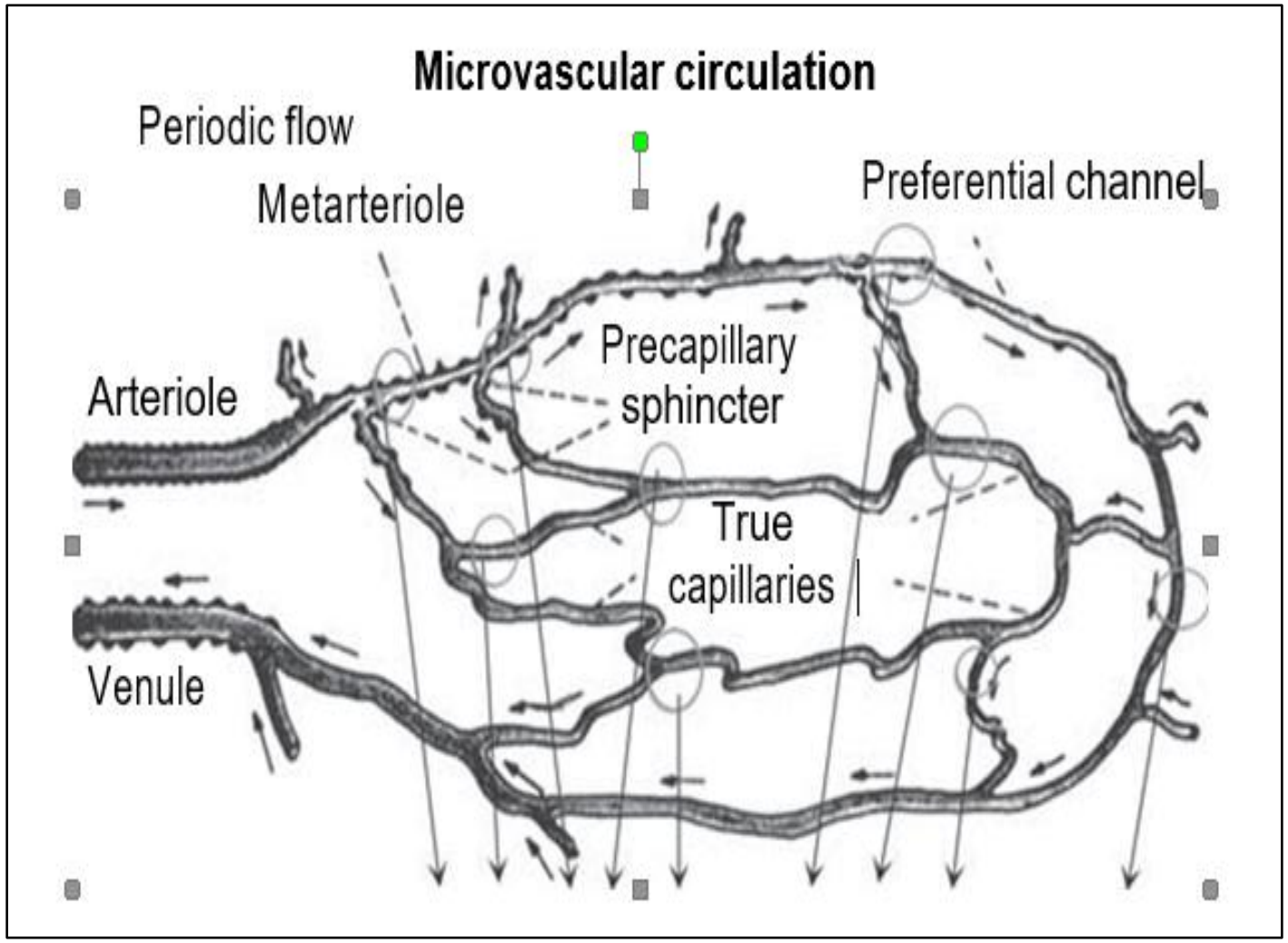
Microcirculation in Lyme Disease

CHRONIC FATIGUE
&-
Microcirculation

MITOCHONDRIAL DYSFUNCTION
Microcirculation in chronic Infection

In microcirculation

- **Blood does not flow continuously through capillaries.**
- **Flow is intermittent, turning on and off every few seconds or minutes. It is like pulse,**
- **Intermittent flow is physiologic and enhances oxygen and nutrient extraction.**
- **But communication appears to flow constantly unimpaired or augmented by this phenomenon.**



