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Immune Modulation: Therapeutic Interventions

Sahar Swidan, Pharm.D., ABAAHP, FAARFM, FACA

Disclosures

- Employment: Pharmacy Solutions
- Speaker: A4M, Amgen, Biohaven

Partners

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Objectives

- Discuss novel therapeutic approaches for modulating immune response
  - Review stressors that affect the immune system and toll like receptors.
  - Review the use of peptides in immune support.
  - Discuss the various uses of LDN in the treatment of autoimmune conditions.
  - Review the various botanicals to support immunocompetency.

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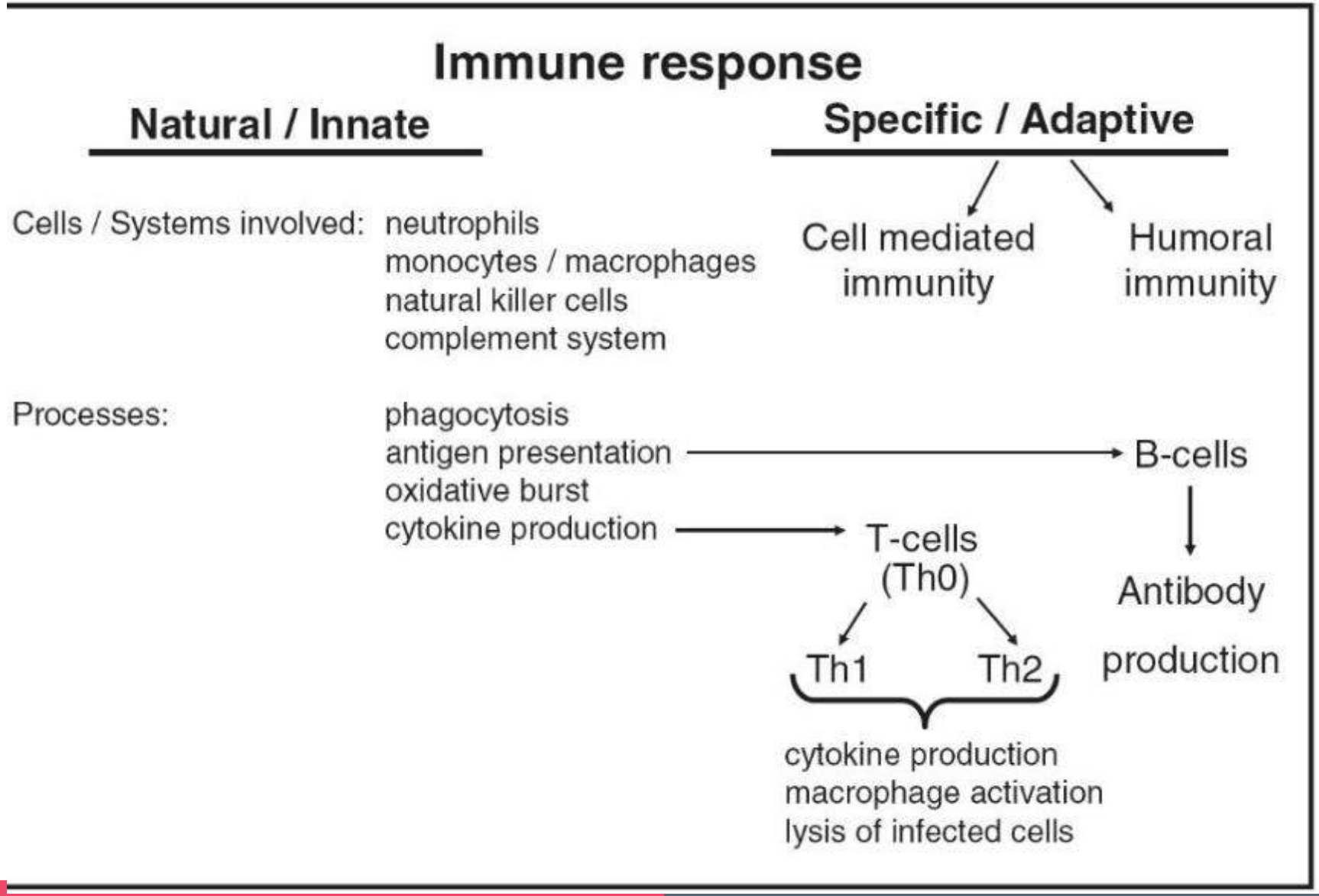
A Properly Functioning Immune System Is…

- Surveillance
- Internal Regulation
- Tolerant
- Resolution
- Restorative



Innate Immune Cells: Neutrophils

Neutrophils are the body's first line of cellular defense against foreign invaders and constitute the major cell type involved in acute and some forms of chronic in inflammation.

The most prevalent leukocytes in the bloodstream, typically constituting more than 50% of all bloodstream leukocytes.

Considered surveillance cells that sweep through the blood- stream, scanning for tissue infections or other inflammatory events.

Unfortunately, the capacity of neutrophils to destroy foreign organisms is matched in some circumstances by a capacity for host tissue destruction.

Innate Immune Cells
Macrophages

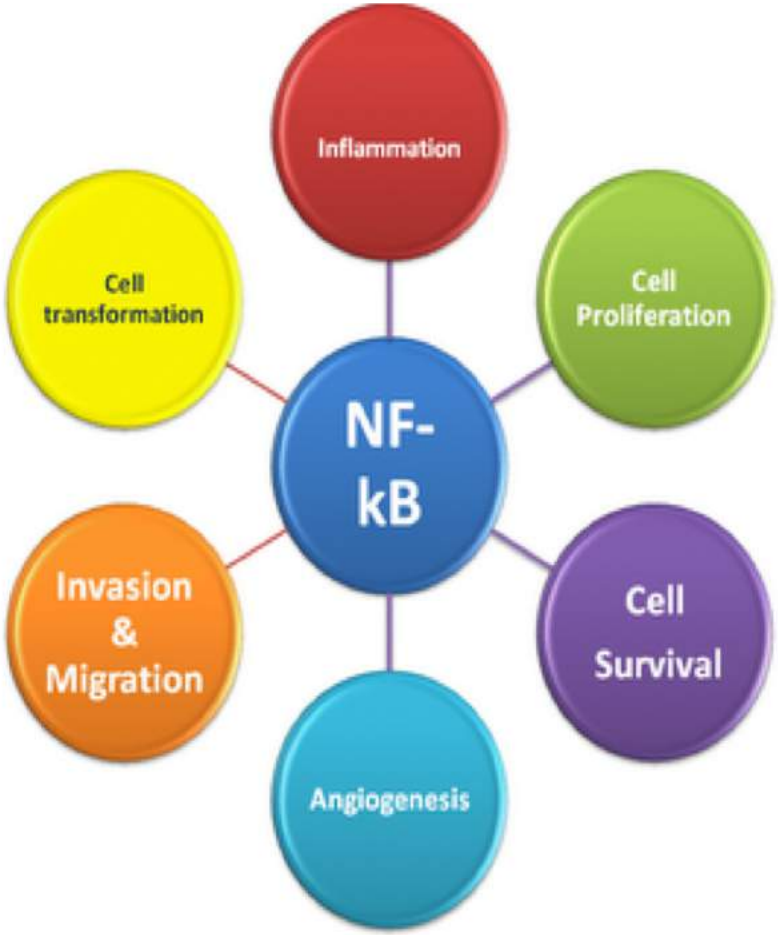
Macrophages (and their precursors, monocytes) are the 'big eaters' of the immune system.

Reside in every tissue of the body, albeit in different guises — such as microglia, Kupffer cells and osteoclasts

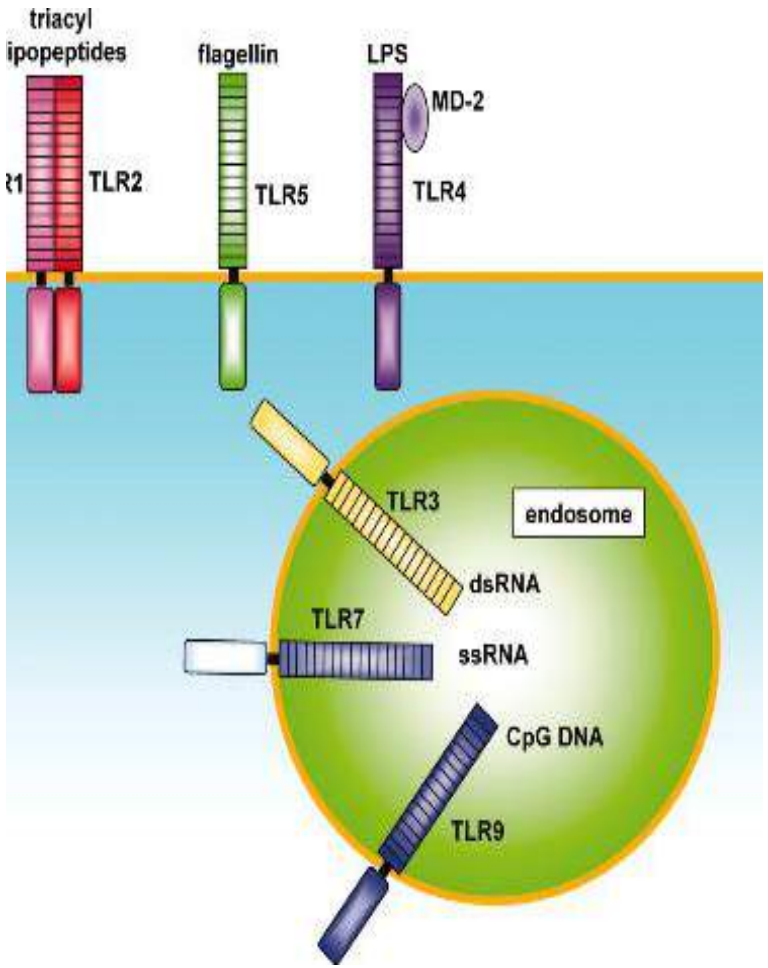
Engulf apoptotic cells and pathogens and produce immune effector molecules.

Various types of macrophages are found throughout the body, including the brain, such as microglial cells.
Microglia account for 10–15% of all cells found within the brain.

- A type of pattern recognition receptor (PRR) are TLRs
- Human genome codes for 10 known TLRs
  - Each recognize specific microbial products
- Lipoproteins of *Borrelia burgdorferi* are recognized by heterodimers of TLR1 and TLR2
  - Leads to activation of downstream signaling pathways and the translocation of nuclear factor kappa B (NFkB)
  - Leads to release of cytokines and chemokines



- TLR1 and TLR2 may also affect *Borrelia burgdorferi* gene expression
- *Borrelia burgdorferi* TLR also plays a role in:
  - Phagocytosis
  - Antigen presentation
  - Development of the adaptive immune response
- TLR is important in the inflammatory response of *Borrelia burgdorferi*



If the innate immune system is unsuccessful in destroying the pathogens, after about four to seven days the specific adaptive immune system responds.

Adaptive defense takes longer,but targets the pathogen more accurately.

Another advantage: It can remember the aggressor and acts specifically against certain antigens since it contains memory cells

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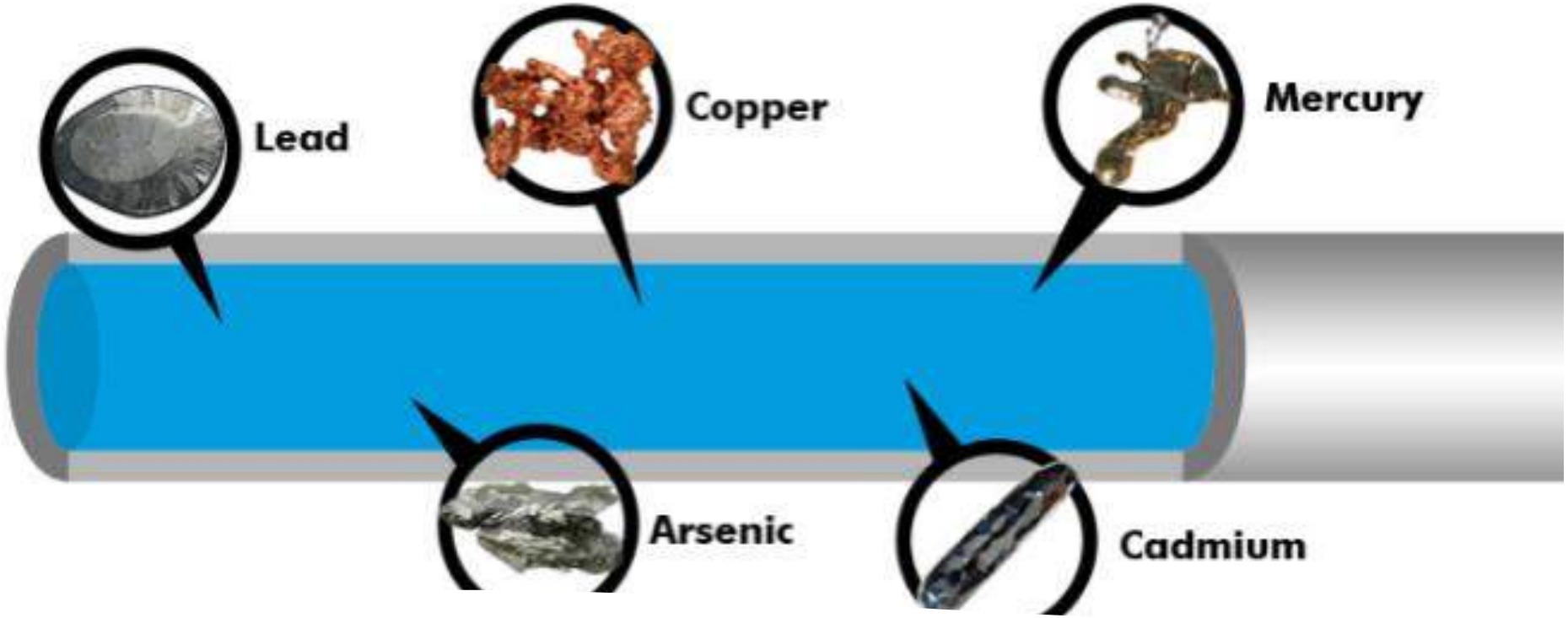
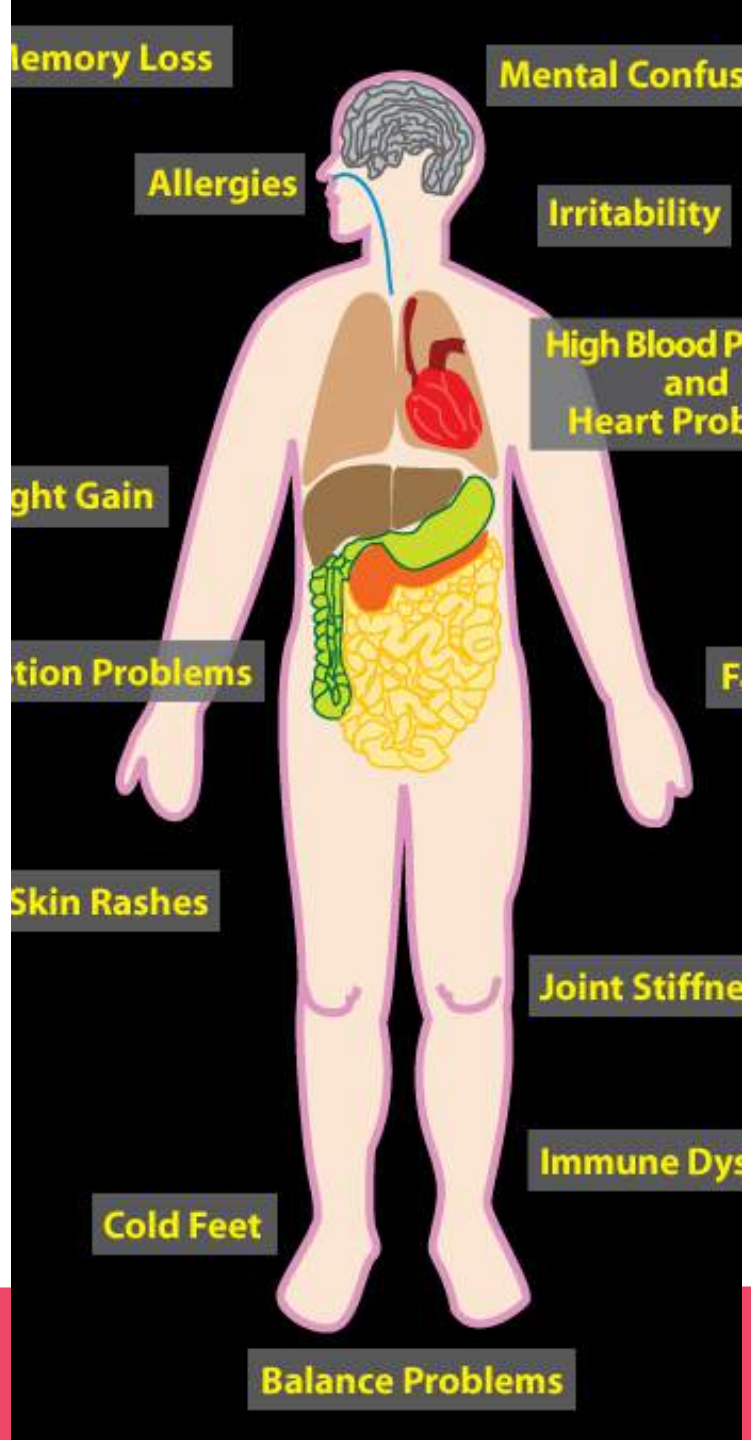
Heavy metals and the immune system



Intro to heavy metals[49]

- Many metals are natural in the environment as organic or inorganic compounds
- Industrial and combustion processes release heavy metals into the air, which leads to deposition and contaminates the soil
- Heavy metals are mostly absorbed in the airways or via the intestines
- Through the respiratory tract, low concentrations of heavy metals can affect endothelial cells, epithelial cells, and alveolar macrophages



heavy metals [50]

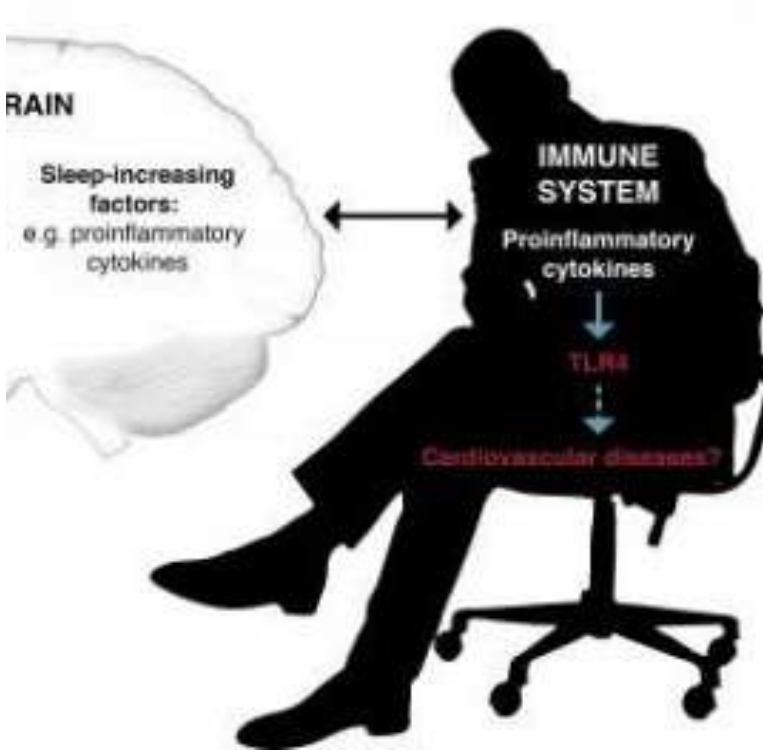
- Metals can have a primary or secondary effect on the immune system
- Some heavy metals may give rise to disordered function of the immune system
  - Result in increased susceptibility to infection, hypersensitivity reactions, autoimmune diseases, and neoplasia

Suppression of the immune system[61]