MITOCHONDRIAL DYSFUNCTION- Microcirculation in Chronic Fatigue

Exposures to Toxins and Toxic substances such as Bio-toxins, mycotoxins, lead, mercury, hydrocarbons and pesticides etc disturb microcirculation

- **Alters capillary sphincter mechanism**
- **Thus shunting of blood from arterioles to venules occur, escaping capillary perfusion. Results in high PVO2- venous 02 concentration**
- **Cellular Oxygen extraction becomes minimal, thus ++ venous O2 (PVo2) results**
- **Then Local tissue hypoxia develops--> local acidosis induces release of Free metals -Cu, Fe from the transporting proteins, Free metals promotes ROS production and activate the signal transduction system.**
- **This results in altered MT O2 diffusion, inefficient oxidative phosphorylation- impaired ATP generation**

Inability to extract sufficient oxygen results in inefficient detoxification. Impaired detoxification occurs in all pathways:

Impaired Oxidation by cytochrome C oxidase systems- Low ATP generation- Fatigue results

CHRONIC FATIGUE
IMMUNE DYSFUNCTION

CHRONIC FATIGUE
&-
IMMUNE DYSFUNCTION

MYCOPLASMA– IMMUNOGLOBULIN-IGM-IGG RESPONSE

- IgM is the first antibody secreted during an immune response. It is important in controlling bacteremia and in activating the classical complement pathway.
- switch to IgG occurs soon after an infection in few weeks,
- There are four subtypes of IgG. IgG1-4 work together effectively to clear most pathogens . **(If one is deficient in IgG does not mount this secondary IgG response)**
- However in some cases B. burgdorferi and Mycoplasma infection coexist, **serum IgM levels remain high throughout the infection-suggestive of chronic persistent infection**.
- The strong and ongoing production of IgM is predominant only in chronically ill patients who are immune challenged

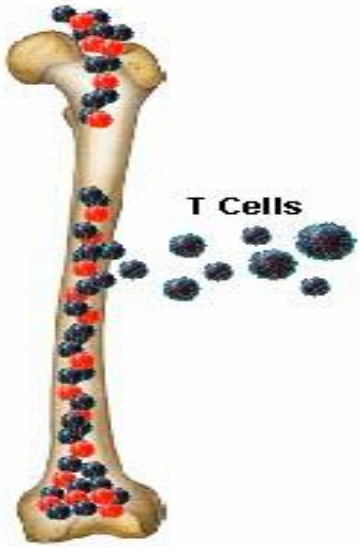
EHC-Buffalo

Journal of Proteomics Volume 199, 15 May 2019, Pages 67-76

DEVELOPMENT OF IMMUNE SYSTEM

The immune system is forever evolving through the functional plasticity of T cells.
It is unlikely that just a few terminally differentiated effector T-cell subsets (Th1, Th2, TReg, Th-17, Th-23) with fixed phenotypes could provide immunity against the multitude of viruses, bacteria, parasites and fungi that invade and infect the host.

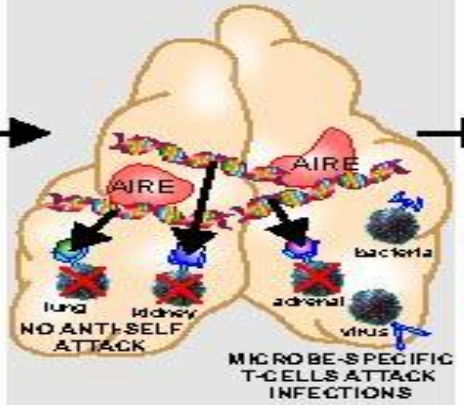
BIRTH



Bone marrow: where T cells are born

KINDERGARTEN

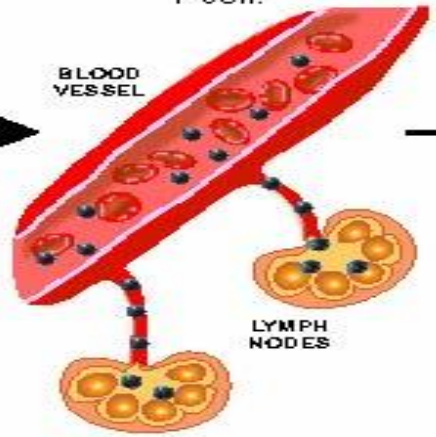
This is where T cells receive their primary education. Here they have very few distinct features and have limited functional characteristics.



Thymus

ELEMENTARY SCHOOL

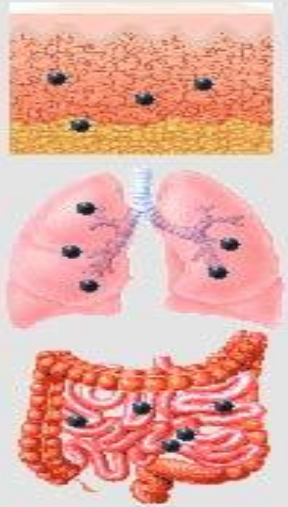
The naive and inexperienced T cells enter the systemic circulation and move into the lymph nodes, where they receive their secondary education and encounter their cognate antigen. This interaction imprints a specific cytokine on the activated T cell.



Systemic circulation and lymph nodes

HIGH SCHOOL

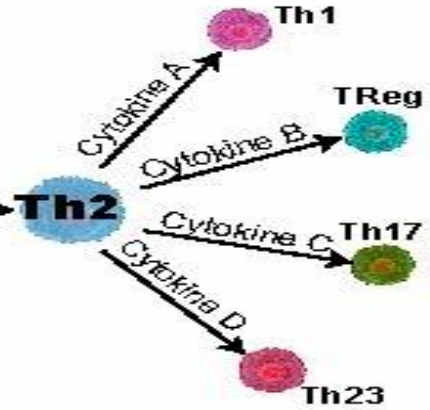
The cells enter the real world of their target organs, where they are exposed to the local cytokine environment. This drives them to a final effector phenotype, a vital factor for successful host defense.



Target organs: skin, lungs, intestines

UNIVERSITY

Depending on the cytokine environment and interconversation between T-cell subsets, differentiated T cells are able to convert from one phenotype to another.



Phenotype plasticity by conversion from one phenotype to another

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HOW TO ASSESS THE IMMUNE SYSTEM

Humoral Immune Response

- **Secretory IgA**
- **Immunoglobulin G (IgG)**
- **Immunoglobulin M (IgM)**
- **Immunoglobulin A (IgA)**
- **Immunoglobulin E (IgE)**
- **IgG Subclasses**
- **Complement Cascade**
- **Immune Complexes**
- **Cytokine Level**

Cell Mediated Immunity

- Macrophages
- T-Cell
- B-Cell
- Helper Cell
- Suppressor Cell
- Natural Killer Cell
- Memory Lymphocytes
- Cytokine Production
- T-Reg

CELLULAR IMMUNE SYSYTEM

- High CD4/CD8 or helper suppressor ratio - a marker of immune activation and autoimmunity - is detected in patients with heavy metal exposure
- Low CD4/CD8 - a marker of immune deficiency - is detected in patients with exposure to pesticides and other xenobiotics
- High NK cell count is an indication of viral infection or early stages of cancer

CHRONIC LYME - PERSISTENCE OF INFECTION

Pathophysiology: Lyme

- Borrelia burgdorferi has the capacity to evade and suppress the immune system. In pathophysiological processes, this can result in persistent infection, persistent inflammation with cytokine effects without adaptive immunity, sometimes accompanied with autoimmune reactions.