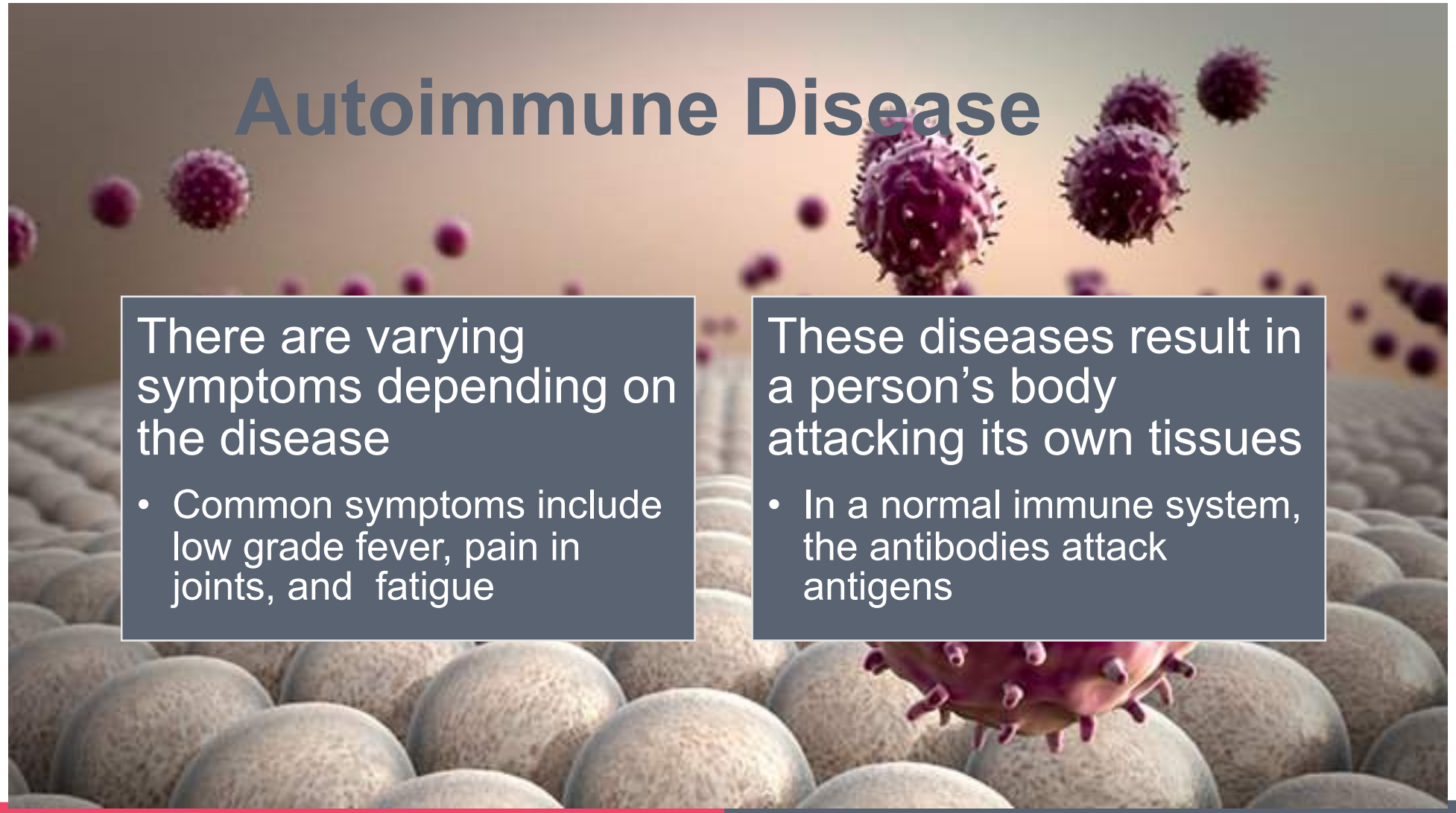
- Heavy metals suppress the immune system in times when the immune system needs to destroy cells
- This leads to the following:
  - Increased free-radical activity and oxidative processes
  - Premature aging and aging diseases
  - Suppression/Deregulation of the immune system
    - Increase in cancer mortality
  - Increase risk of heart disease

Sleep deprivation and the immune

- Chronic sleep deprivation affects your hormones
  - It can impair glucose tolerance and lead to diabetes and cardiovascular disease
  - Increases cortisol levels leading to a higher risk of diabetes and obesity
- During the night in the early stages of sleep, immune cells often peak in concentration
  - T helper cells
  - Antigen presenting cells
- Sleep deprivation leads to an increase in inflammation



Autoimmune Disease



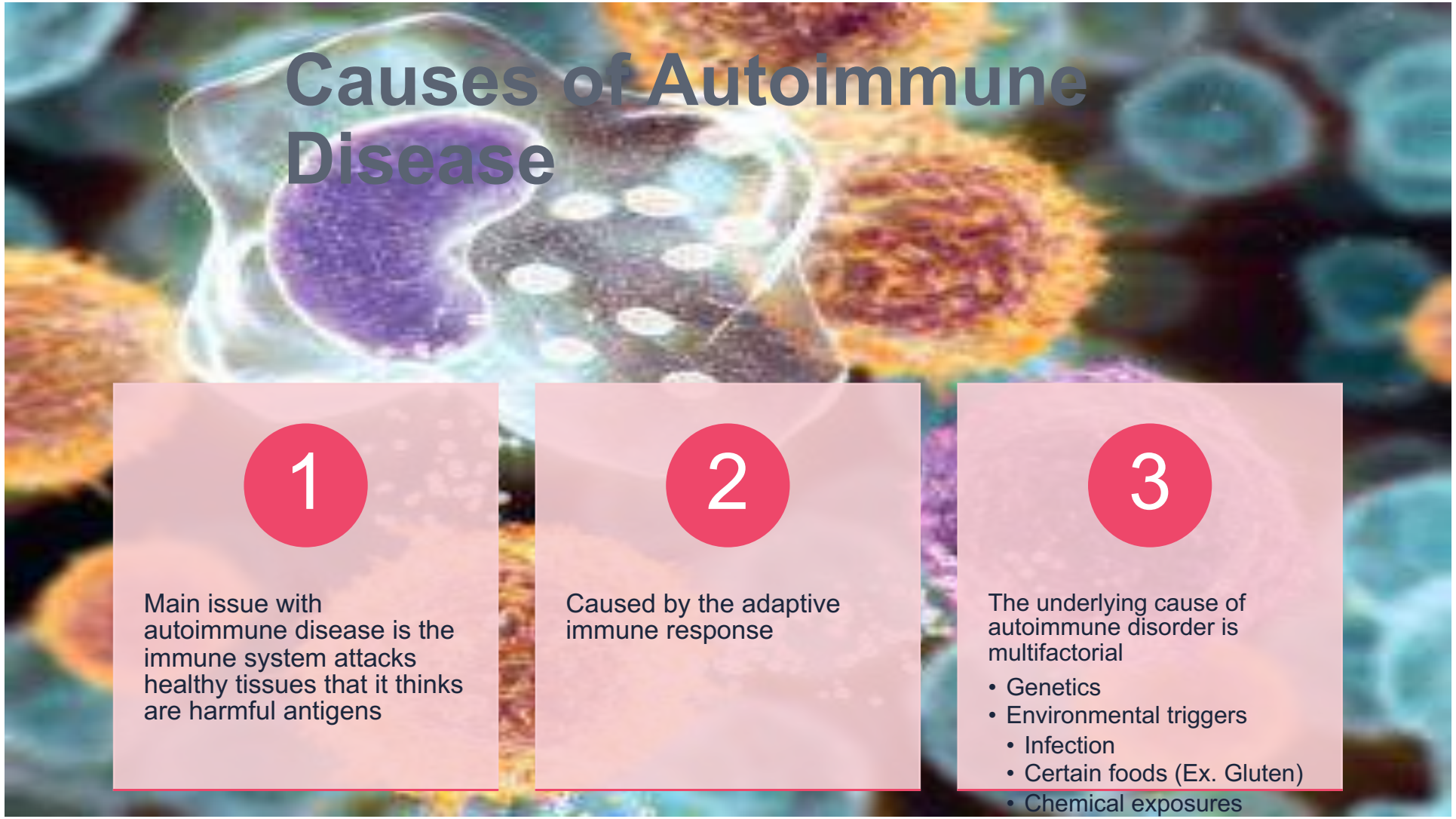
There are varying symptoms depending on the disease

- Common symptoms include low grade fever, pain in joints, and fatigue

These diseases result in a person's body attacking its own tissues

- In a normal immune system, the antibodies attack antigens

Causes of Autoimmune Disease



1

Main issue with autoimmune disease is the immune system attacks healthy tissues that it thinks are harmful antigens

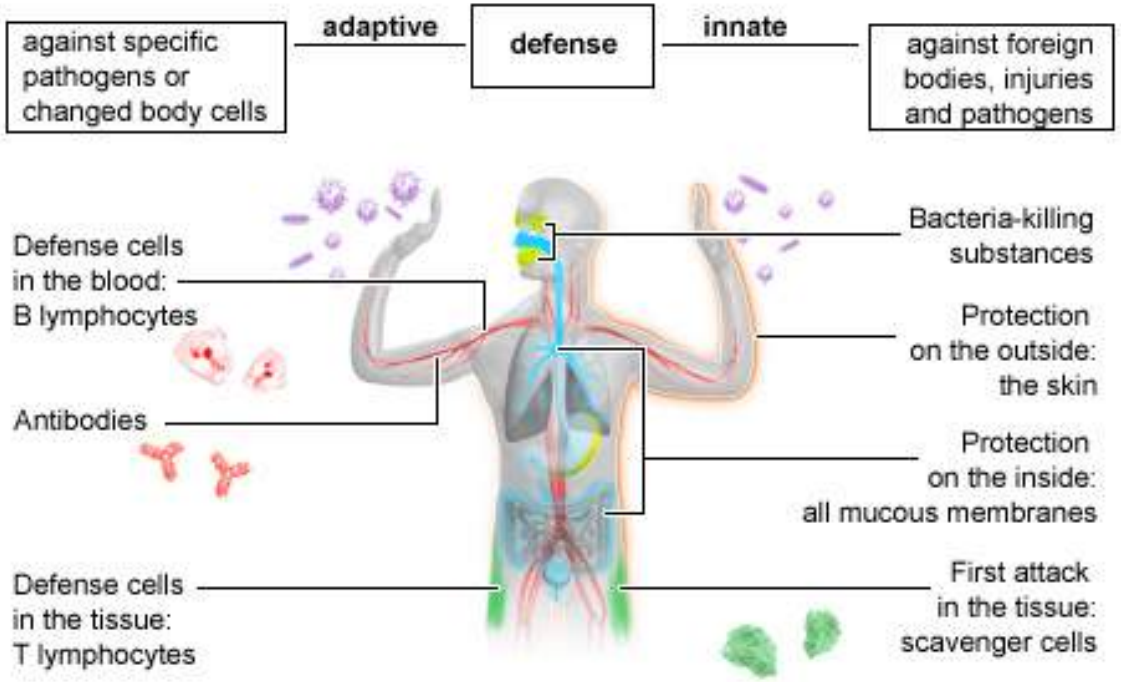
2

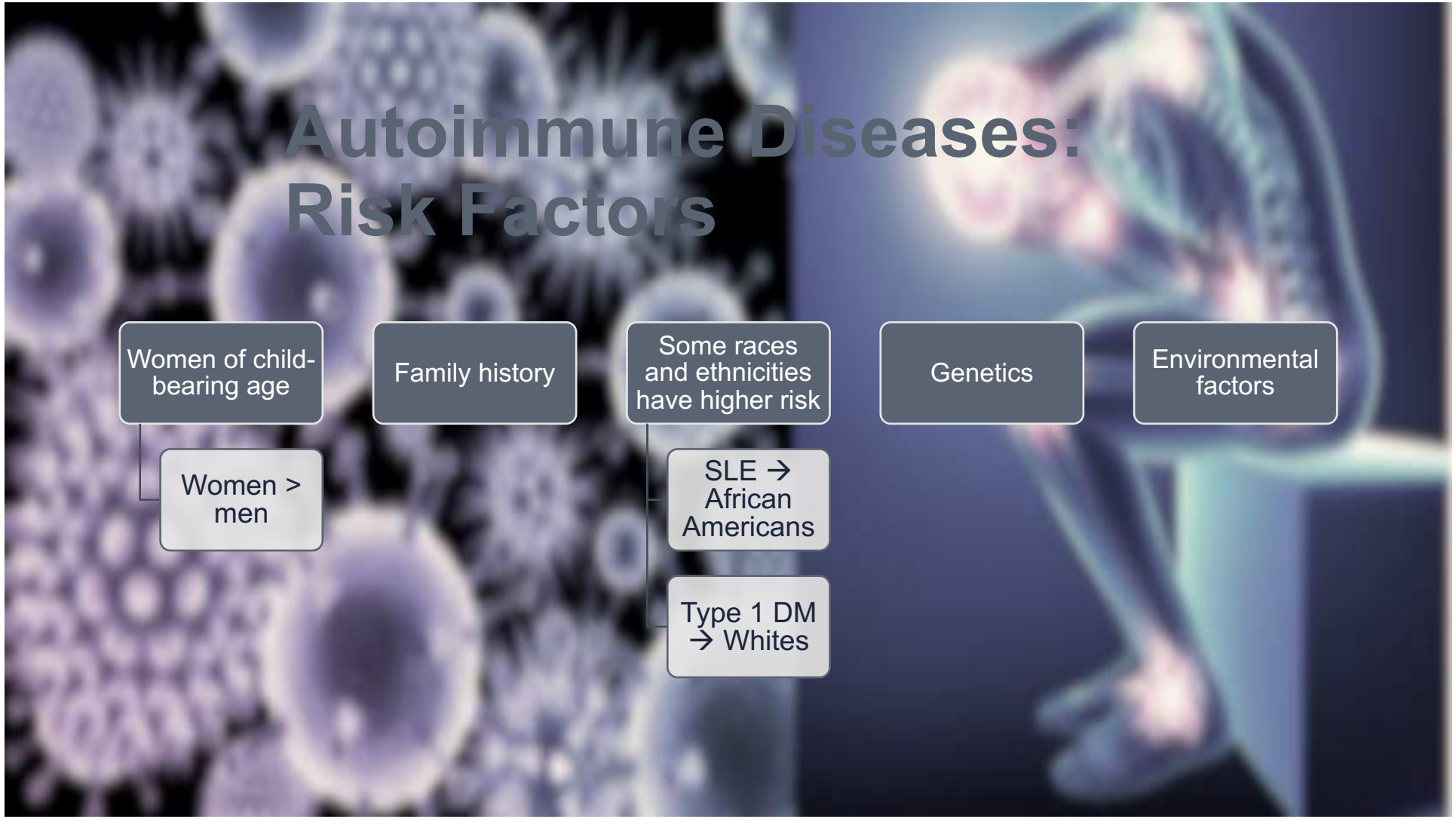
Caused by the adaptive immune response

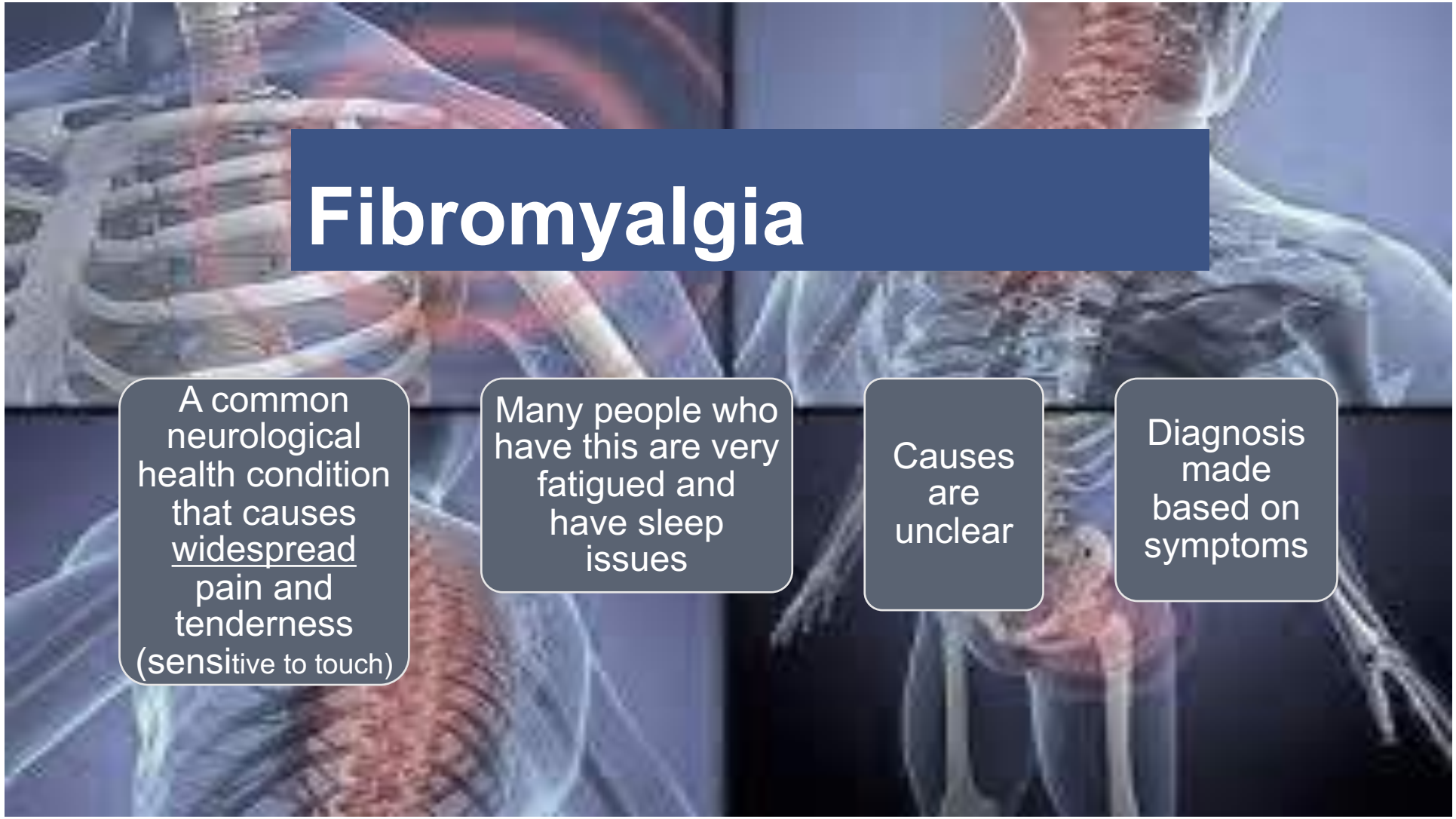
3

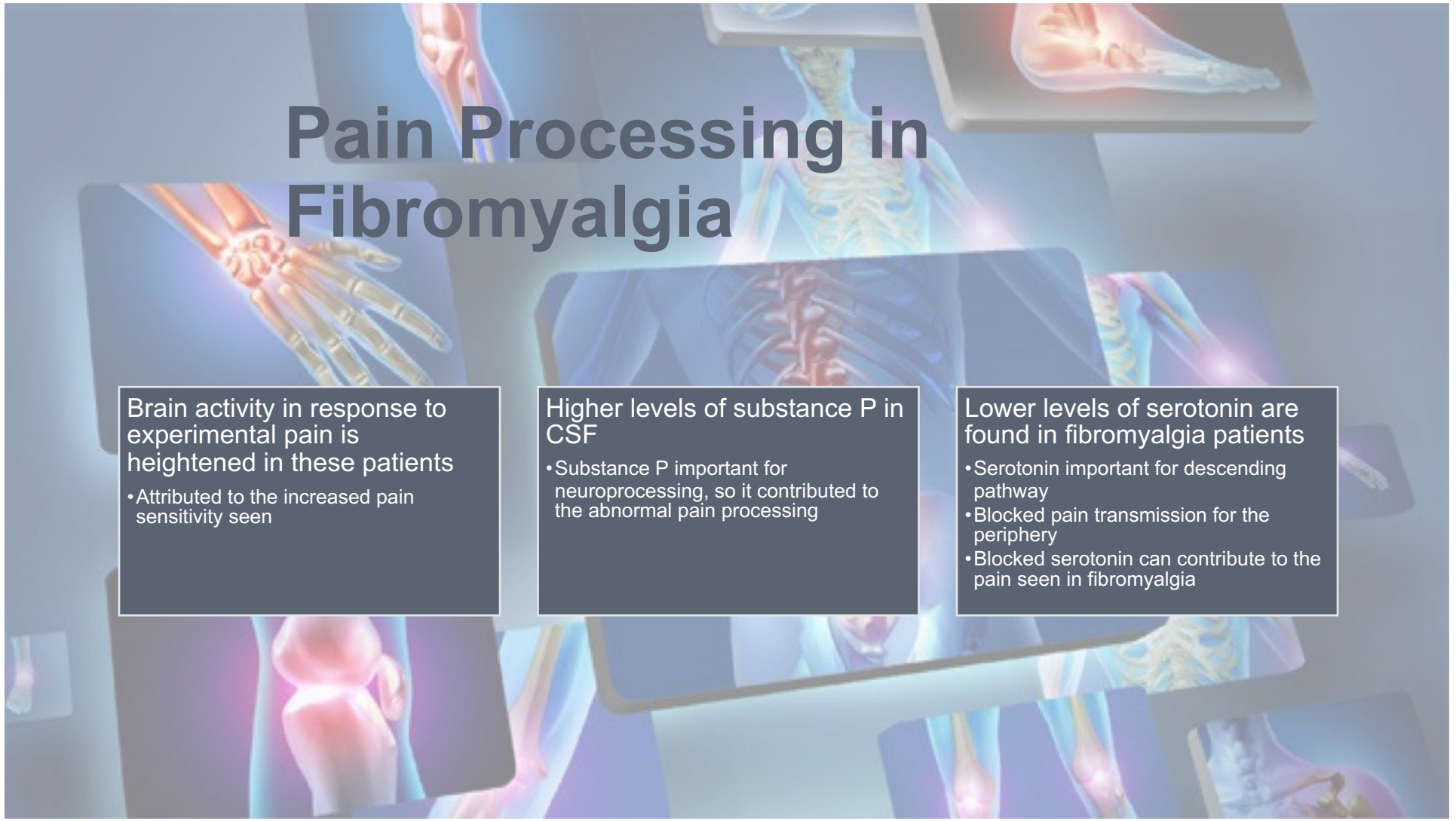
The underlying cause of autoimmune disorder is multifactorial

- Genetics
- Environmental triggers
  - Infection
  - Certain foods (Ex. Gluten)
  - Chemical exposures
  - Pharmaceutical drugs
  - Extreme stress or physical trauma




Autoimmune Diseases:
Risk Factors
Women of child-bearing age
Women > men
Family history
Some races and ethnicities have higher risk
SLE → African Americans
Type 1 DM → Whites
Genetics
Environmental factors