CHRONIC LYME DISEASE is similar to Chronic mycoplasma infection
BACTERIA PERSIST AS
Bb HAS THE CAPACITY TO

- **EVADE**
- **SUPPRESS IMMUNE** SYSTEM
- **POOR ADAPTIVE IMMUNITY**
- Thus it results in
  - PERSISTENT INFECTION,
  - PERSISTENT INFLAMMATION
  - CYTOKINE EFFECT
  - Poor adaptive response
  - Autoimmune activation

CHRONIC FATIGUE- CHRONIC LYME DISEASE

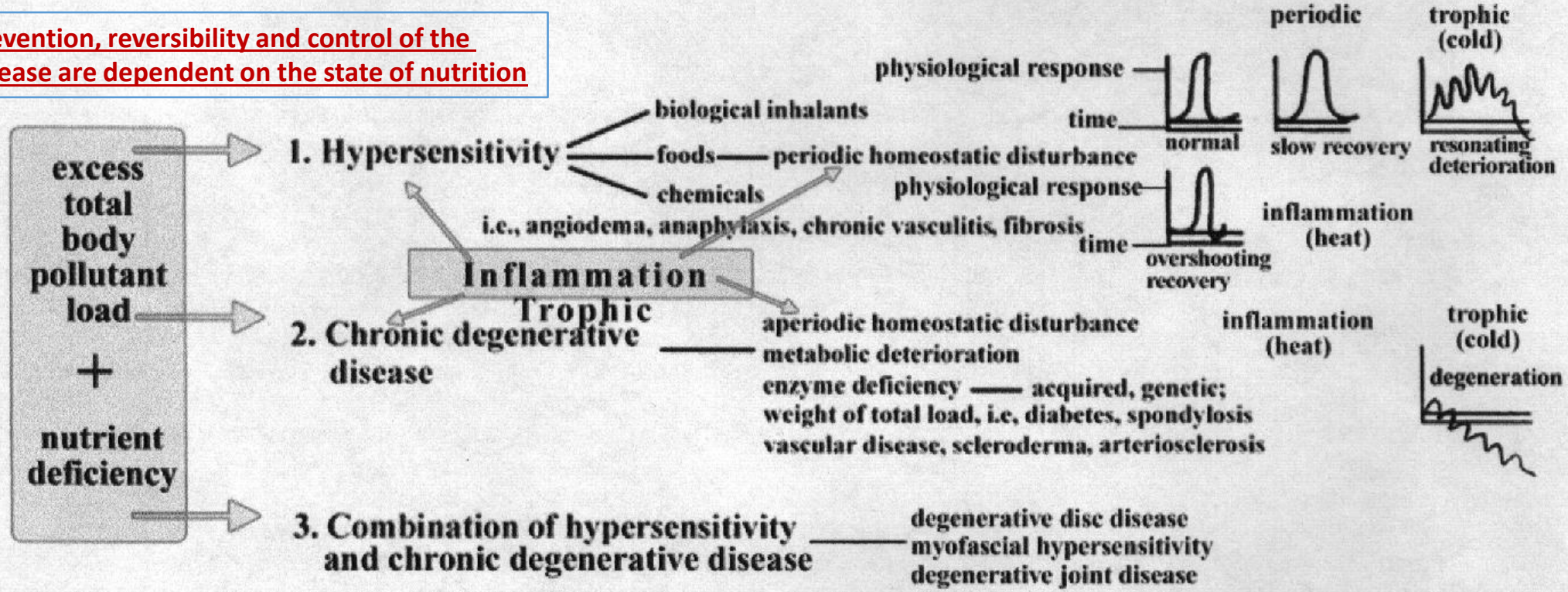
INFLAMMATION

INFLAMMATION

Dynamic nutritional status is essential for the proper
Homeodynamic response in presence of excess Total body pollutant load

Types of Normal Physiologic Changes from the Dynamics of Homeostasis to the Pathological Changes of Dyshomeostasis

Prevention, reversibility and control of the disease are dependent on the state of nutrition



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Reversibility of Chronic Degenerative Disease and Chemical sensitivity Volume 1 -WJ Rea-K Patel

Chronic Infection– NEUROINFLAMMATION

Chronic Infection triggers oxidative stress induced

NEURO inflammation

Hallmark of neurodegenerative diseases

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M. Simkó, “Cell type specific redox status is responsible for diverse electromagnetic field effects,” *Current Medicinal Chemistry*, vol. 14, no. 10, pp. 1141–1152, 2007.

CHRONIC INFECTION -INFLAMMATION OF BRAIN

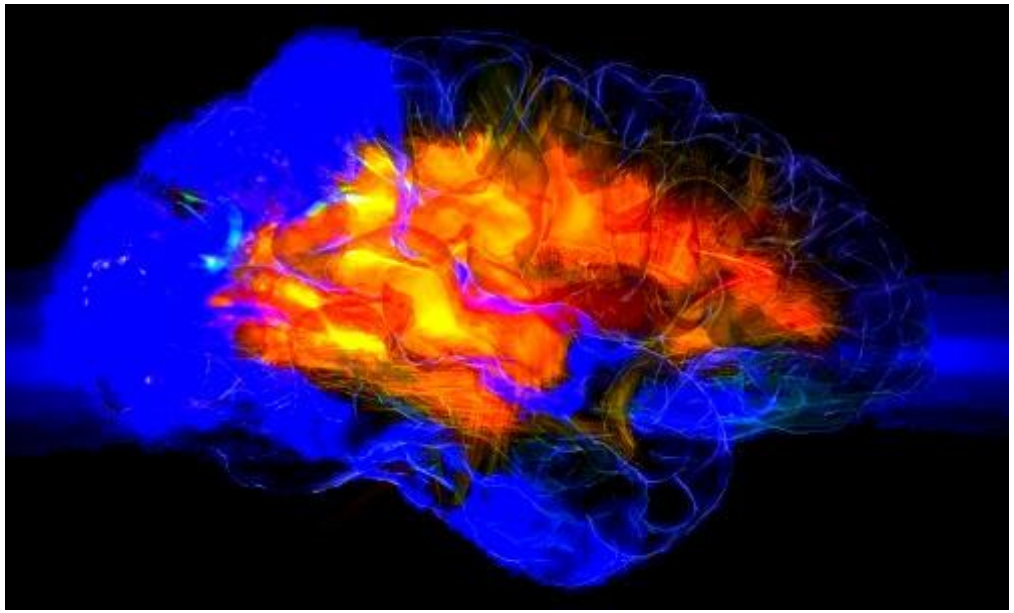

Image courtesy Glass Brain Project, Adam Gazzaley, UCSF

Limbic system is on fire
HPA axis is on fire

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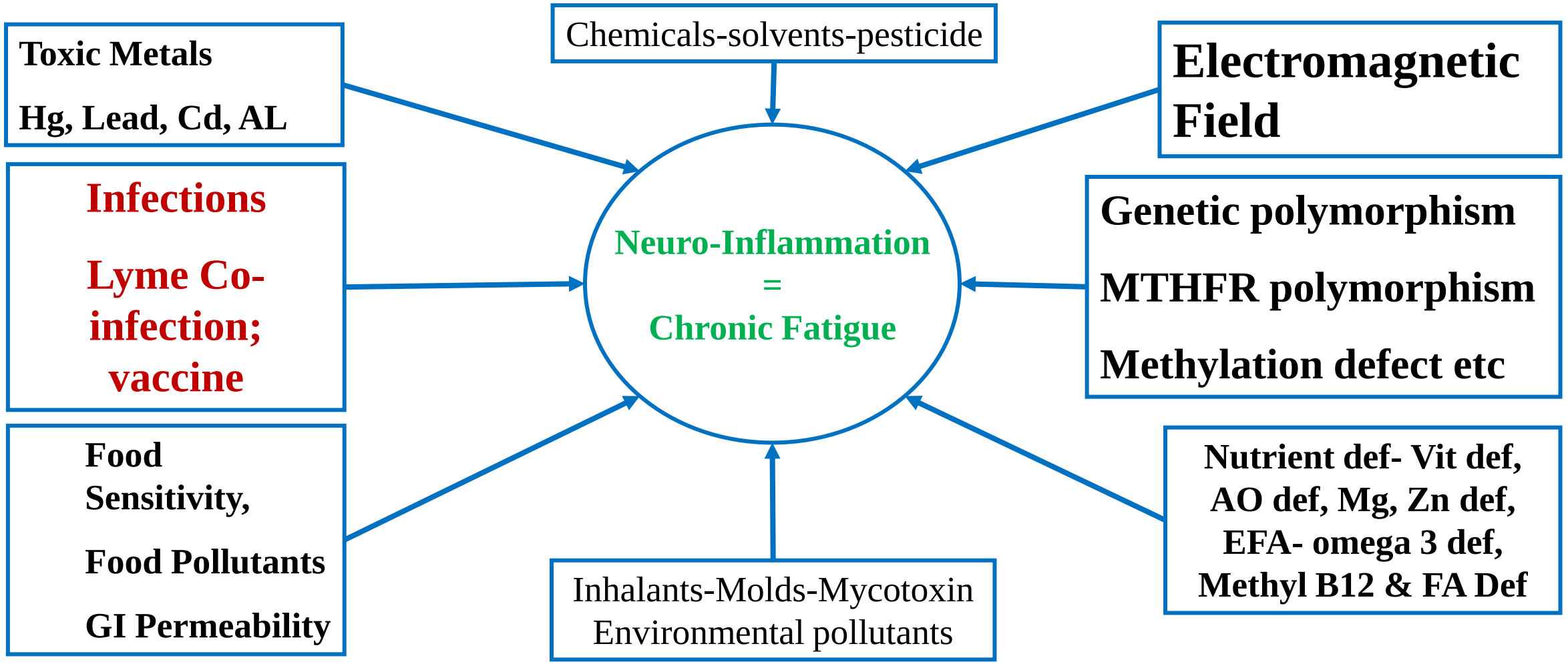
"Psychiatric and neurodevelopmental disorders are being thought of more and more as systemic illnesses in which inflammation is involved," Eric Hollander, of New York City's Albert Einstein College of Medicine.