Pain Processing in Fibromyalgia

Brain activity in response to experimental pain is heightened in these patients

- Attributed to the increased pain sensitivity seen

Higher levels of substance P in CSF

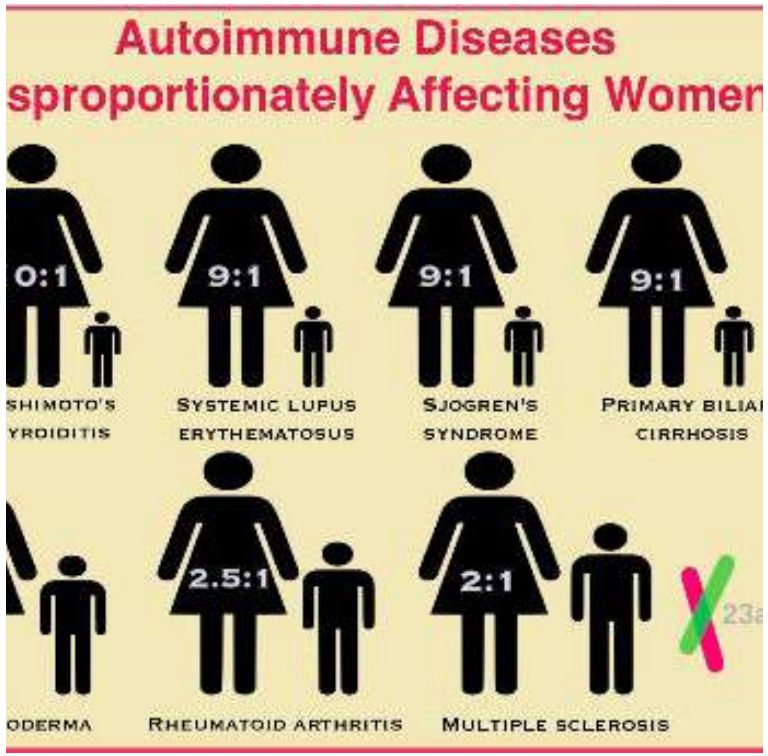
- Substance P important for neuroprocessing, so it contributed to the abnormal pain processing

Lower levels of serotonin are found in fibromyalgia patients

- Serotonin important for descending pathway
- Blocked pain transmission for the periphery
- Blocked serotonin can contribute to the pain seen in fibromyalgia

Women and Autoimmune

- Females have greater basal and stimulated axis activity compare to men
- Females also have more pronounced immune/inflammatory reaction compared to that of men
- Women have a higher incidence of autoimmune disorders
- The overall higher occurrence in women may be attributed to the gonadal steroid regulation of the HPA axis and inflammatory mediators



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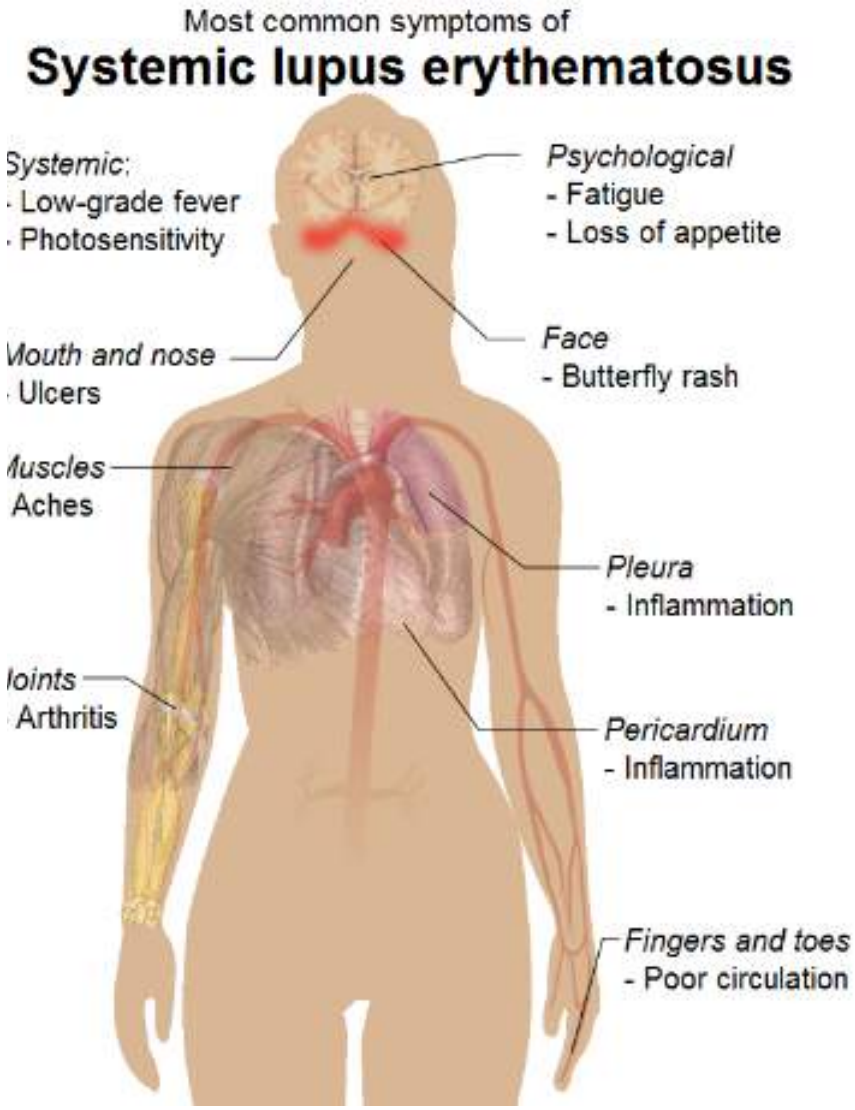
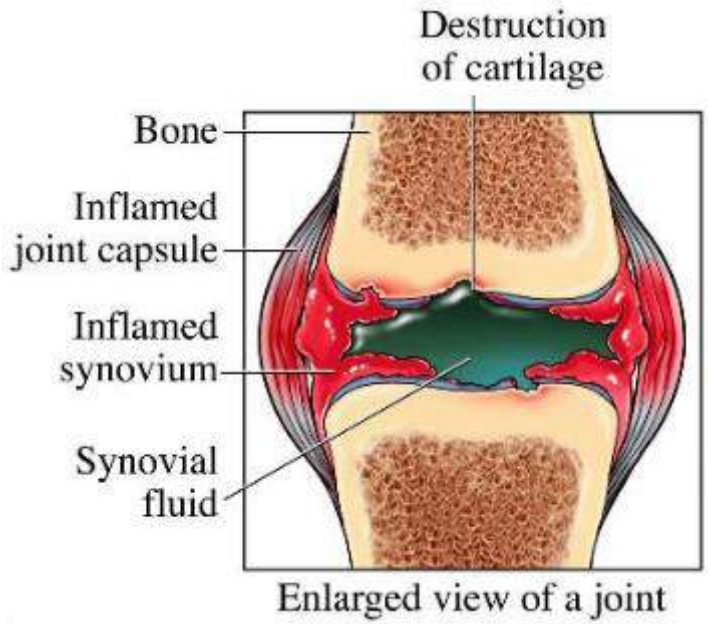
Systemic lupus erythematous (SLE)[57]

- It is a chronic autoimmune disease
- Characterized by production of autoantibodies
- Affected by environmental, genetic, infectious, and hormonal factors
- This disease predominates in reproductive-aged women
- Females with this disease have an increase in testosterone oxidation, leading to decreased testosterone levels
    - Independent of the severity of the disease
    - Also decreases in DHEA



Rheumatoid Arthritis[55]

- Hypothalamic-pituitary-gonadal (HPG) axis function and adrenal androgen (AA) are interrelated
  - Play a role in rheumatoid arthritis
- In rheumatoid arthritis, the concentration of glucocorticoid receptors in circulating lymphocytes are reduced
  - Glucocorticoid resistance in target tissues
- Thought to be less likely in men due to the immunosuppressive effect of androgens



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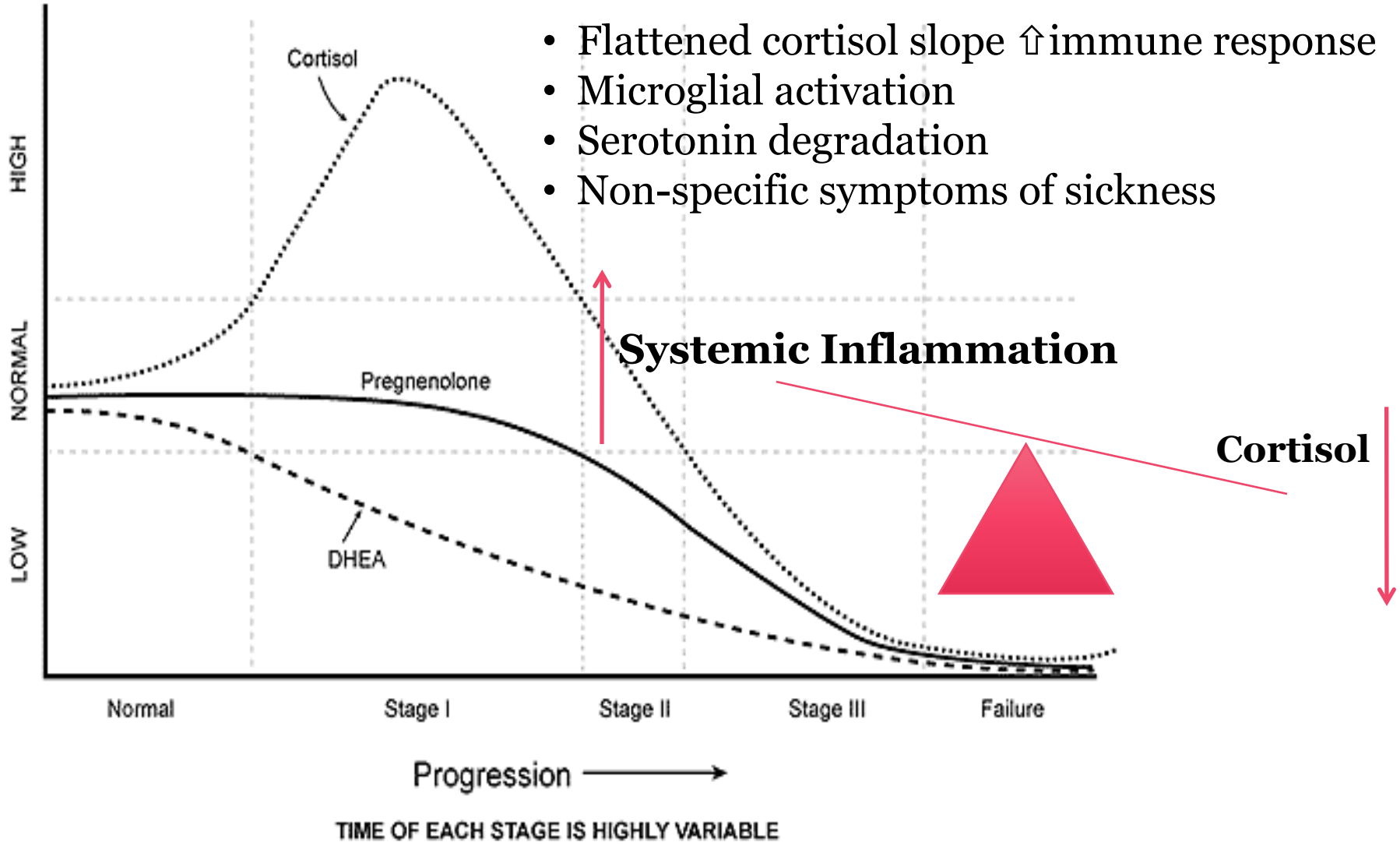
Hormones and the immune system

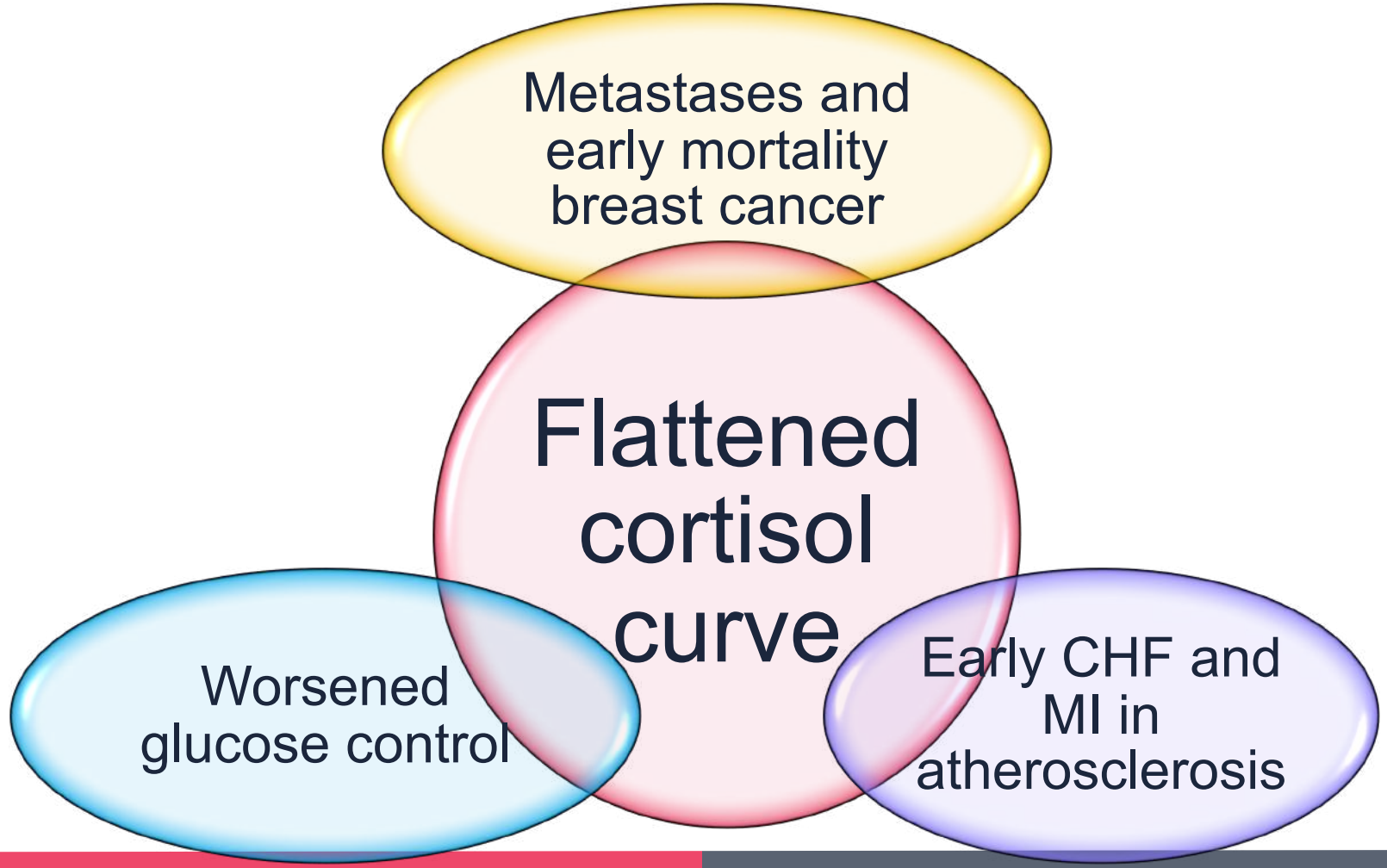
- Flattened cortisol slope ⇧immune response
- Microglial activation
- Serotonin degradation
- Non-specific symptoms of sickness



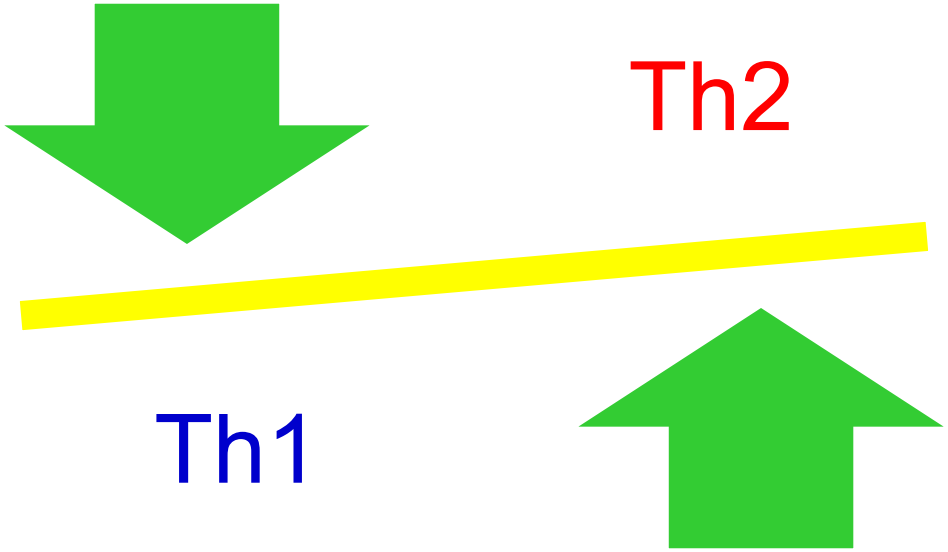
Diagnostic Assays: Salivary Cortisol Patterns Matter

- Flattening of the cortisol curve
  - Most predictive of adrenal dysfunction
  - Most well studied
  - Hypocortisolism induces:

Diagnostic Assays:
Salivary Cortisol Patterns Matter



Cortisol Immune Connection



Loss of negative feedback from cortisol results in a rise in Th1 dominance

A new view on hypocortisolism

Eva Fries, Judith Hesse, Juliane Hellhammer, Dirk H. Hellhammer*

Department for Psychobiology, University of Trier, Johanniterufer 15, 54290 Trier, Germany

Received 18 November 2004; received in revised form 6 April 2005; accepted 6 April 2005

KEYWORDS
Hypocortisolism;
Cortisol;
Allostatic load index;

Summary Low cortisol levels have been observed in patients with different stress-related disorders such as chronic fatigue syndrome, fibromyalgia, and post-traumatic stress disorder. Data suggest that these disorders are characterized by a symptom triad of enhanced stress sensitivity, pain, and fatigue. This overview will

Raison and Miller (2003) assume that prolonged or repeated exposure to immune stimuli might predispose an individual to reduced glucocorticoid signaling as a means of freeing bodily defenses from inhibitory control in the face of an ongoing infectious threat. Thus, an enhanced release of