TOTAL BODY POLLUTANT LOAD

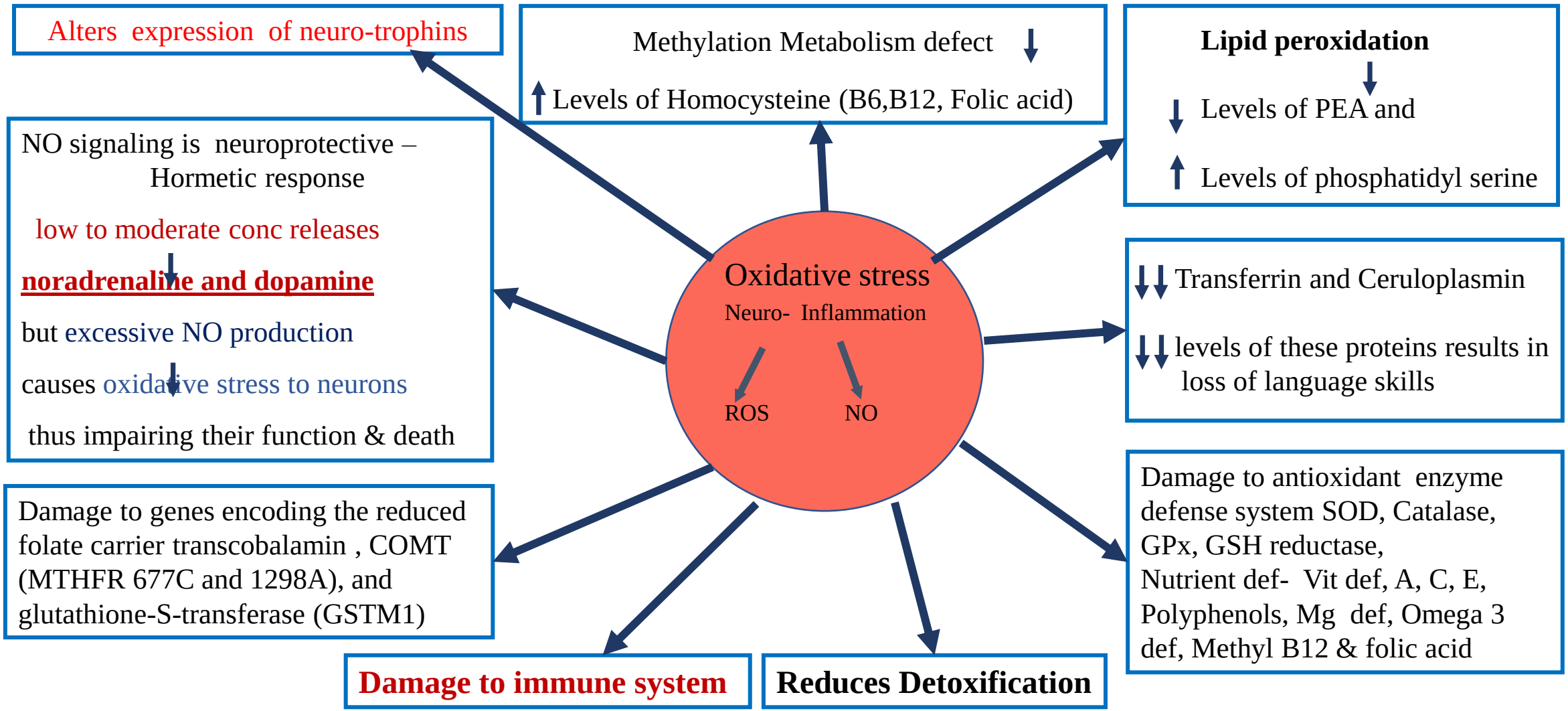
NEURO INFLAMMATION –

N.I is a multifactorial condition



Neuroinflammation is associated with Impaired repair processes and regeneration

TOTAL BODY LOAD- OXIDATIVE STRESS MITOCHONDRIAL DYSFUNCTION-Lyme



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http://www.autismcalciumchannelopathy.com/Oxidative_Stress.html#

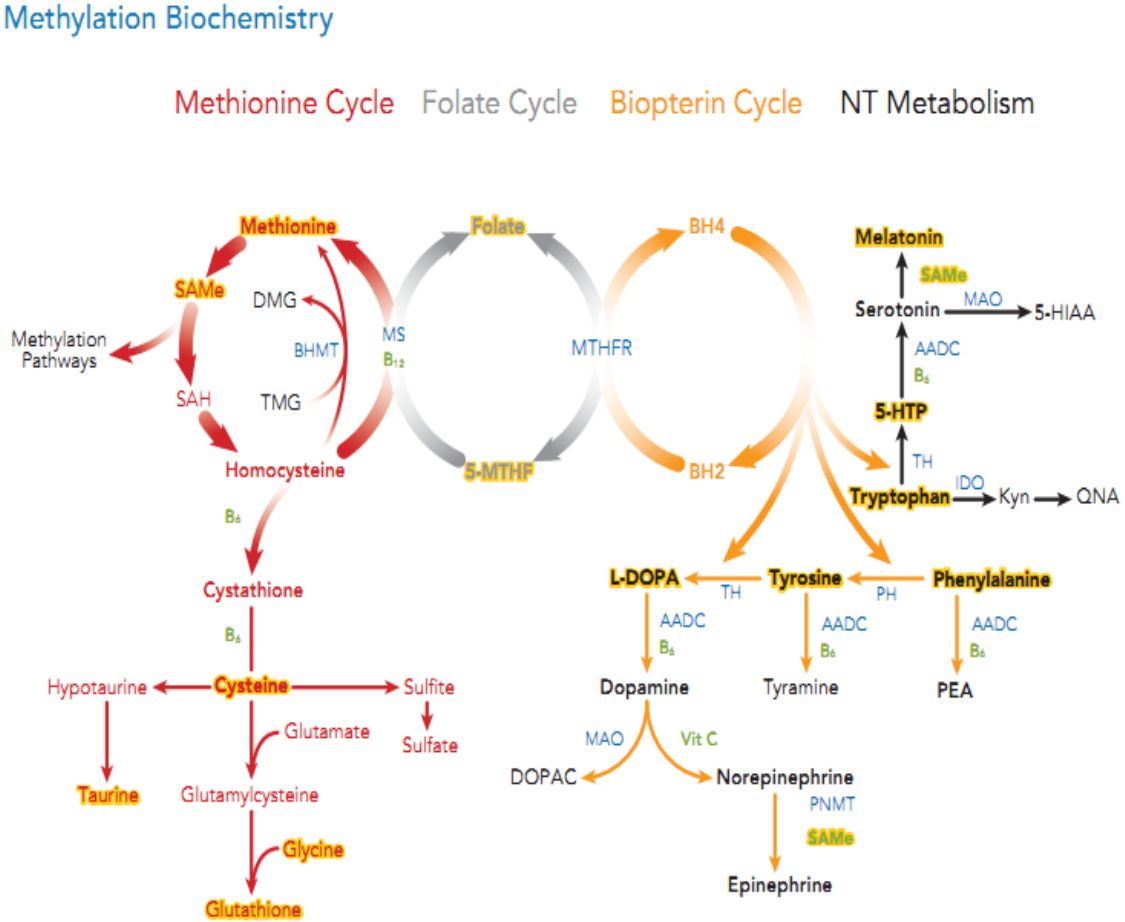
TOTAL LOAD EFFECT - ROS- METHYLATION PATHWAY

Lyme Bio toxins, mycotoxins,pollutant overload cause disturbances in methylation pathways.

It results in

- **Low glutathione levels**, imbalances in glutamate and Taurine
- **Neurotransmitter abnormalities**, particularly serotonin, melatonin, dopamine, norepinephrine
- **Sleep onset disorder** (with behavioral therapy and melatonin)
- **Metabolic abnormalities in folate, cobalamin, tetrahydrobiopterin, carnitine, and redox pathways**

Methylation pathway



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Life Sci. 2006 Apr 4;78(19):2244-8. Epub 2005 Nov 17

Mitochondrial DYSFUNCTION–OXIDATIVE STRESS

Dysfunctional mitochondria produces more ROS

- Extensive oxidative damage
- Immune activation- increase of circulating IL-6 indicates immune activation
- changes in Innate and adaptive immunity
- Release of pro-inflammatory cytokines, and signaling molecules like

  NF-κB , TNFa,

Int J Immunopathol Pharmacol. 2012 Apr-Jun;25(2):345-53.

MITOCHONDRIAL DYSFUNCTION VITAMIN D

Oxidative stress depresses:

- Vit-D Level
- Vit-D receptor expression and
- Mitochondrial Vit-D hydroxylase activities
- GSH synthesis

Low Vit-D and altered receptor function are linked to risk of autoimmune disease

Curr Hypertens Rep. 2015 Jan;17(1):504.

CHRONIC FATIGUE-DYSHOMEOSTASIS-MITOCHONDRIAL DYSFUNCTION

Summary:

- Evaluation of sick patient must be done prior to providing optimal treatment plan.
- Every part of the homeostasis and ground regulation system dysfunction must be considered
- Role of dysfunctioning CTM cells-Mast cells, macrophages and fibroblast .
- Role of Vitamin c and Basement membrane-oxidative damage-organ dysfunction
- Role of Total body burden and Neuro-immune- endocrine dysfunction
- Role of immune dysfunction and autoimmune dysfunction
- Role of Mitochondrial dysfunction-ETC dysfunction -role of NAD-maintenance of Sirtuin genes -role of Glutathione powerful antioxidant
- Role of PBM
- Role of Methylation
- Role of Vitamin D, C and antioxidant enzyme system
- Role of Microcirculation-