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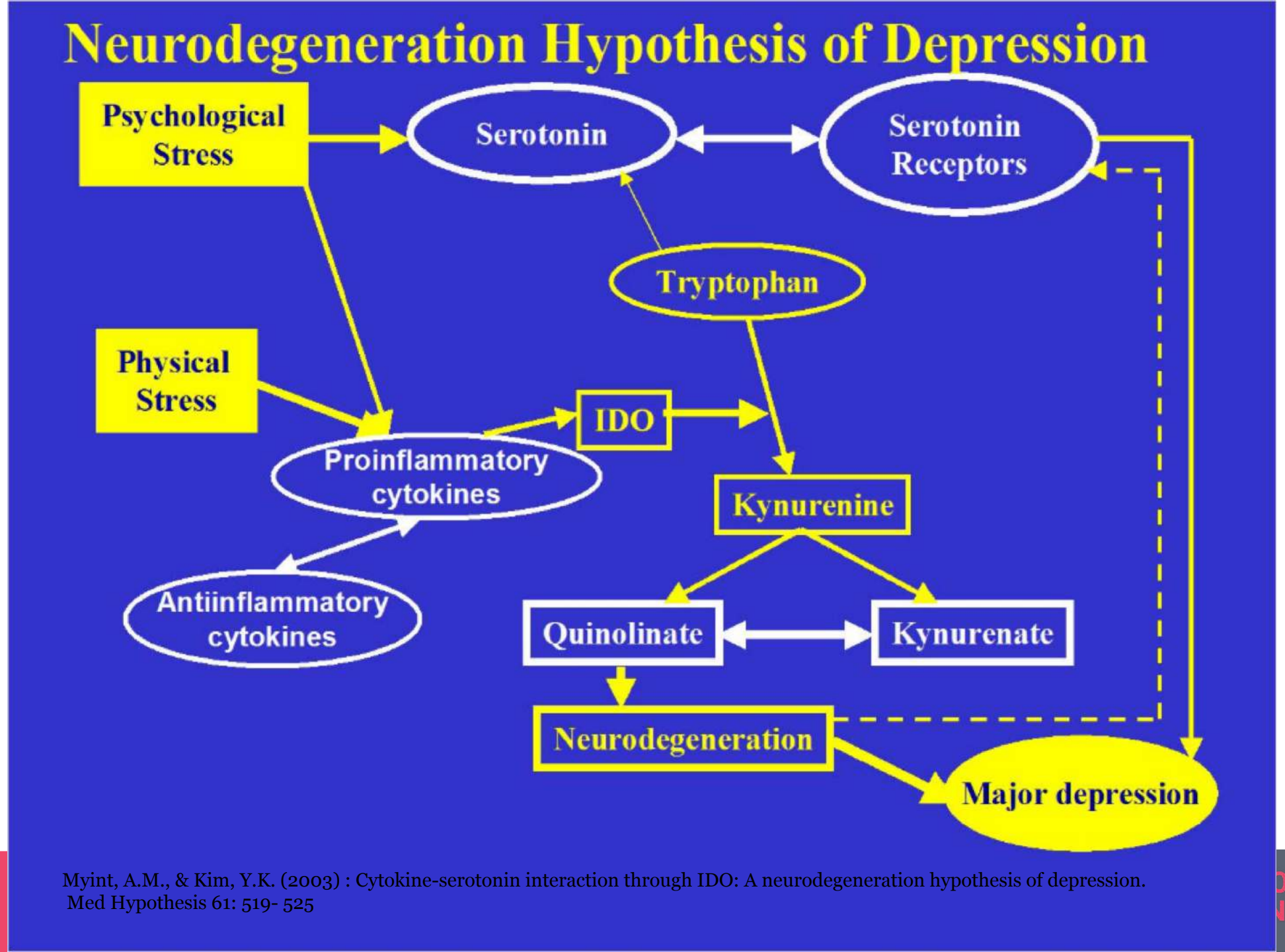
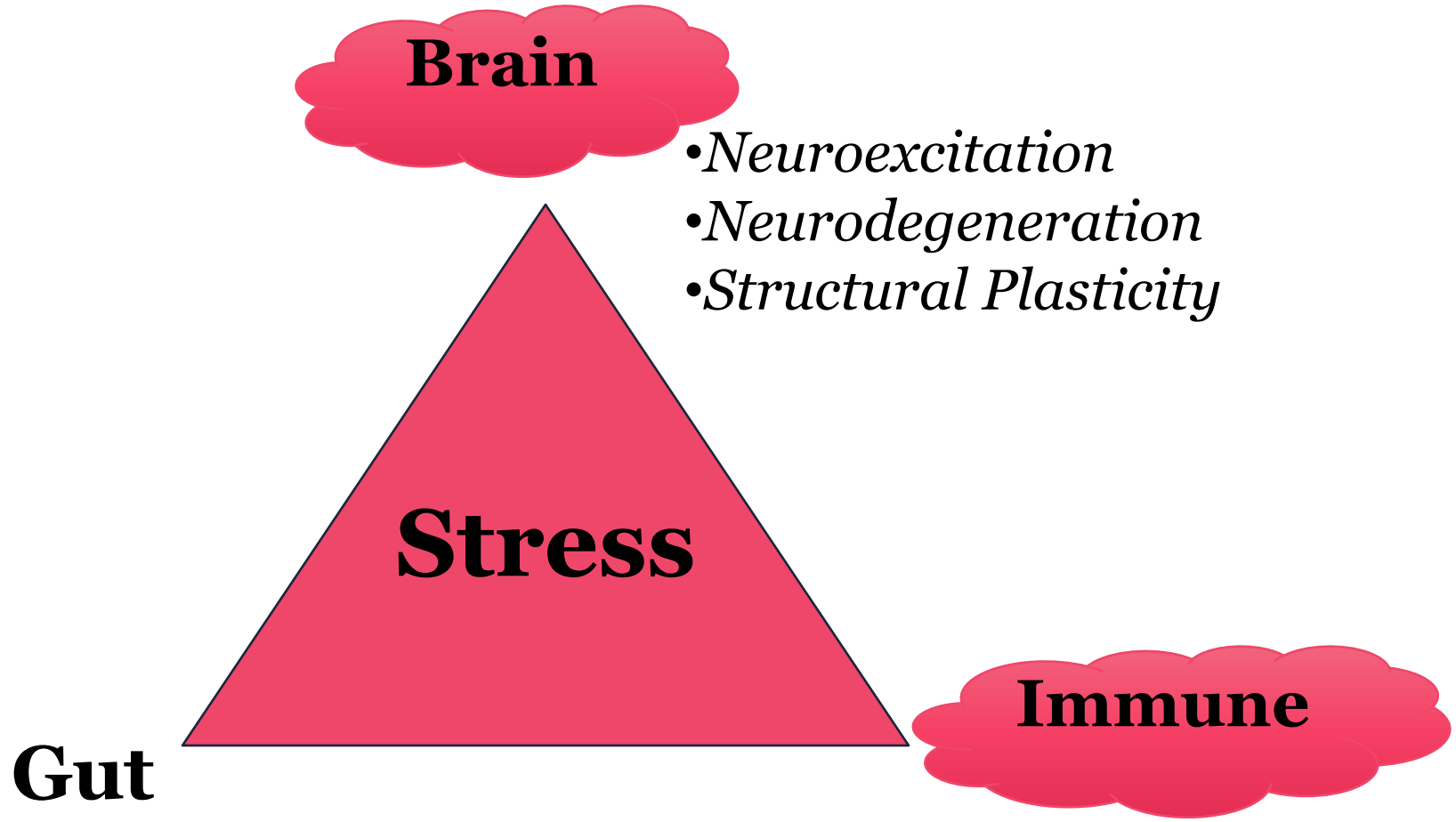
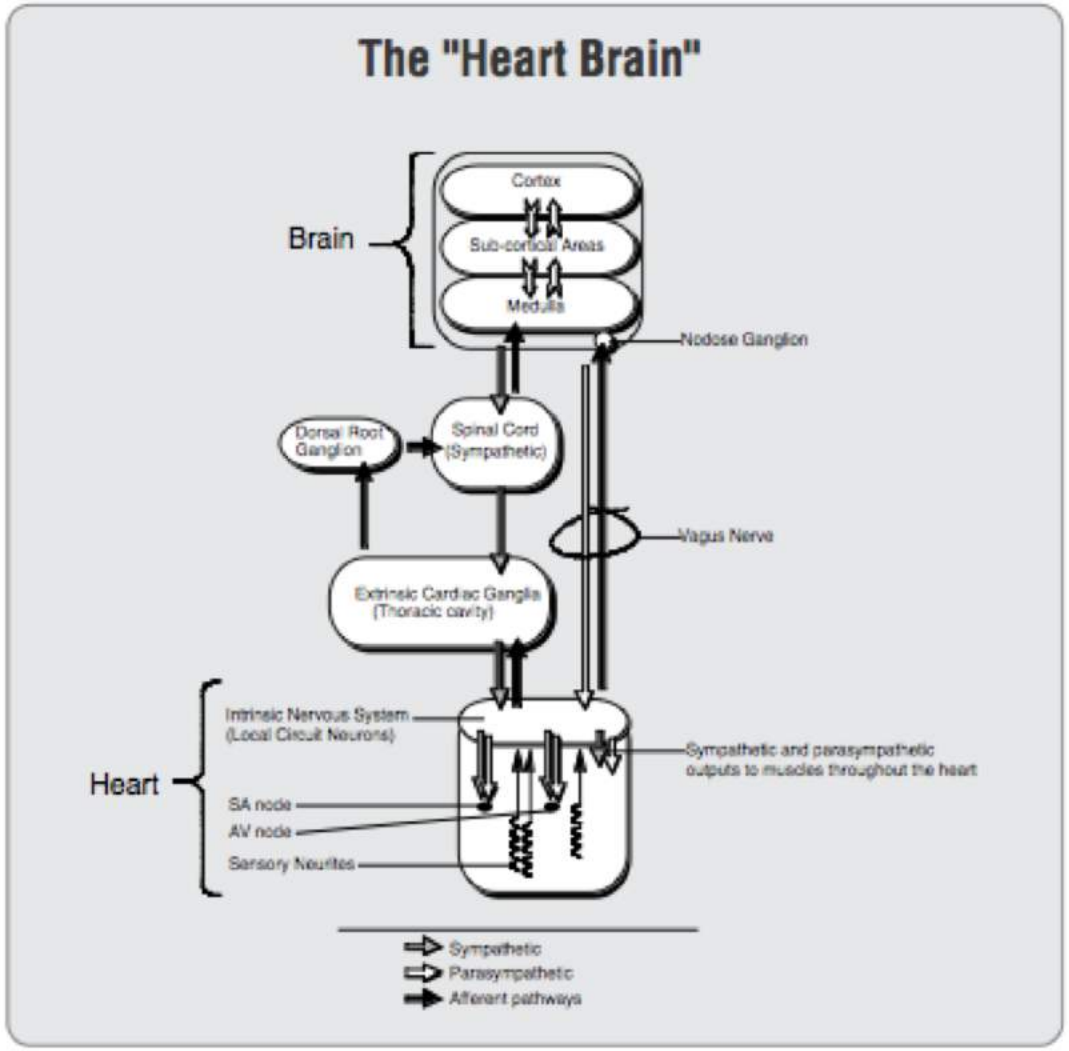
may be beneficial for health and survival. Most strikingly, the demonstration of a low allostatic load index in hypocortisolemic subjects suggests that a down-regulation of the HPA axis in chronically stressed subjects protects those subjects against the harmful effects of a high allostatic load index.

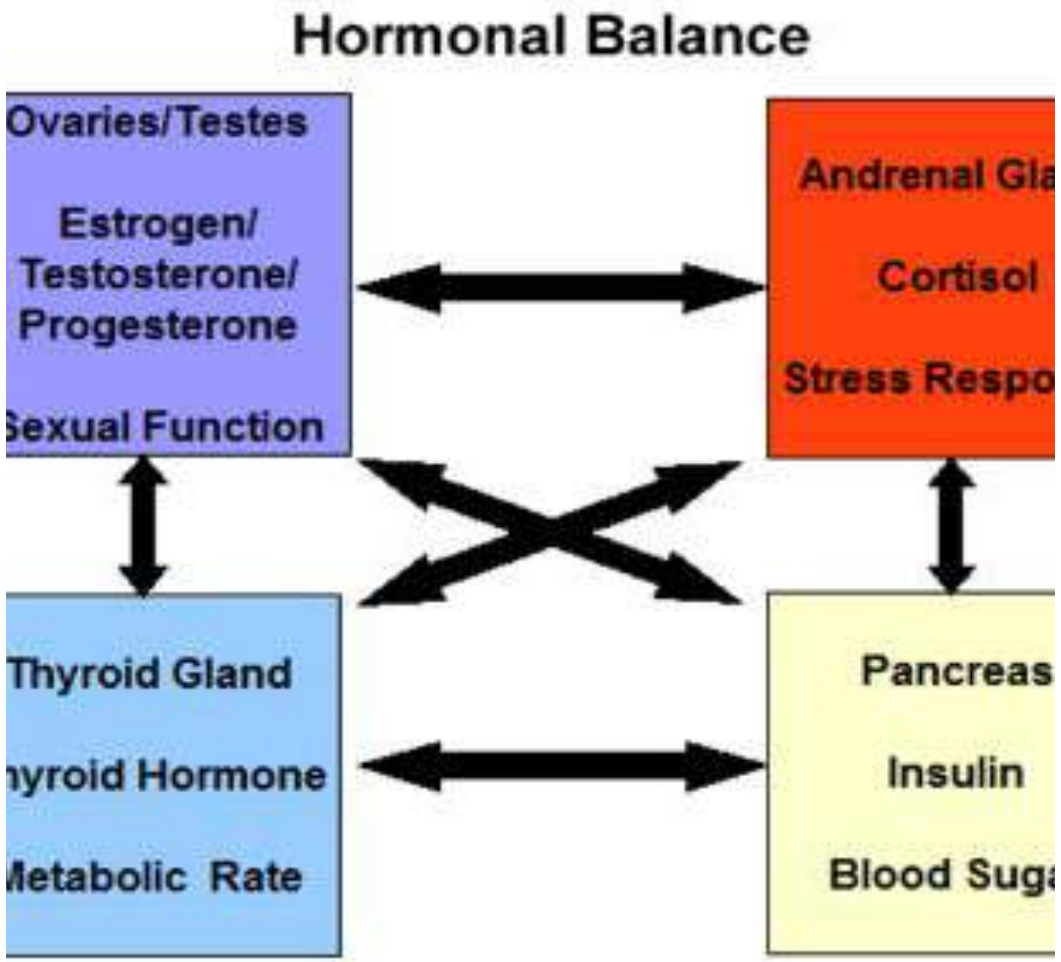


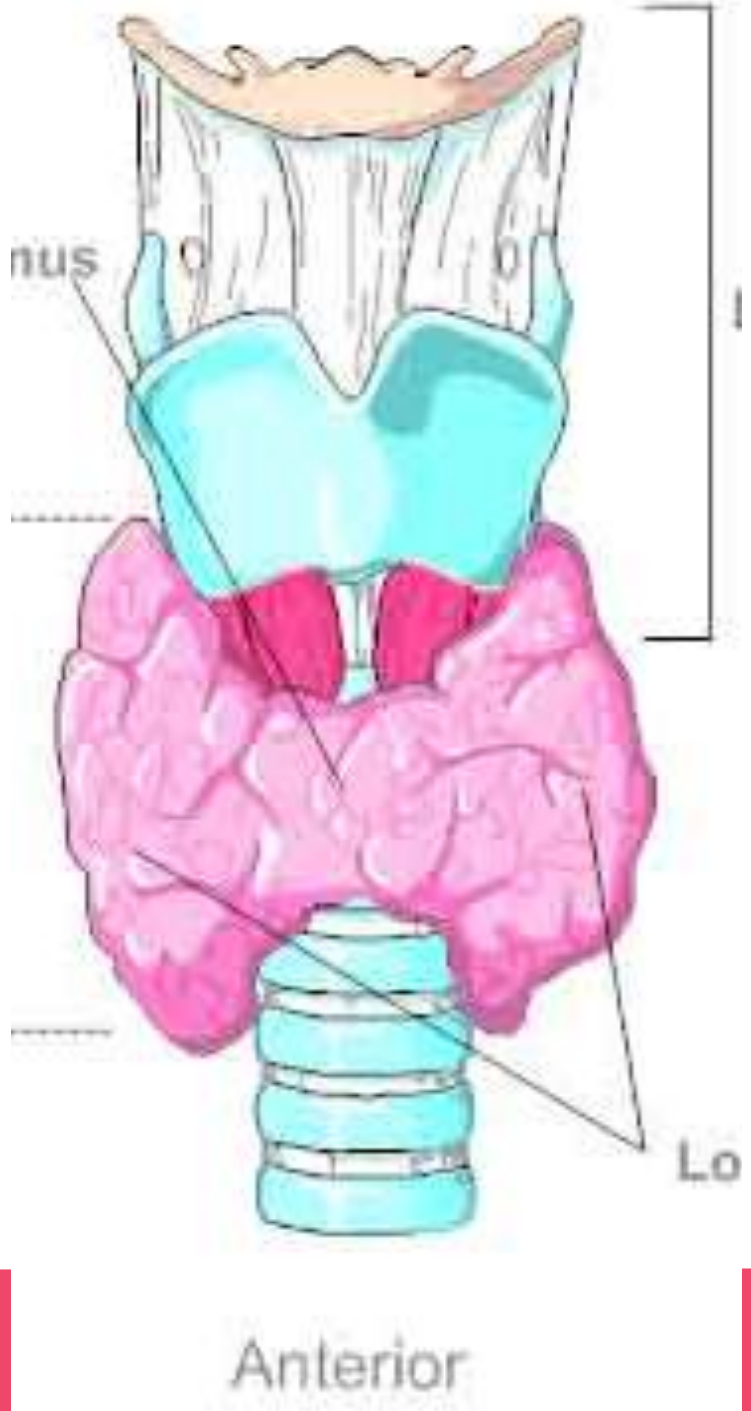
Myint, A.M., & Kim, Y.K. (2003) : Cytokine-serotonin interaction through IDO: A neurodegeneration hypothesis of depression. Med Hypothesis 61: 519- 525


Brain
•Neuroexcitation
•Neurodegeneration
•Structural Plasticity
Stress
Gut
Immune
•Th1/Th2/Th17 balance
•Innate immunity
•Microglial activation



- No hormone works in isolation for other hormones
  - They are all interconnected
- Many hormones have an effect on the immune system, diseases, and other hormones
- An imbalance in thyroid, adrenal hormones (testosterone, estrogen, and progesterone) can affect the immune system
- The chemical environment and nutrition also contribute to hormone imbalance



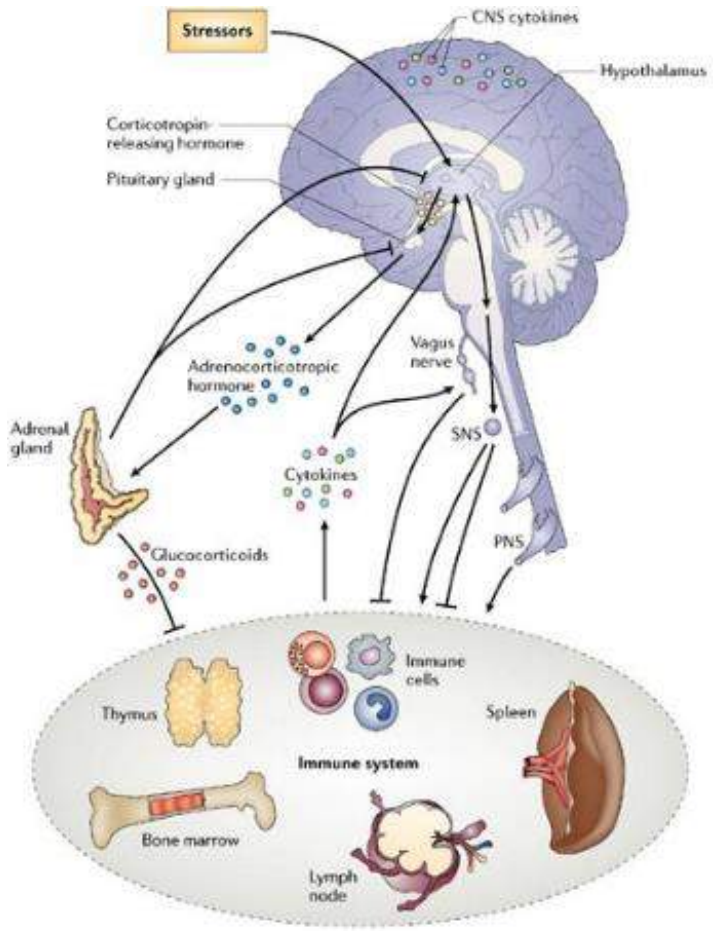


Thyroid hormone and the immune system[64, 71]

- Thyroid hormone stimulates the activity of NK cells
- TSH can be produced by leukocytes
  - TSH may act as a cytokine-like regulatory molecule within the immune system
- TSH elicits elevated antibody responses and has potentiating effects on leukocyte proliferation

Adrenal gland and the immune system[64]

- As a result of stress and nutritional deficiencies, the body produces hormones that inhibit the production of prostaglandins
  - This interferes with immune response
- Adrenal hormones deplete thymus function
  - Thymus gland is responsible for training T cells



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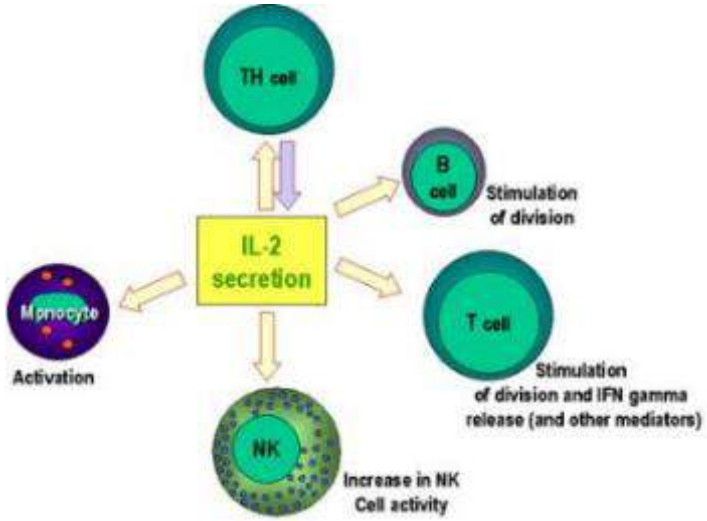
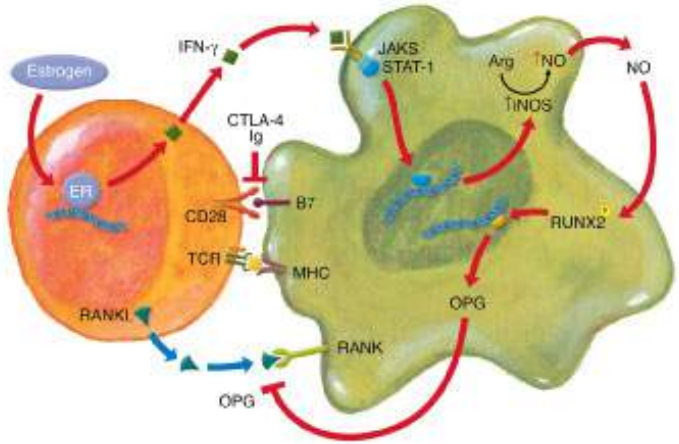
Estrogen & Progesterone and the immune system[64]

- NK cell activity and IL-2 are compromised by estrogen dominance and they are promoted by progesterone
- Estrogen has been shown to decrease the size of the thymus
  - This causes a reduction of thymic hormone in the blood
  - This depresses the immune system
- Autoimmune disorders are often associated with estrogen dominance
  - Occur more in women compared to men



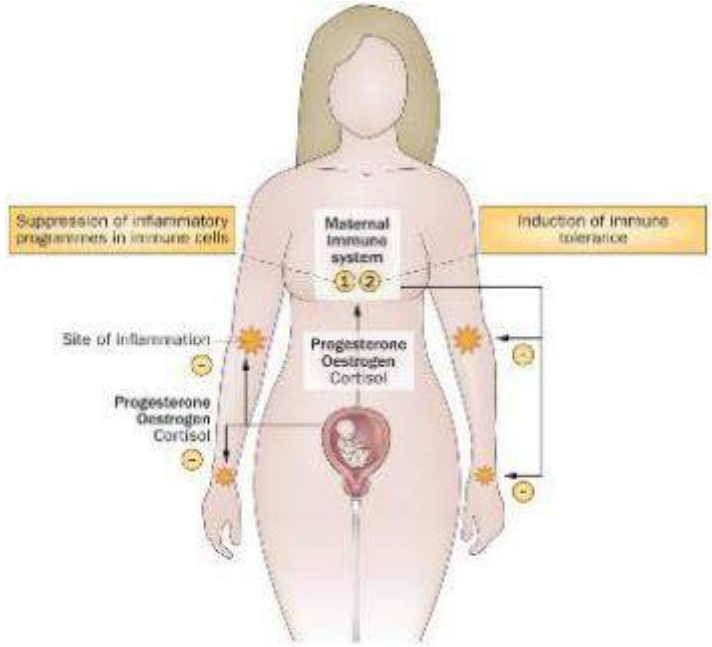
Estradiol (E2)[66]

- E2 increases TNF-αin immune cells
- E2 decreases IL-10 and NO synthesis in immune cells
  - However, E2 increases NO synthase activity in endothelial cells
- The effects of E2 can vary based on the different cell targets



Progesterone[6]
5

- High progesterone levels are immunosuppressive
  - May contribute to the beneficial effects of pregnancy on rheumatoid arthritis
- Progesterone suppresses immune responses
  - Been show to suppress cell-mediated immunity
  - It enhances suppressor cell activity
  - It inhibits mitogen induced lymphocyte proliferation



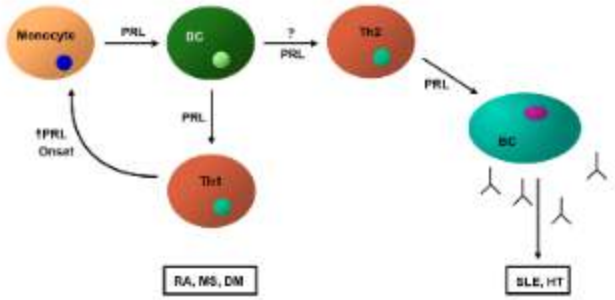
anti-inflammatory effects

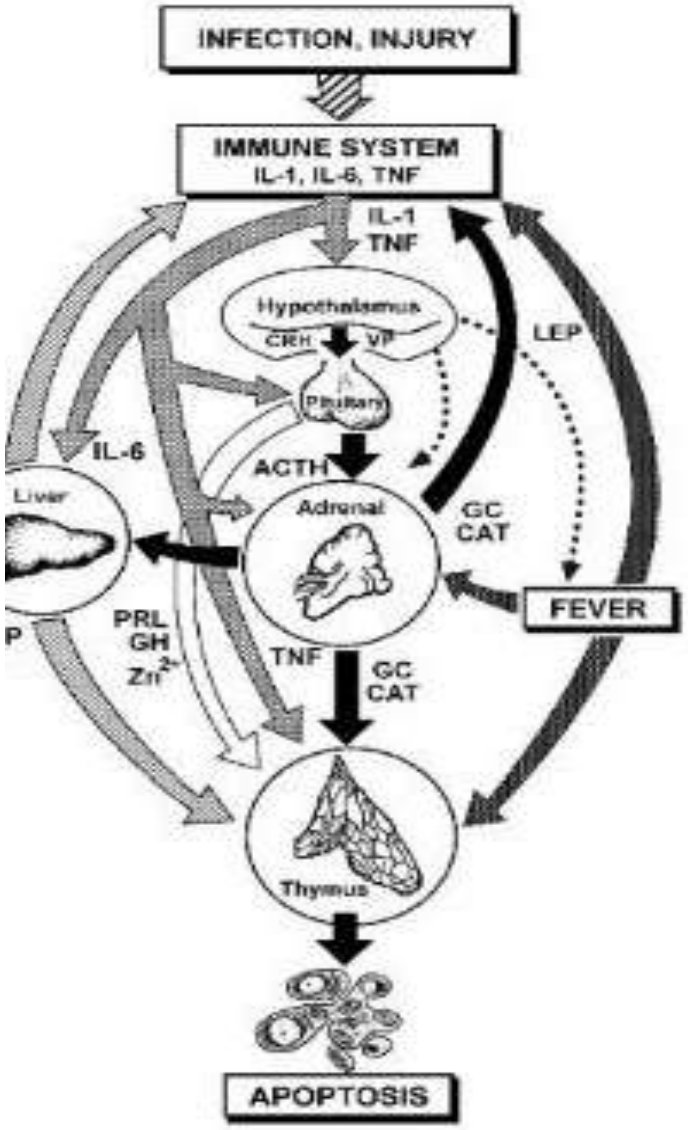
- Inhibits TNF-α and NO
- Induces synthesis of IL-10

- Testosterone can be mediated by its own nuclear receptor
- Androgens and estrogen operate in an opposite matter
  - They work to either suppress (E2) or activate (testosterone) cell function

Prolactin and Growth Hormone[65, 72]

- Prolactin (PRL) and growth hormone (GH) are needed for the development of the immune system and the function of immunostimulators
- Prolactin restores the immune response
- Those who are deficient in growth hormone have thymic atrophy and are immunodeficient
    - Growth hormone receptor are present on lymphocytes



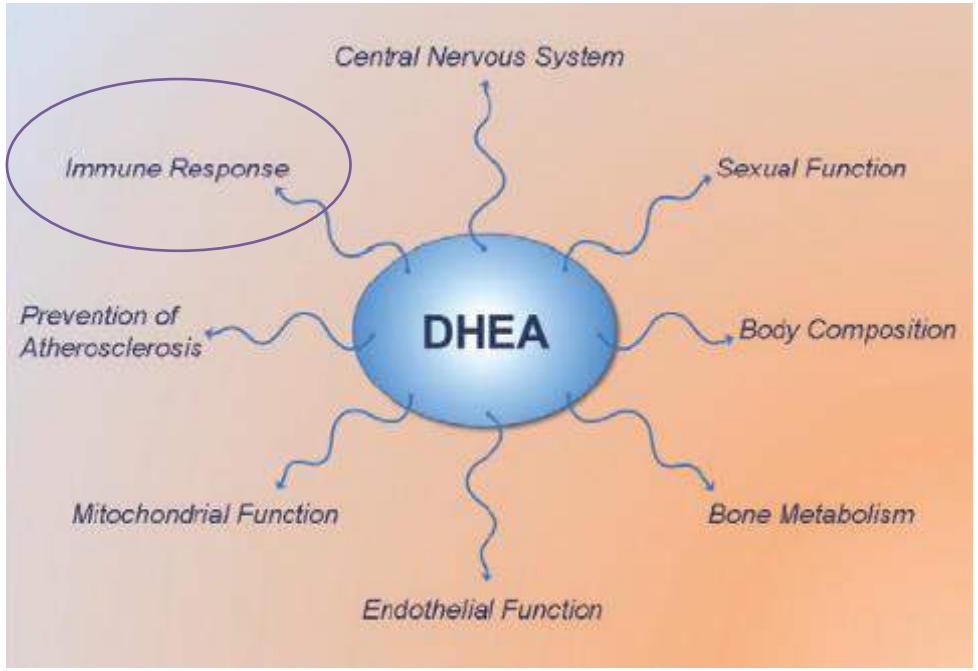


CRH and Vasopressin on immunity[72]

- There is an increase in the secretion by the pituitary and adrenal glands following inflammation
- IL-1, IL-6,, and TNFαdirectly stimulate the synthesis and secretion of CRH and vasopressin at the hypothalamus
- This activation of the pituitary-adrenal axis leads to a lower intensity of the immune response because all of the components of the immune response are inhibited by cortisol

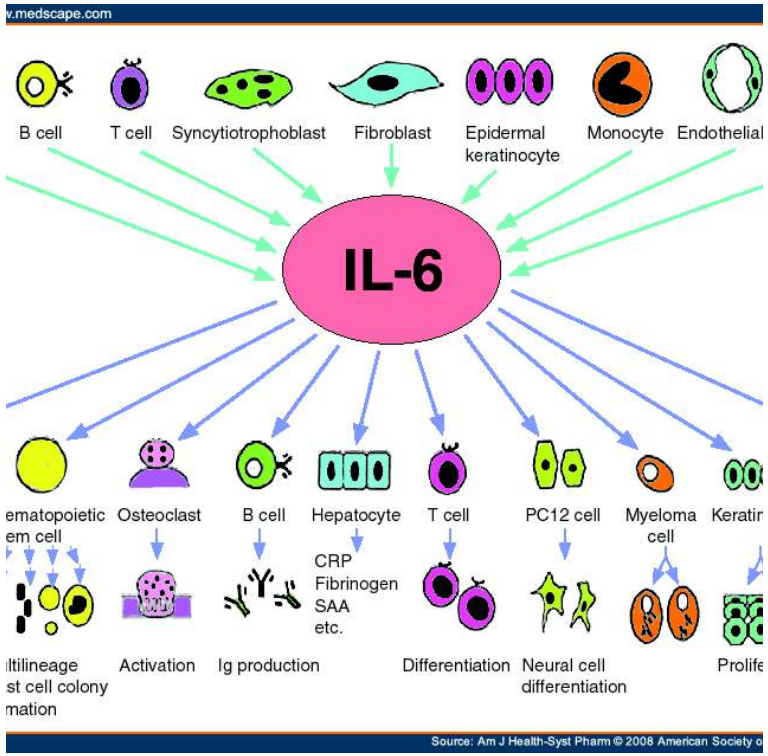
DHEA[66]

- A decline in the body's DHEA levels cause a decline in immune function
- DHEA impact T cell function
  - DHEA regulates IGF-1
  - IGF-1 regulates T lymphocyte function – including TH1 to TH2 balance via IL-12 production



DHEA[68]

- DHEA stimulates production of IL-2
- It inhibits NK cells differentiation
- DHEA prevents increase in age-related IL-6 production in lymphocytes



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Immunoregulatory Peptides

Background

- Peptides on “fringes” of medicine until recently

- Past Problems
  - High costs
  - Limited availability
  - Short half-lives
  - Lack of oral bioavailability
  - Side effects
  - Poor patient compliance with injections
  - Regulatory environment
  - Sub-quality products readily available on internet

Bruno BJ, Miller GD, Lim CS. Basics and recent advances in peptide and protein drug delivery. Ther Deliv. 2013;4(!1):1443-1467.

Background

- What Changed?
  - Genomics, Metabolomics, Proteomics
  - Recombinant technology and genetic engineering
  - Pharma directed
- Improved bioavailability
- Decreased side effects
- Improved efficacy and safety

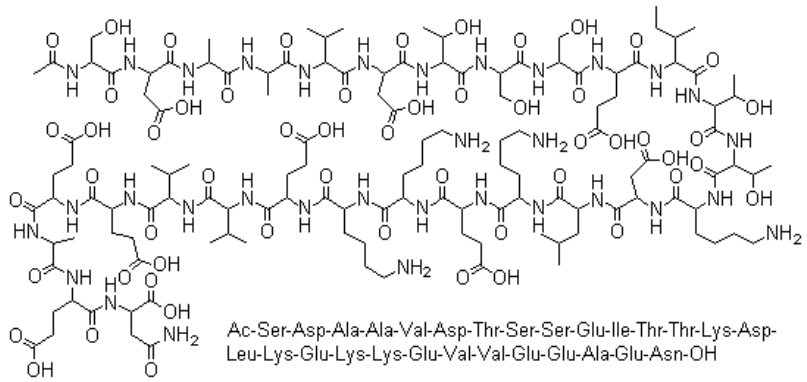
Bruno BJ, Miller GD, Lim CS. Basics and recent advances in peptide and protein drug delivery. Ther Deliv. 2013;4(!1):1443-1467.

Immune Peptides

- Critical for mobilizing immune system
- Adaptive and Innate Immunity
- Adds additional therapeutic choices

Thymosin Alpha 1

- Synthetic thymic peptide
- 28 amino acids
- MW = 3108.28
- Modulates innate immunity
- Pleiotropic immune modulation
- Helps maintain Immune homeostasis
- Toll-like receptor (TLR)9 agonist
- Vaccine agonist



Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH

Yang X, Qian F, He H, et al. Effect of thymosin alpha-1 on subpopulations of Th1, Th2, Th17 and regulatory T cells (Tregs) in vitrol. Braz J Med Biol Res. 2012;45(1):25-32.
Romani L, MorettiS, Fallarino F, et al. Jack of all trades: thymosin alpha-1 and its pleiotropy. Ann NY Acad Sci. 2012;1269:1-6.

Thymosin Alpha 1

- Promotes T cell differentiation and maturation
  - In vivo and in vitro data
- Decreases T cell apoptosis
- Improves Th1 responses
- Balances Th1/Th2
- Activates indoleamine 2.3-dioxygenase enzyme

Yang X, Qian F, He H, et al. Effect of thymosin alpha-1 on subpopulations of Th1, Th2, Th17 and regulatory T cells (Tregs) in vitrol. Braz J Med Biol Res. 2012;45(1):25-32.

Romani L, MorettiS, Fallarino F, et al. Jack of all trades: thymosin alpha-1 and its pleiotropy. Ann NY Acad Sci. 2012;1269:1-6.

Thymosin Alpha 1

- Promotes IFN type 1 production
- Decreases immune senescence
- Activates CD3+, CD4+, CD8+
- Improves production of IL-1 beta, IFN-γ, IL-2, IL-3,
- IL-6, IL-10
- Improves NK cell activity and TNF-alpha
- Inhibits viral replication
- Antioxidant

Yang X, Qian F, He H, et al. Effect of thymosin alpha-1 on subpopulations of Th1, Th2, Th17 and regulatory T cells (Tregs) in vitrol. Braz J Med Biol Res. 2012;45(1):25-32.

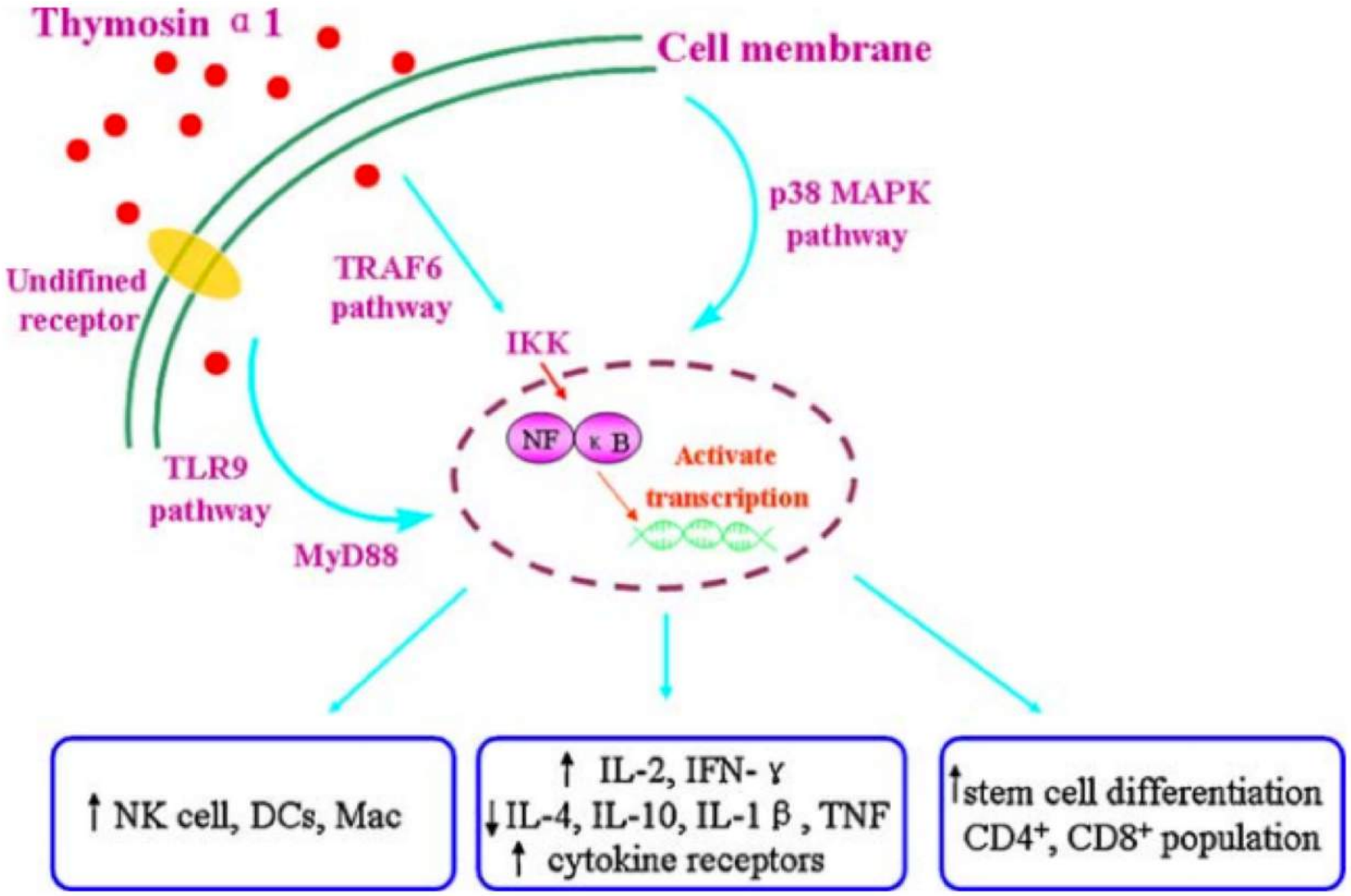
Romani L, MorettiS, Fallarino F, et al. Jack of all trades: thymosin alpha-1 and its pleiotropy. Ann NY Acad Sci. 2012;1269:1-6.

Th1 Th2 Imbalance

Studies report immune dysfunction is associated with a wide-variety of common chronic illnesses

- Chronic Stress
- Depression
- Metabolic Syndrome
- Weight management issues
- Insulin resistance and type 2 diabetes
- Anti-Aging effects – increased oxidative stress
- Chronic fatigue syndrome/fibromyalgia
- Autoimmune conditions
- Cancer
- Chronic
- Environmental toxins
- Chronic infections, including Lyme, viruses, candida and many parasites
- Glutathione depletion consistently results in TH1-TH2 shift
- Dysbiosis
- Food allergies or sensitivities
- Zinc and selenium deficiencies

Ta1 Mechanism



Ta1 Applications

- Conditions requiring immune response modulation
- COVID-19 immune support – restoration of lymphocytopenia
- Hepatitis B and C
- Treatment of HIV/AIDS
  - Can be used in conjunction with oral antiretroviral treatments
- Cancer treatment/chemotherapy adjunct
  - Non-small cell lung , hepatocellular, malignant melanoma
- DiGeorge's Syndrome

Rasi G, Terzoli E, Izzo F, et al. Combined treatment with thymosin alpha 1 and low-dose interferon alpha after dacarbazine in advanced melanoma. Melanoma Res. 2000;10:189-192.

Matteucci C, Grelli S, Balestrieri E, et al. Thymosin alpha 1 and HIV-1: recent advances and future prospectives. Future Microbiol. 2017;12:141-155.

Ta1 Dosage

- 3mg/ml 5ml vial
- 450mcg (0.15ml) SQ 1-2 x daily OR 1.5 mg (0.5 ml) SQ every 3rd day
- Treatment from 2 weeks for viral infection and 3 months or longer for HIV/ cancer / Hepatitis B, C or complicated immune suppression or over-activation
- Multiple overlap of usage
- Transient increases in ALT have been reported to occur
- Do not use in individuals being deliberately immunosuppressed.

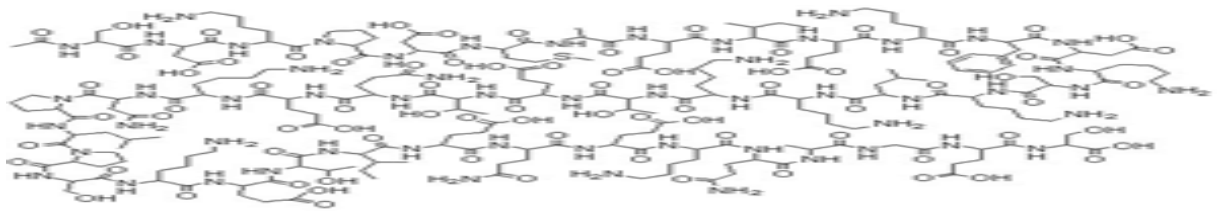
Yang X,, et al. Effect of thymosin alpha-1 on subpopulations of Th1, Th2, Th17 and regulatory T cells (Tregs) in vitrol. Braz J Med Biol Res. 2012;45(1):25-32.

Safety - Zadaxin®

- Chinese patented thymosin alpha-1
- Approved in over 35 Countries
- Well tolerated
- Used in over 300,000 patients
- No significant side-effects
- Used in elderly up to 101 yrs and children 13 months
- No SE's like interferon
- None of these studies led to an irreversible or overtly inflammatory immune system response when using Ta1

Thymosin Beta-4

- TB4 or TB-500
  - Originally isolated from calf thymus
  - More ubiquitous – occurs in most all cells
  - 43 amino acids
  - Ac-Ser-Asp-Lys-Pro-Asp-Met-Ala-Glu-Ile-Glu-Lys-Phe-Asp-Lys-Ser-Lys-Leu-Lys-Lys-Thr-Glu-Thr-Gln-Glu-Lys-Asn-Pro-Leu-Pro-Ser-Lys-Glu-Thr-Ile-Glu-Gln-Glu-Lys-Gln-Ala-Gly-Glu-Ser
  - Higher levels in platelets and white cells



TB4

- Helps decrease scar tissue formation
  - Reduces level of myofibroblasts

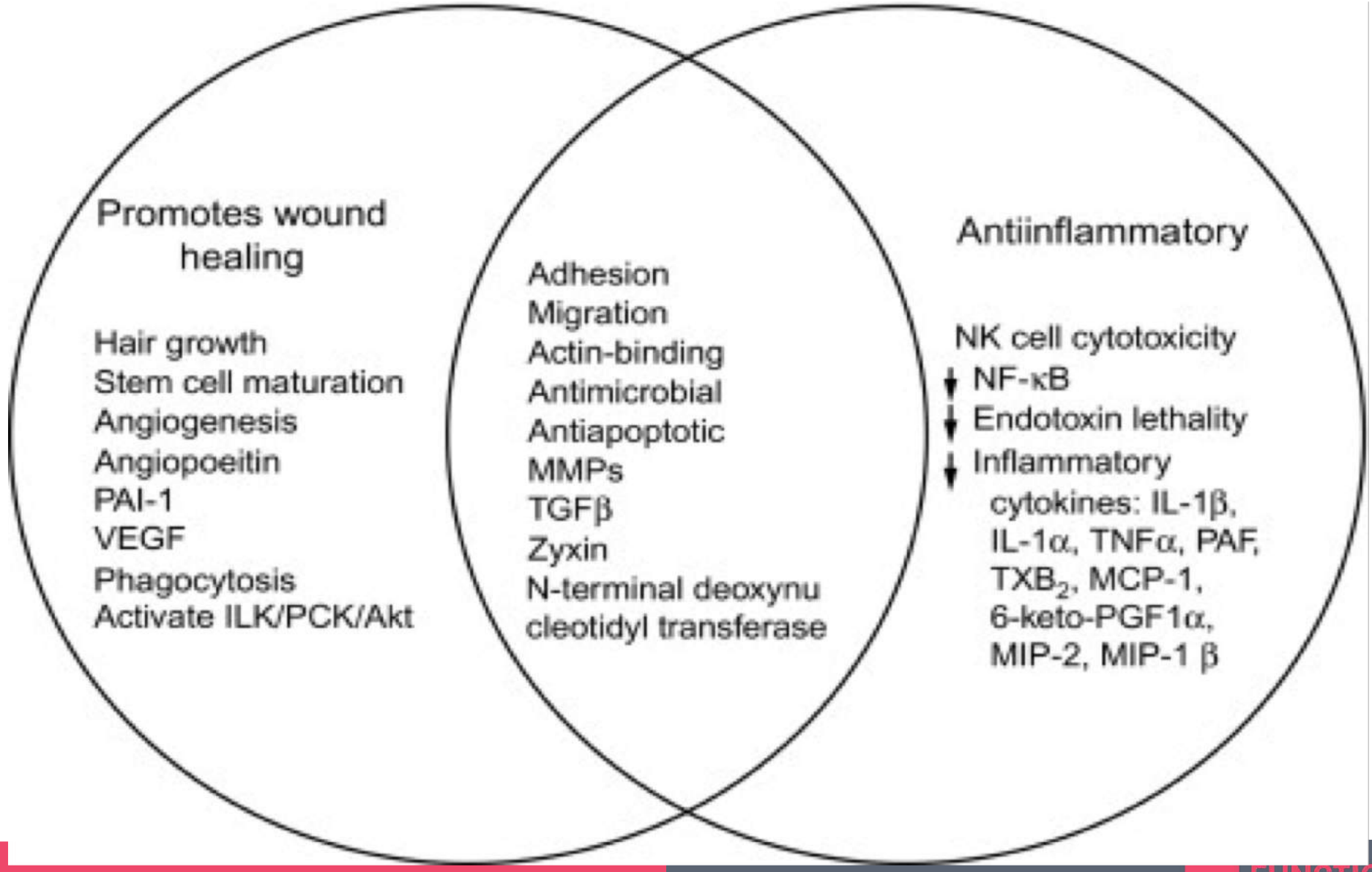
- Also supports immunity
  - Antimicrobial
  - Improves T cells
  - Use with Thymosin alpha 1

- Neuroprotective

Reti R, Kwon E, Qui P, et al. Thymosin B4 is cytoprotective in human gingival fibroblasts. Eur J Oral Sci. 2008;116(5):424-30.

Popoli PR, Pepponi A, Martire et al. Neuroprotective Effects of Thymosin B4 in Experimental Models of Excitotoxicity. Ann. N.Y. Acad. Sci.2007;1112: 219–224.

TB4 Summary



Reti R, Kwon E, Qui P, et al. Thymosin B4 is cytoprotective in human gingival fibroblasts. Eur J Oral Sci. 2008;116(5):424-30.
Popoli PR, Pepponi A, Martire et al. Neuroprotective Effects of Thymosin B4 in Experimental Models of Excitotoxicity. Ann. N.Y. Acad. Sci.2007;1112: 219–224.

TB4 Applications

- **Soft Tissue Repair – tendon, ligament, muscle**
  - **Sports/athletic injuries**
- Pressure or venous stasis ulcers
- Conditions requiring immune response modulation
- Brain issues if autoimmunity suspected
- Ischemic stroke

Kleinman HK, Sosne G. Thymosin B4 promotes dermal healing. Vitam Horm. 2016;102:251-75.

Yarmola EG, Kilmenko ES, Fujita G, et al. Thymosin beta4: actin regulation and more. Ann NY Acad Sci. 2007;1112:76-85.

TB4 Applications

- Spinal cord injuries
- TBI / concussion (in conjunction with BPC-157)
- Dry eye disorders
  - Phase II clinical trials – RegeneRx
- Corneal injuries
- Phase 3 US trial for Epidermolysis bullosa
- Lung inflammation – fibrosis
- May improve hair growth

Goldstein AL, Hannappei E, Sosne G, et al. Thymosin beta4: a multifunctional regenerative peptide: Basic properties and clinical applications. Expert Opin Biol Ther. 2012;12(1):37-51.

TB4 Applications

- Cardio protection
  - Improves cardiac wound repair
  - Antifibrotic
  - Proangiogenic
  - Reduces infarct volume and preserves cardiac function in preclinical models of cardiac ischemic injury.
  - Used in hypoxic heart disease

- NAFLD (non alcoholic fatty liver disease)
  - Inhibits oxidative stress
  - Decreases proinflammatory factors
  - Decrease hepatic fibrosis

Shrivastava S, Srivastava D, Olson EN, et al. Thymosin beta4 and cardiac repair. Ann NY Acad Sci. 2010;1194:87-96.
Jiang Y, Han T, Zhang Z, et al. Potential role of thymosin beta 4 in the treatment of nonalcoholic fatty liver disease. Chron Dis Trans Med. 2017;3:165-68.

TB4 Applications

- Decreases endotoxemia – use in sepsis and elevated LPS

- Reported in lab studies to reduce polymerization

for G-actin into F-actin

- Improves mortality rate

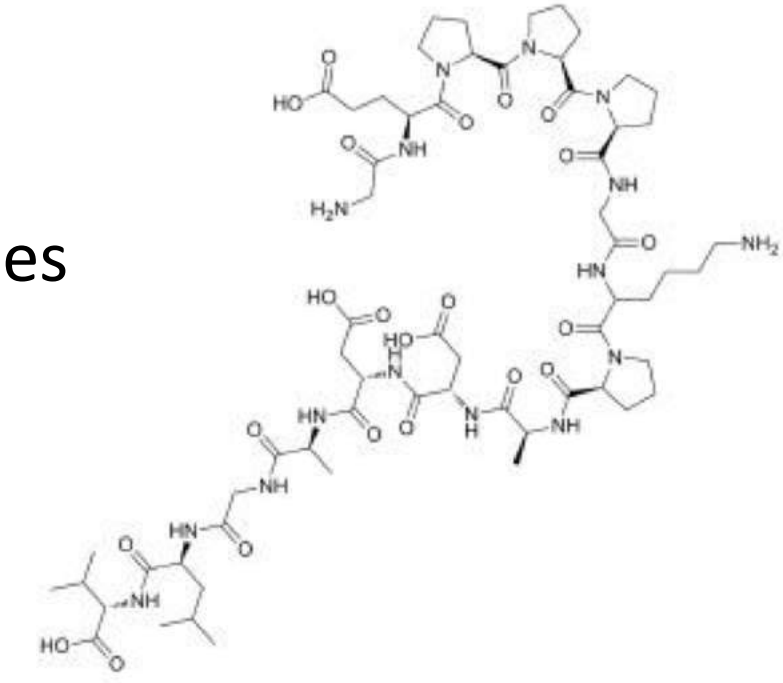
Badamchian M, et al. Thymosin beta 4 reduces lethality and down-regulates inflammatory mediators in endotoxin-induced septic shock. Int Immunopharmacol. 2003;3(8):1225-33.

TB4 Dosage

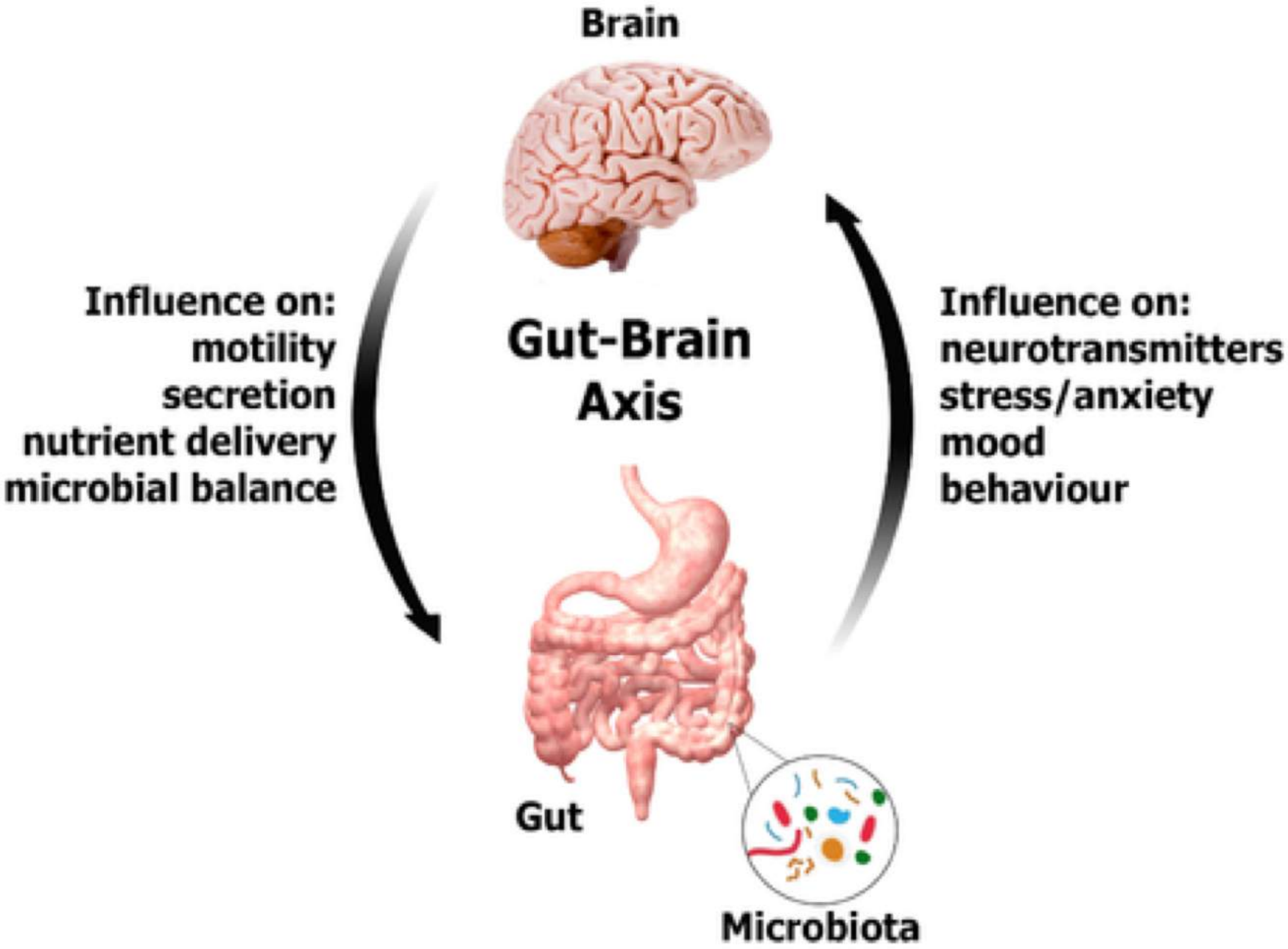
- General dosage
  - 300 mcg – 1 gram daily, SubQ
  - Depending upon clinical presentation
  - Do not dose for more than 3 months
  - Cycle if needed long-term – 3 months on, 1 month off
- TB4 use with Thymosin alpha 1 and BPC-157 concurrently
- Individual dosage requirements may vary based on clinical presentation

BPC 157

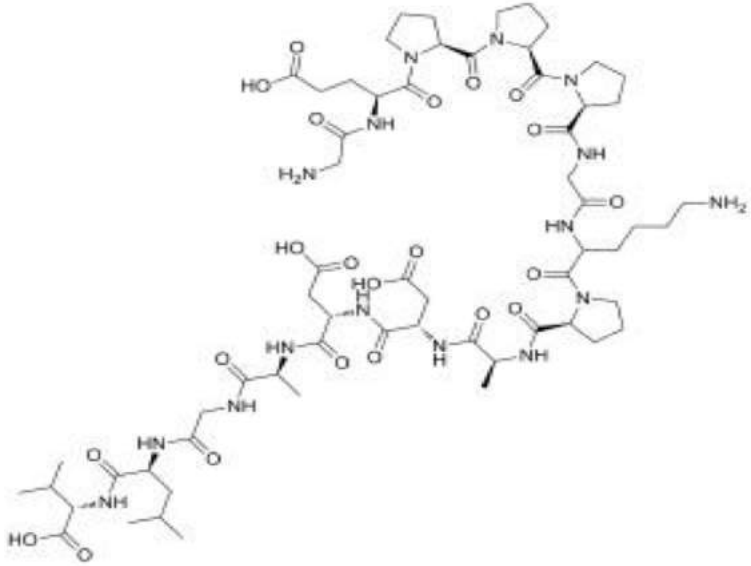
- Body protection compound 157
- Pentadecapeptide MW 1419
- Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val
- Focuses on Gut-Brain Axis
- Human BPC is found in gastric juices



Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and Practical Implications. Curr Neuropharmacol. 2016;14(8):957-865.


Brain
Influence on:
motility
secretion
nutrient delivery
microbial balance
Gut-Brain Axis
Influence on:
neurotransmitters
stress/anxiety
mood
behaviour
Gut
Microbiota

BPC 157



- Gastric protection
  - Antiulcer peptidergic agent
  - Cytoprotective
  - Nitric Oxide (NO) improvement
    - BPC 157 interacts with nitric oxide (NO)

      system, both NOS-substrate (L-arginine) and NOS-blocker (L-NAME), including the regulation of a blood pressure
  - Helps improve GI mucosal integrity
  - Ulcerative colitis in lab studies
  - Decreases NSAID and alcohol gastric side effects

Sikiric P, et al. Focus on ulcerative colitis: stable gastric pentadecapeptide BPC 157. Curr Med Chem. 2012;19(1):126-32.

BPC 157

- Helps heal tissues
  - Reported to improve cell survival under oxidative stress
  - Increased fibroblast migration and dispersal
  - Induces F-actin formation in fibroblasts
  - Improves angiogenesis
  - Enhances vascular expression of VEGFR2
  - BPC-157 increases the extent of phosphorylation of paxillin and FAK proteins without affecting the amounts produced
- used in deep skin burns, corneal injuries
- injured muscle, tendon, ligament or bone

Duzel A, et al. Stable gastric pentadecapeptide BPC 157 in the treatment of colitis and ischemia and reperfuction in rates: new insights. World J Gastroenterol. 2017;23(48):8465-88.

BPC 157

- Neuroprotective
  - Influences serotonergic, dopaminergic, opioid and GABAergic systems
  - Improves nerve regeneration
  - Decreases neuroinflammation
  - May help in depression
  - Ameliorates alcohol withdrawal symptoms and opposes alcohol intoxication

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.

BPC 157

- Cardioprotective
  - May help regulate blood pressure
  - Nitric oxide improvement
  - BPC 157 rapidly and permanently counteracts the QTc prolongation induced by neuroleptics (such as haloperidol, fluphenazine, clozapine, olanzapine, quetiapine) and prokinetics

Strinic D, et al. BPC 157 counteracts QTc prolongatino induced by haloperidol, fluphenazine, clozapine, olanzapine, quetiapine, sulpiride and metoclopramide in rats. Life Sciences. 2017;186(1):66-79.

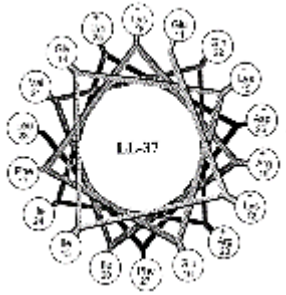
Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des, 2014;20(7):1121-35.

BPC 157 -Dosage

- SubQ
  - Half life approx. 4 hours
  - 400 – 600 mcg/day total
  - If injury specific = split dosing into 20-300 mcg BID
  - Oral = 500 mcg daily
- Corticosteroids may reduce BPC-157's ability to heal muscles
- Results can be spontaneous and improve over 2-4 weeks treatment
- Safe in recommended dosages

Pevec D, et al. Impact of pentadecapeptide BPC 157 on muscle healing impaired by systemic corticosteroid application. Med Sci Monit. 2010;16(3):BR81-88.

LL-37



- LL-37 is a cathelicidin antimicrobial peptide
- Part of a mammal's innate immunity – natural antibiotic
- Endogenously expressed in epithelial cells of the testis, skin, the gastrointestinal tract, and the respiratory tract, and in leukocytes such as monocytes, neutrophils, T cells, NK cells, and B cells
- Disrupts microbe's outer membrane
- Also exerts "alarmin" activity – recruits immune and inflammatory cells
- Possibility for use in COVID-19 infections
- Dose
  - 2,000 mcg/ml 5ml vial
  - General dosage: 0.1 ml (200 mcg) SQ daily for 6-8 weeks
  - Add vitamin D3 5,000 IU (125mcg) daily if level < 50ng/ml
  - LL-37 is activated in the body by vitamin D

Ulrich HND, et al. LL-37, the only human member of the cathelicidin family of antimicrobial peptides. Boichem Biophys Acta Biomembrane. 2006;1758(9):1408-25.

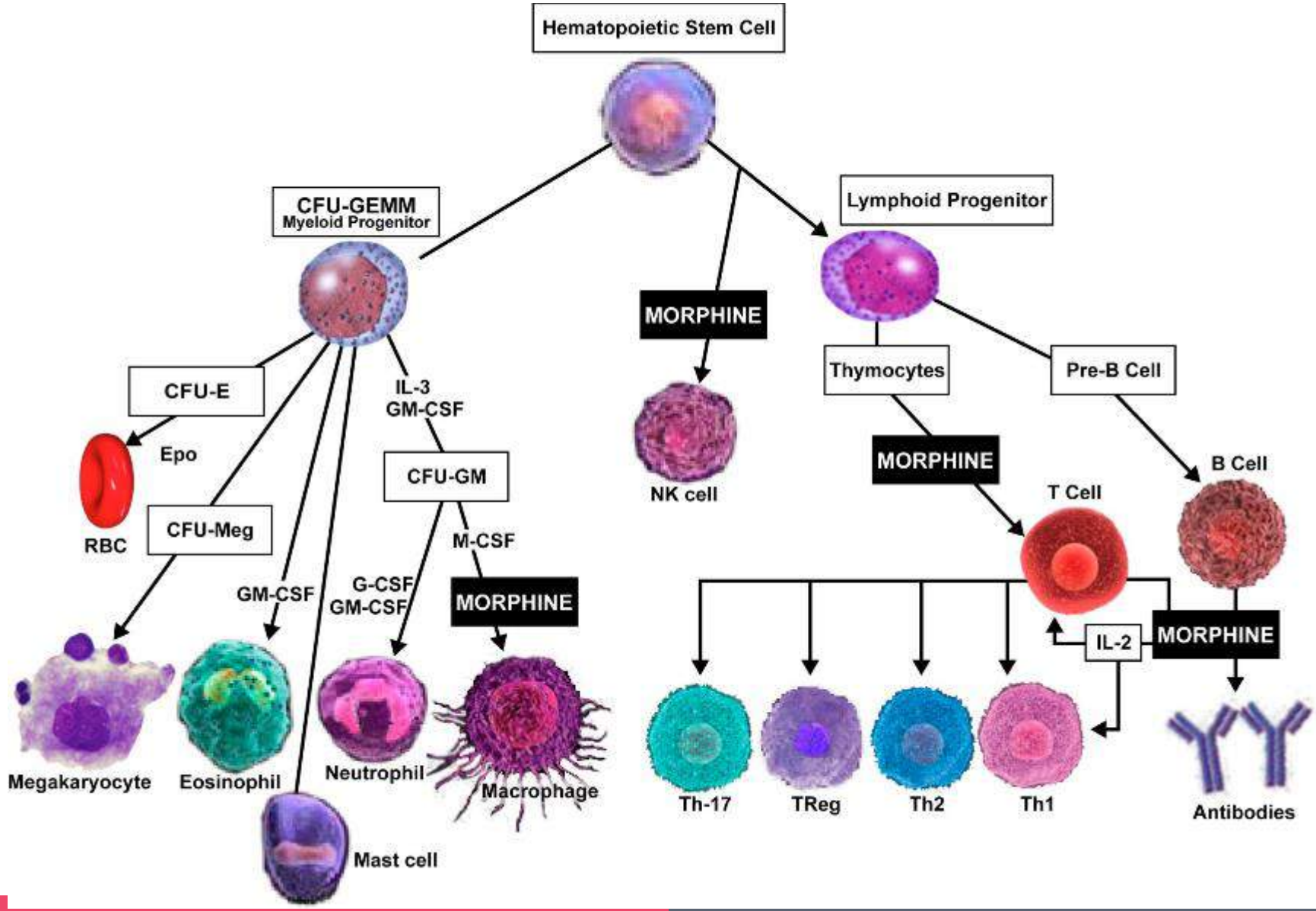
FUNCTIONAL MEDICINE
Continuing Education

Low-Dose Naltrexone Studies

Low Dose Naltrexone (LDN)

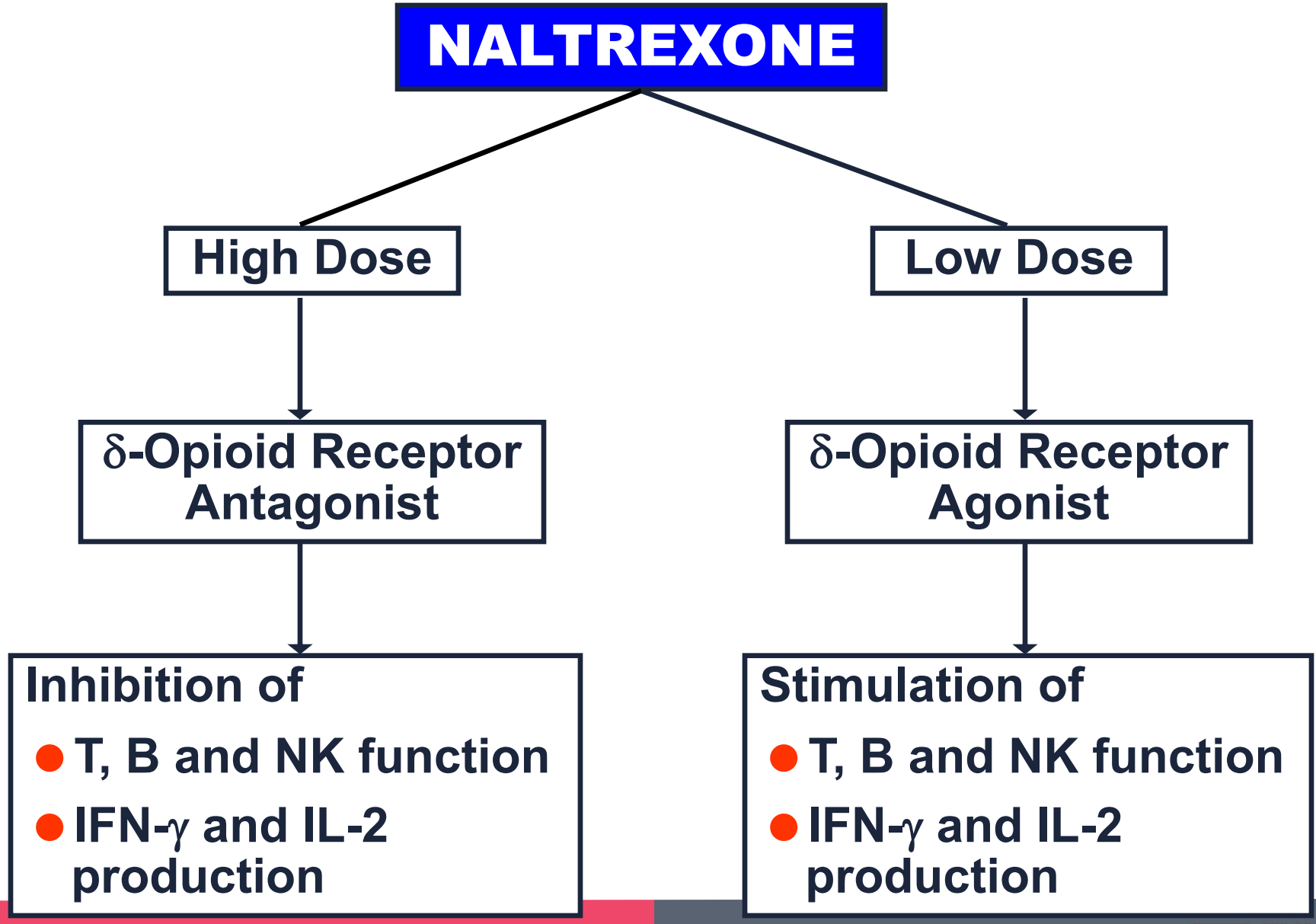
- Dose: 3 to 4.5 mg/d
- Hypothesized to increase production of endogenous opioids during short term blockade of opioid receptors
  - Involved in growth and in the immune system and immune modulation

Effects of Opioids on the Immune System

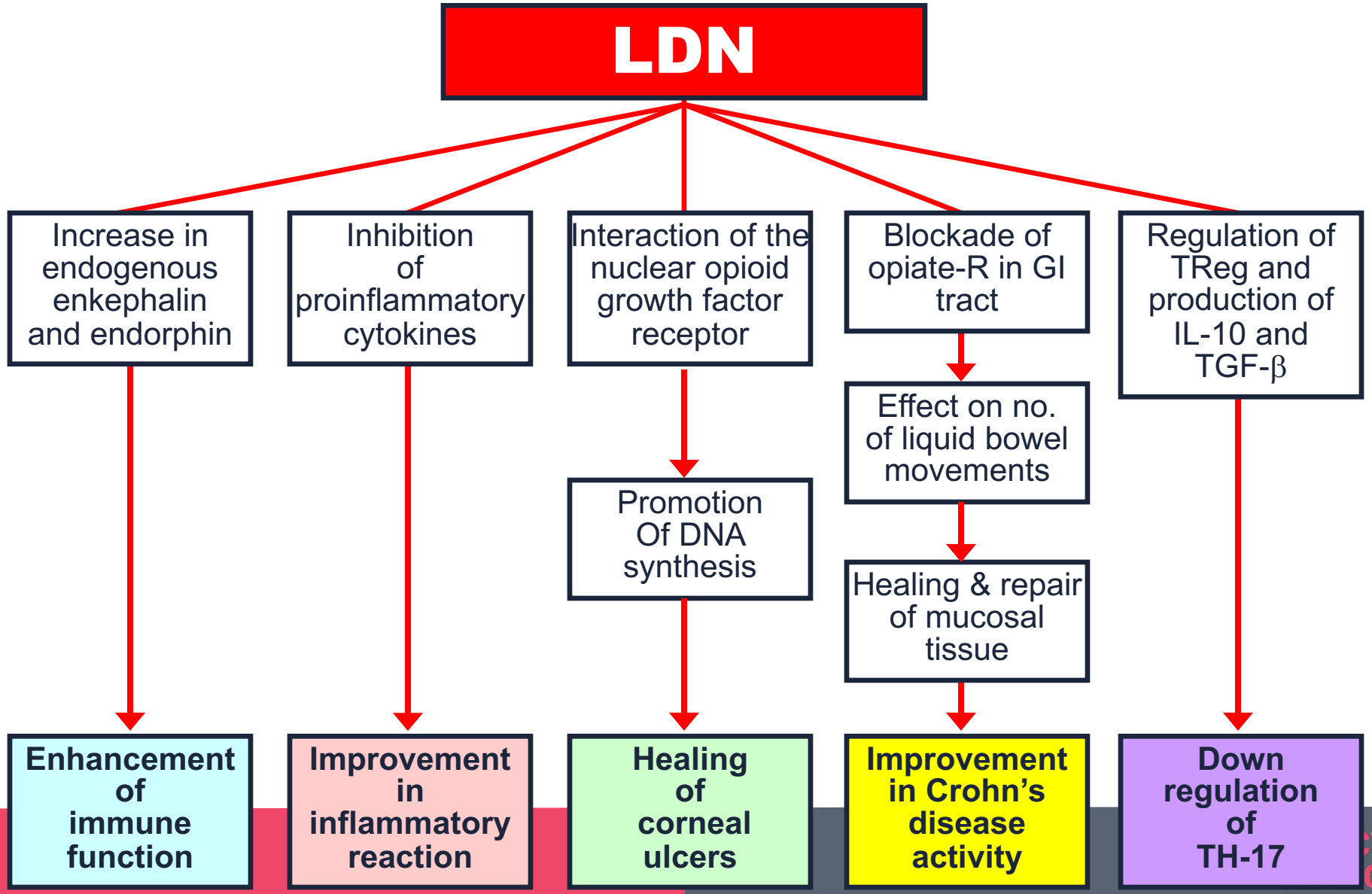


Schematic representation of the hematopoietic system showing the differentiation pathways sensitive to opioids.

from Effects of Opioids on the Immune System – Roy S. and Loh H.H., Neurochemical Research, 21:1375-1386, 1996


NALTREXONE
High Dose
Low Dose
δ-Opioid Receptor Antagonist
δ-Opioid Receptor Agonist
Inhibition of
T, B and NK function
IFN-γ and IL-2 production
Stimulation of
T, B and NK function
IFN-γ and IL-2 production

MECHANISM OF ACTION OF LDN



The Use of LDN as a Novel Anti-Inflammatory Treatment for Chronic Pain

- Review of evidence that LDN may operate as a novel anti-inflammatory agent in the central nervous system, via action of microglial cells
- Currently used in fibromyalgia, Crohn's disease, multiple sclerosis, and complex regional pain syndrome
- Effects may be unique to LDN and appears to be independent from naltrexone's better known activity on opioid receptors
- LDN is well tolerated
- Current literature has small sample sizes, and few replications have been performed to help promote data
- LDN may represent on of the first glial cell modulators to be used for the management of chronic pain disorders

Initial Findings of an Open-Label Trial of Low-Dose Naltrexone for Symptomatic Mesenteric Panniculitis

- Lack of prospective studies and appropriate treatments for mesenteric panniculitis
- 4.5 mg for 12 weeks administered to 3 patients
- Primary endpoint: reduction in Mesenteric Panniculitis Subjective Assessment Score
- ESR and c-reactive protein tested at baseline
- All 3 patients had decrease in MPSAS at 4 weeks
  - 2 of 3 had decrease at 8 weeks
- Conclusion*:* LDN was safe, had minimal side effects , and showed efficacy in patients with symptomatic mesenteric panniculitis
- Further studies need to be conducted

Low Dose Naltrexone for Treatment of Multiple Sclerosis

- Retrospective chart review of safety and tolerability
- Multiple sclerosis is autoimmune disease of central nervous system
- Chart review of 215 patients with MS given oral LDN
- Study showed significant number of combination therapy of immunomodulating agent and LDN
- LDN did not cause any unexpected side effects and did not potentiate side effects of immunomodulating therapies

Low Dose Naltrexone Treatment of Established Relapsing-Remitting Experimental Autoimmune Encephalomyelitis

- Examined the modulation of opioid growth factor with low doses of naltrexone as disease modifying therapy for relapse-remitting autoimmune encephalomyelitis
- LDN treatment reduced behavioral scores across the 40 day observation point
- LDN increase the length of remission as well as the duration of mild disease
- Conducted in mice, so needs to be demonstrated in humans as well in further studies

Off-Label, LDN for Refractory Painful Diabetic Neuropathy

- 2 mg dose of LDN showed to have partial improvement in burning pain of diabetic neuropathy
- 4 mg dose for 2 weeks produced even better pain relief
- Sleep improved after the treatment
- On examination, there was no hyperalgesia, but the sensory loss was not improved
- Initially, mild diarrhea, nausea, and somnolence occurred with treatment but subsided spontaneously after a few days
- Proposed mechanisms includes:
  - Opioid receptor blockage causing compensatory release of endogenous opioids
  - Antagonism of TLR-4 on microalga, which produces a variety of inflammatory factors such as pro-inflammatory cytokines, substance P, nitric oxide, and excitatory amino acids

Low-Dose Naltrexone for the Treatment of Sarcoidosis

- Case report of a patient with Systemic sarcoidosis treated with LDN
- LDN increased endorphin levels and helped regulate inflammation including lymphocyte activity
- Radiographic improvement was seen
- Clinical improvement marked by less fatigue and no more need for antibiotic therapy for a sarcoid rash
- Unclear is the perceived improvement in dyspnea is directly responsible from the LDN
- Fatigue is the most common problem in sarcoidosis and can be secondary to pulmonary hypertension, chronic inflammation, infections, and drug side effects
  - LDN may have improved fatigue by reducing inflammation burden

Low-Dose Naltrexone Treatment of Familial Benign Pemphigus

- 3 patients with biopsy proven recalcitrant Hailey Hailey Disease were evaluated and treated with LDN 1.5 mg to 3 mg
- Clinical response included healing of erosions, improvement of erythema, and alleviation of pain
- 3 patients exhibited at least 80% improvement in extent of disease
  - One patient had 90% clearance
  - All 3 patients had substantial improvement in QOL
- No adverse effects recorded

Naltrexone Inhibits IL-6 and TNF-alpha

- Analyzed effects of LDN on IL-6 secretion by peripheral blood mononuclear cells
  - In vitro following stimulation with ligands for TLR4 and for intracellular receptors TLR7, TLR8, and TLR9
- Naltrexone did not affect cell viability or induce apoptosis of PBMC
- Intracellular staining showed that naltrexone inhibited production of IL-6 and TNF-alpha by monocyte and plasmacytoid dendritic cell subsets
  - Within PBMC population following treatment with ligands for TLR7/8 and TL9, respectively

Naltrexone Inhibits IL-6 and TNF-alpha

- Naltrexone inhibited IL-6 production in isolated monocytes and B cells after TLR7/8 and TLR9 stimulation
- Findings indicate that naltrexone has potential to modulate the secretion of inflammatory cytokines in response to intracellular TLR activity
  - May have potential for use as an immunomodulator

LDN for Breakthrough MDD on Antidepressants

- Dopaminergic mechanisms of LDN proposed as augmentation for depressive breakthrough on pro-dopaminergic antidepressant regimens
- 12 adults with recurrent DSM-IV MDD on dopaminergic antidepressant regimens
  - Stimulants
  - Dopamine agonists
  - Bupropion $\geq$ 300 mg/day
  - Aripiprazole $\leq$ 2.5 mg/day
  - Sertraline $\geq$ 150 mg/day
- Given LDN 1 mg BID or placebo for 3 weeks

LDN for Breakthrough MDD on Antidepressants

- All 12 subjects completed the trial
- Hamilton depression rating scale (HAM-D-17 scores decreased from 12.2 to 11.7 for LDN
- Conclussion: LDN augmentations showed some benefit for MDD relapse on dopaminergic agents
- Larger studies needed to confirm data

Reduced Pro-Inflammatory Cytokines after Eight Weeks of LDN for Fibromyalgia

- Fibromyalgia is a complex, multi-symptom condition that predominantly affects women
- 10 week single-blind crossover trial to test the immune effects of eight weeks of oral administration of LDN
- 8 women enrolled
  - Average symptom severity was 62 out of 100
  - Average symptom duration of 14 years

Reduced Pro-Inflammatory Cytokines after Eight Weeks of LDN for Fibromyalgia

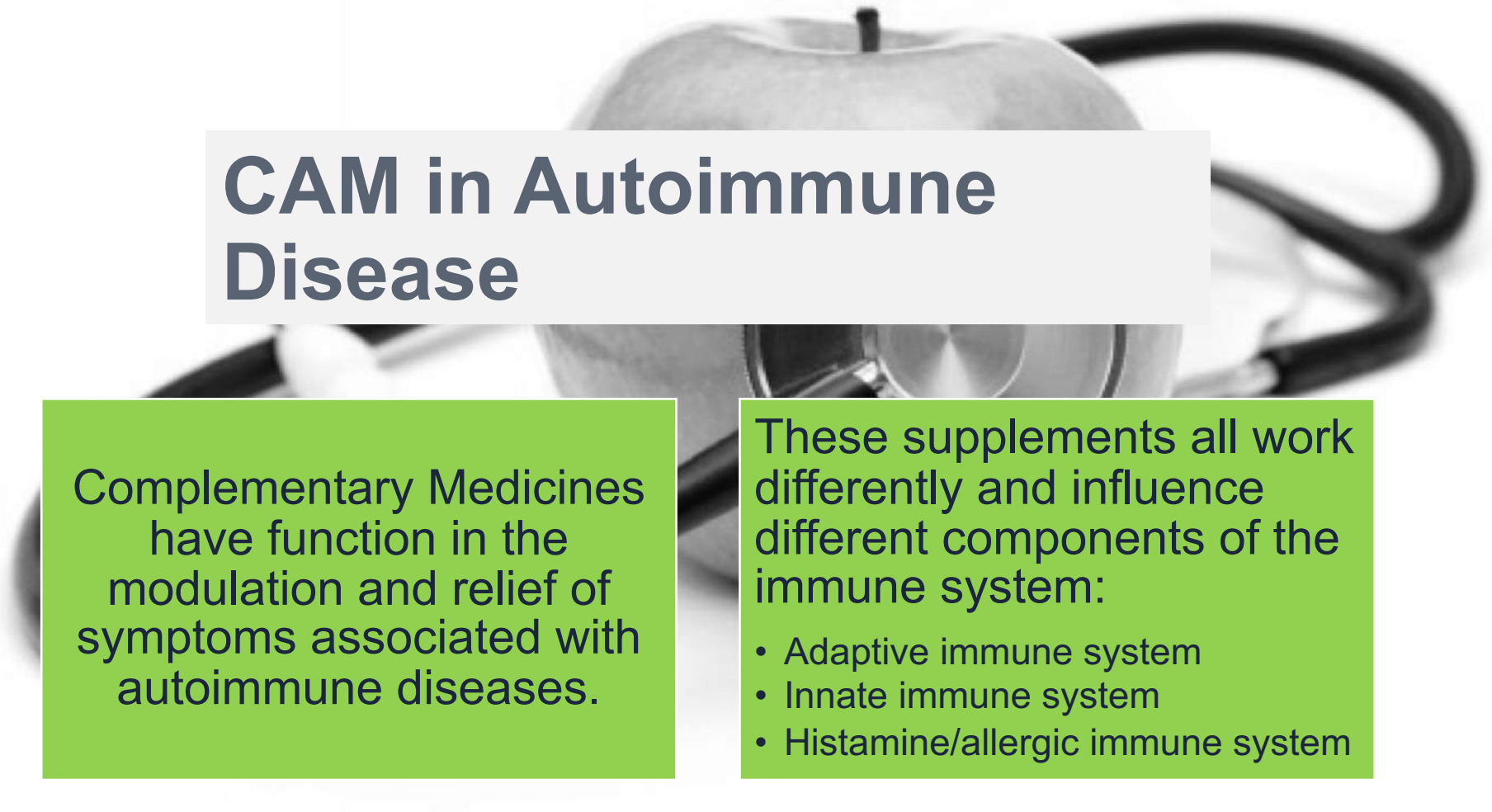
- Found that LDN was associated with reduced plasma concentrations of interleukins
  - Including: IL-1beta, IL1Ra, IL-2, IL-4, IL-5, IL6, IL-10, IL-12p40, IL-15, IL-17A, IL-27, INF alpha, TGF-alpha
- 15% reduction of fibromyalgia-associated pain and 18% reduction in overall symptoms
- Conclusion: LDN treatment in fibromyalgia is associated with a reduction of several key pro-inflammatory cytokines and symptoms
- More research needs to be conducted

Treatment of Hailey-Hailey Disease with Low-Dose Naltrexone

- Hailey-Hailey disease is a severe genetic blistering disease of intertriginous skin locations that can lead to poor QOL and increased morbidities
- The objective of this study was to determine if LDN is an effective treatment for Hailey-Hailey Disease
- Study was a case series performed at an outpatient dermatology clinic to 3 patients with severe Hailey-Hailey Disease recalcitrant to at least 4 therapies
- LDN 3 mg nightly, titrated to 4.5 mg in 2 patients
- Reductions in the size of lesions as well as subjective improvement of symptoms was found

Treatment of Hailey-Hailey Disease with Low-Dose Naltrexone

- All 3 patients noted significant healing of erosions and plaques starting from the peripheral aspect within 1 to 2 weeks of treatment
- Clinical resolution of lesions within 2 months of treatment
- Discontinuation of LDN resulted in flaring of symptoms, which cleared 2 to 3 days when re-challenged with LDN
- Conclusion: LDN is a novel therapy for Hailey-Hailey disease
- Possible mechanism may involve LDN influencing opioid or TLR signaling to improve calcium mobilization and improve keratinocyte differentiation and wound healing
- Further studies need to be conducted with larger samples sizes and to clarify the mechanism



CAM in Autoimmune Disease

Complementary Medicines have function in the modulation and relief of symptoms associated with autoimmune diseases.

These supplements all work differently and influence different components of the immune system:

- Adaptive immune system
- Innate immune system
- Histamine/allergic immune system

CAM that Affect Innate Immunity

Astaxanthin	Curcumin	Gymnema	Vitamin A
Betaine HCl with pepsin	DHEA	L-Glutamine	Vitamin C
Carnitine	Ginger	Pycnogenol	Vitamin D
Cayenne pepper	Green Tea Extract	Resveratrol	Vitamin E
Coenzyme Q10	Glutathione	SAMe	5HTP

CAM that Affect Adaptive Immunity

Boswellia	Green tea extract	SAMe
Carnitine	Glutathione	Selenium
Cromolyn	Peony	Vitamin B6
Curcumin	Resveratrol	Vitamin D

CAM that Affect Histamine/Allergic Immunity

Borage Oil	Evening primrose	Ketotifen	Selenium
Capsaicin	Curcumin	Omega-3	Vitamin C
Cat's claw	Ginger	Probiotic	Vitamin E
Coenzyme Q10	Green tea extract	Rosemary	White willow bark

Specialized Compounds for Silencing the Auto-Immune Inflammation

FUNCTIONAL MEDICINE
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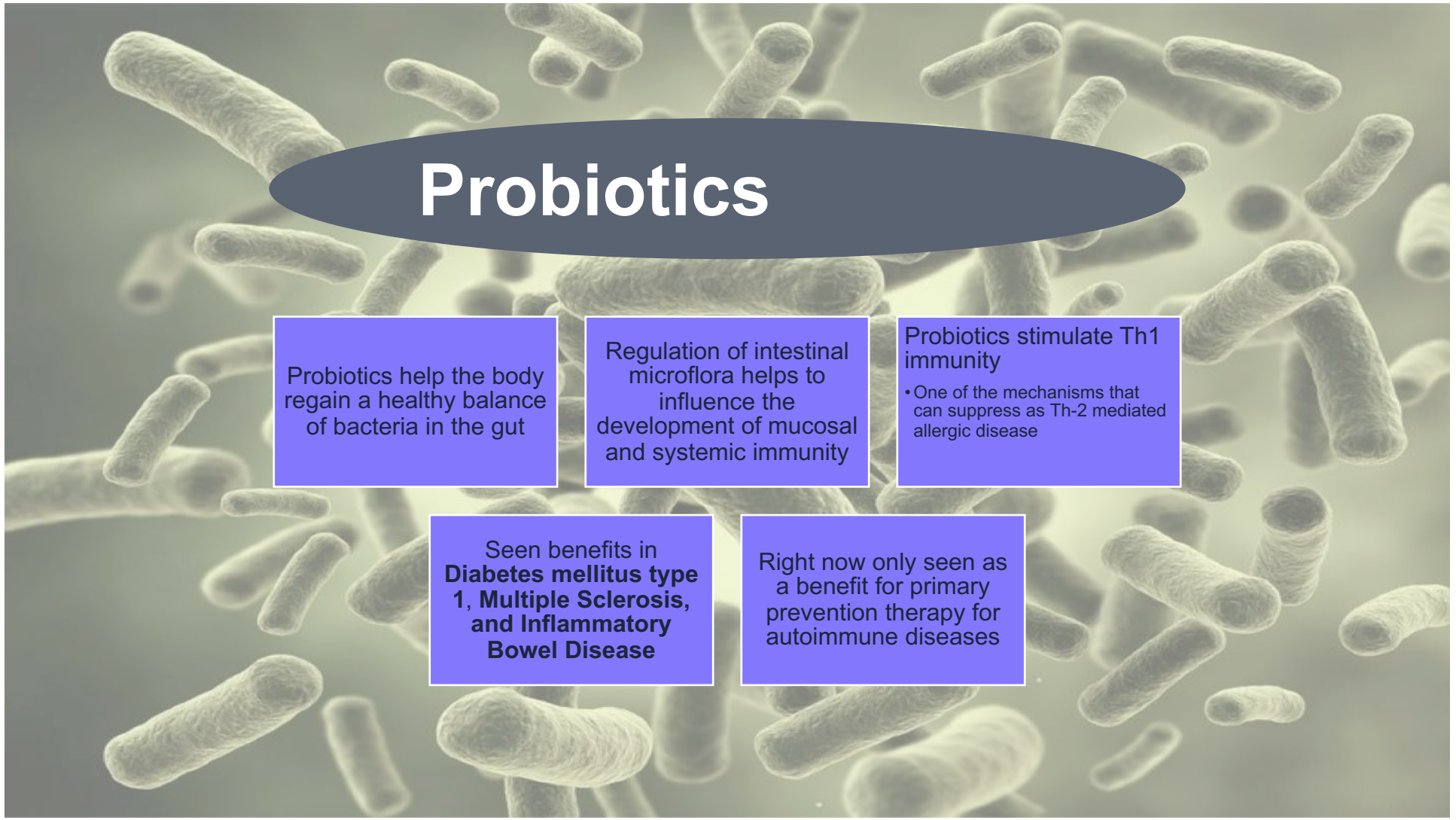
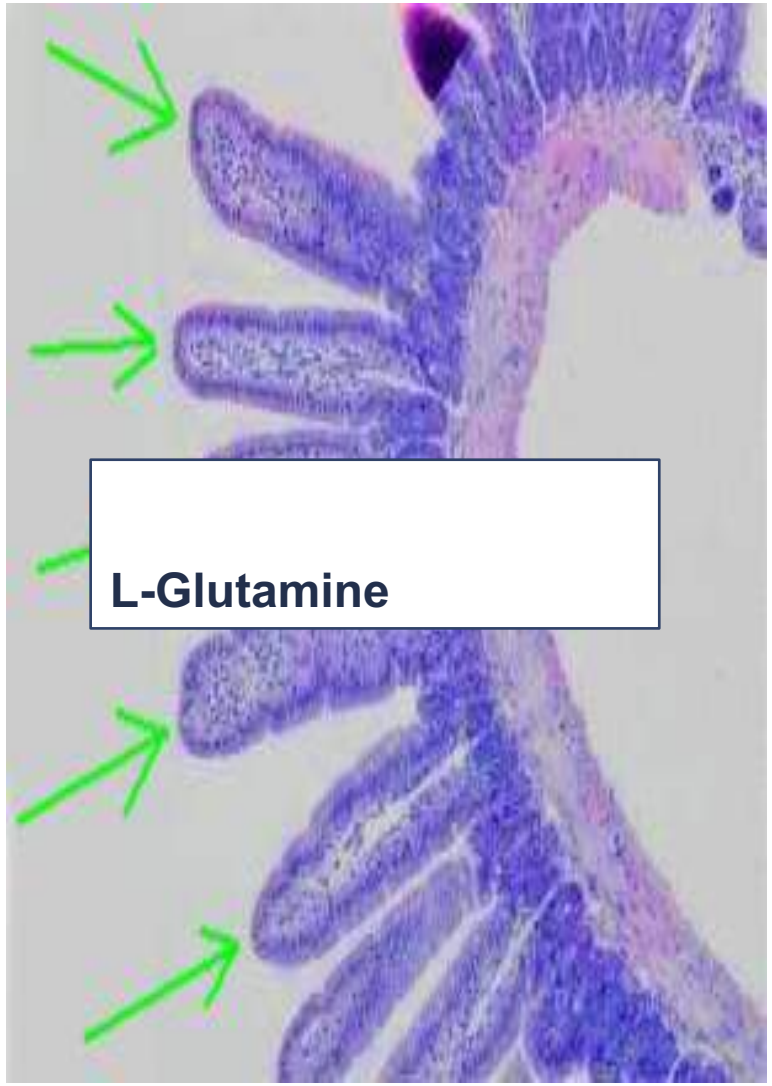
Specialized Pro-Resolving Lipid Mediators

- Biosynthesized in the resolution phase of acute inflammation and the mediators are potent agonists that control the duration and magnitude of inflammation.
- Four distinct new chemical families: lipoxins, resolvins, protectins and maresins, which are involved in acute inflammation.
- Resolvins and protectins are derived from ω3-unsaturated fatty acid-derivatives
- For example, Resolvin E1 binds G coupled-protein receptors on monocytes, macrophages and dendritic cells to attenuate TNF-mediated NFκB activation

Pro-Resolving Mediators Characteristics

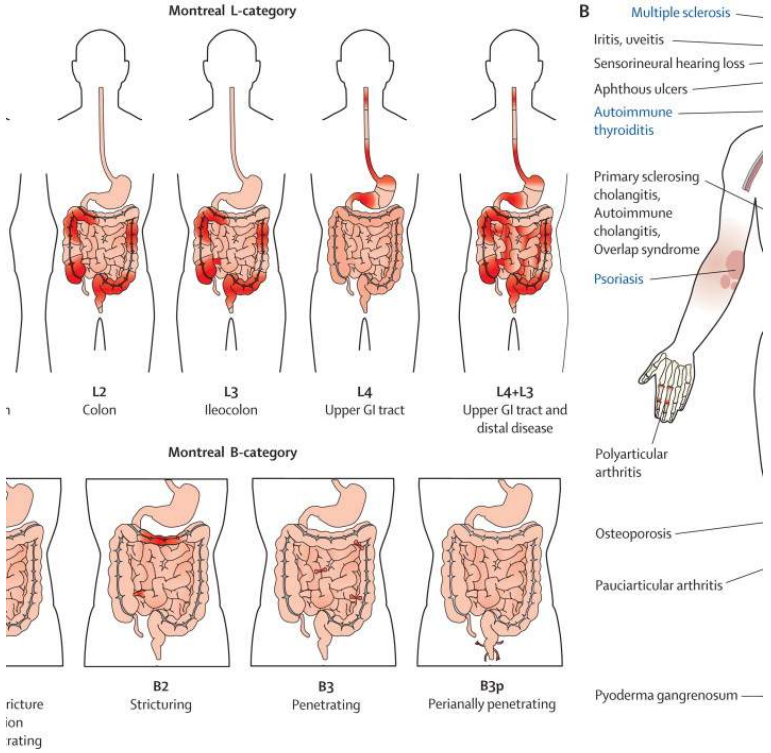
- Stop of inflammatory cell recruitment
- Induction of neutrophil apoptosis and clearance
- Egress of immune cells
- Positive modulation of the immune response
- Induction of tissue repair


Probiotics
Probiotics help the body regain a healthy balance of bacteria in the gut
Regulation of intestinal microflora helps to influence the development of mucosal and systemic immunity
Probiotics stimulate Th1 immunity
• One of the mechanisms that can suppress as Th-2 mediated allergic disease
Seen benefits in **Diabetes mellitus type 1**, **Multiple Sclerosis, and Inflammatory Bowel Disease**
Right now only seen as a benefit for primary prevention therapy for autoimmune diseases



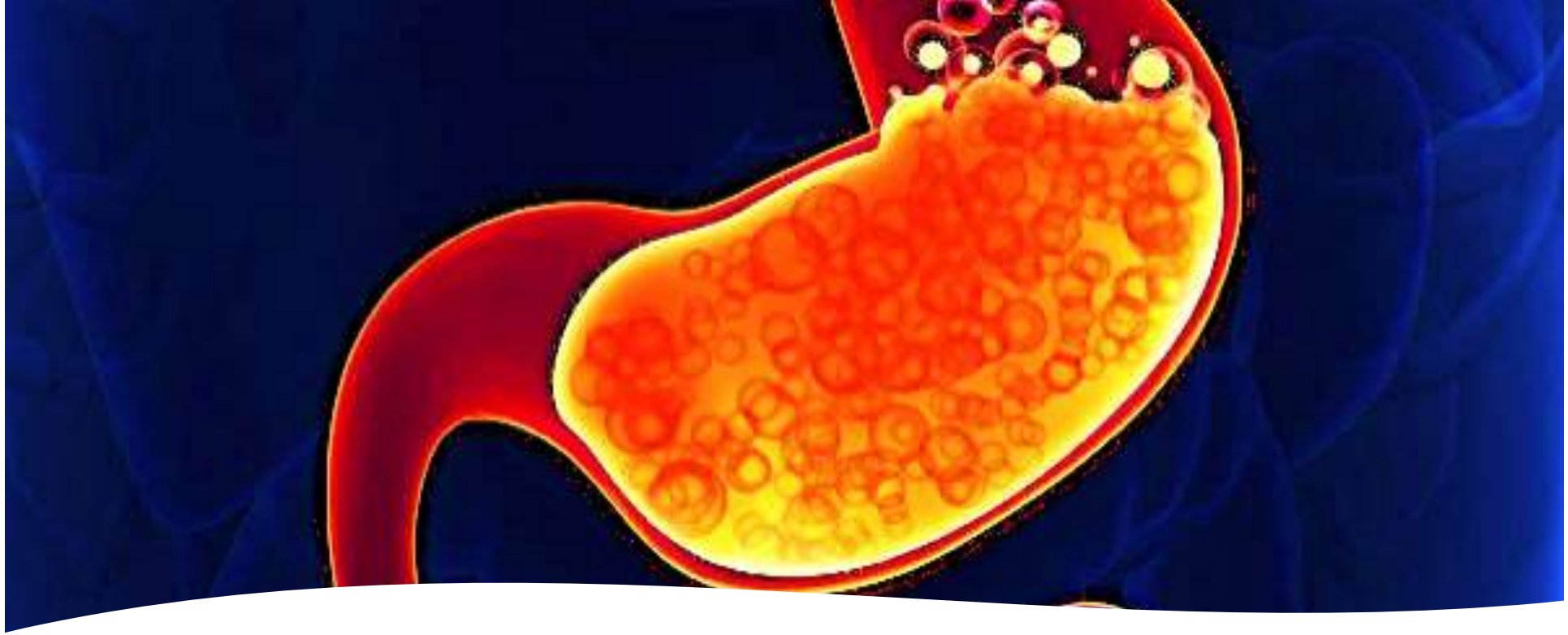
- Non-essential amino acid fundamental to the digestive and immune systems
  - Essential for lymphocyte function
- Helps repair damage to the gut
  - Helps the gut lining to regrow and repair
- Increases number of cells in the small intestine along with the number and height of villi of those cells

- **Type 1 Diabetes Mellitus**
- **Crohn's Disease**
  - Increase permeability of intestinal wall
  - Improve the ability for vital substances to properly come through the body



Proteolytic Enzymes

- Common proteolytic enzymes: pepsin, bromelain, papain
- Mechanism of Action
  - Digest protein by aiding in the digestion process, breaking it down into amino acids
- Safety
  - Generally safe



Betaine Hydrochloride with Pepsin

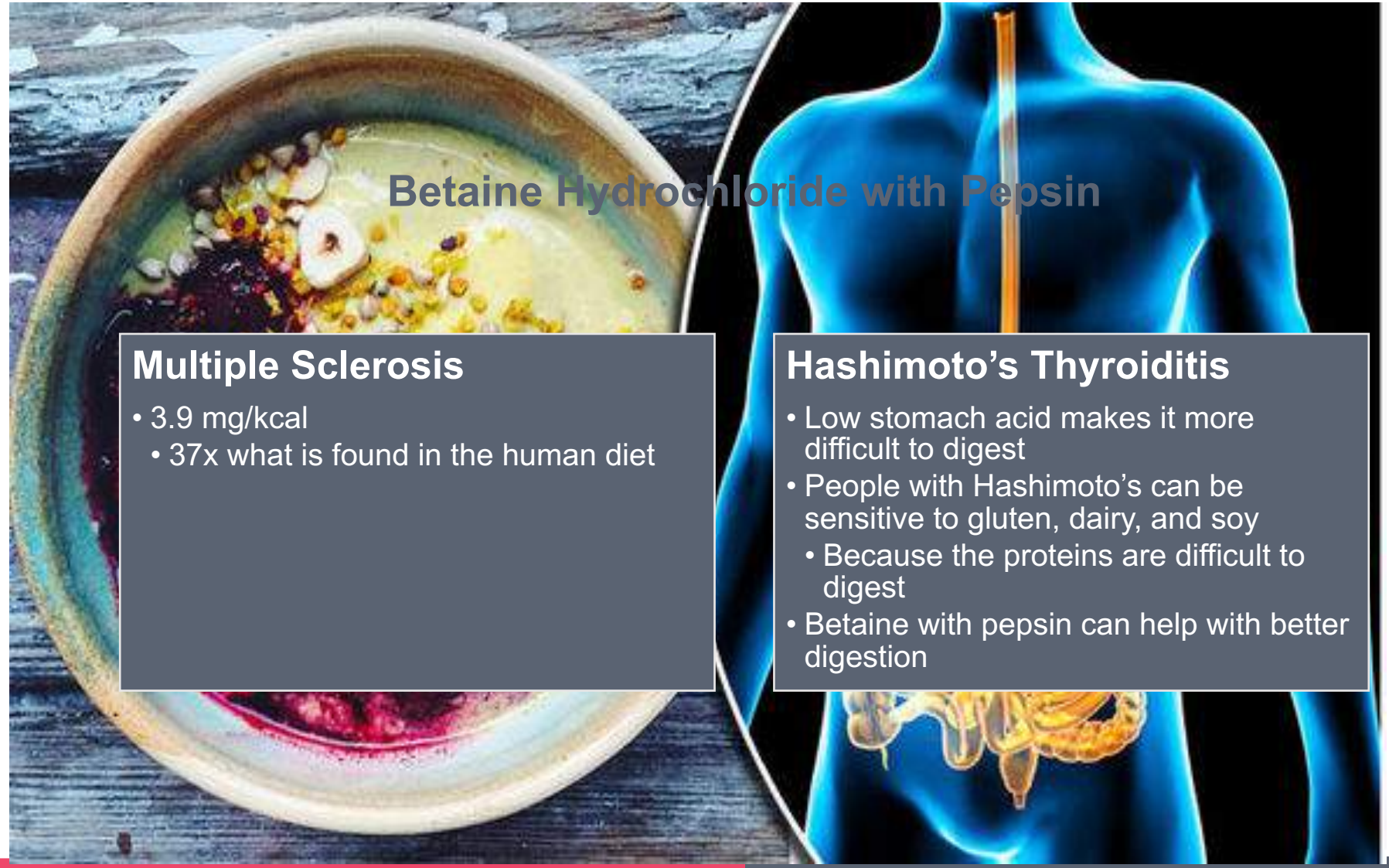
Used to increase stomach acid

Lowers gastric pH by 4.5 units

Lack of acid in the gastric fluid can be caused by autoimmune diseases

Can also be induced by infection (H. pylori) and medications (PPIs, H2-RAs)

Stimulates immune function



Betaine Hydrochloride with Pepsin

Multiple Sclerosis

- 3.9 mg/kcal
  - 37x what is found in the human diet

Hashimoto's Thyroiditis

- Low stomach acid makes it more difficult to digest
- People with Hashimoto's can be sensitive to gluten, dairy, and soy
  - Because the proteins are difficult to digest
- Betaine with pepsin can help with better digestion

Omega-3 Fatty Acids

- Help reduce inflammation
- Highly concentrated in the brain and important for cognition
- **Side effects:** flatulence, bloating, belching, diarrhea

Omega-3 Fatty Acids: Uses

Rheumatoid Arthritis	Systemic Lupus Erythematosus	Inflammatory Bowel Disease
Fish oils helps reduce symptoms of RA, including joint pain and morning stiffness One study suggest that people with RA who take fish oil may be able to lower their dose of NSAIDs Does not slow progression of RA, only treats symptoms	EPA and fish oil may reduce symptoms of SLE Two studies found that fish oil had no effect on lupus nephritis	Mixed results Some studies suggest that omega-3 fatty acids may help when added to sulfasalazine More studies needed Have similar side effects to IBD: flatulence, belching, bloating, diarrhea

Borage Oil (*Borago officinalis):* Uses

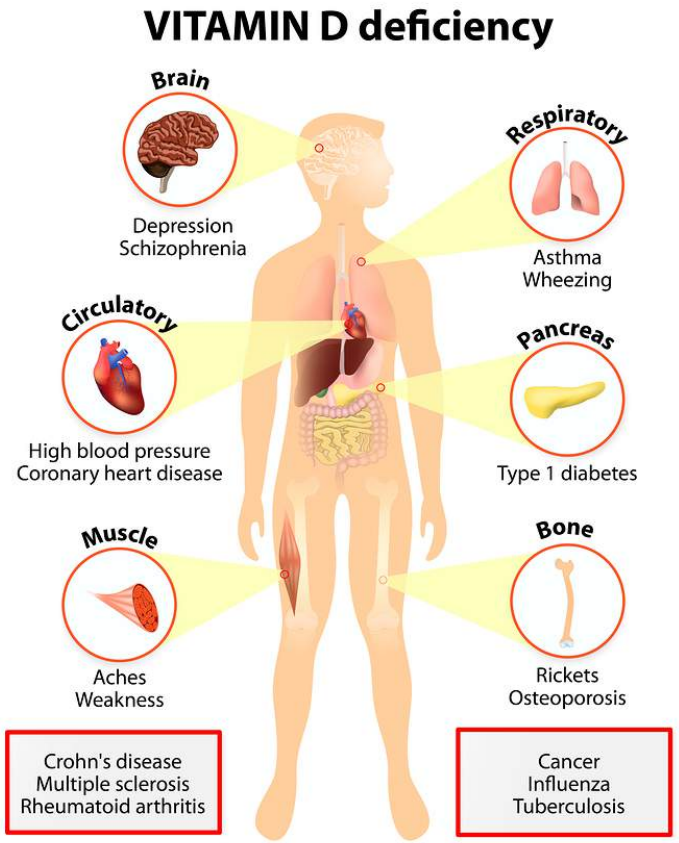
- **Rheumatoid Arthritis**
  - Take in combination with conventional treatment
  - Decrease symptoms of RA after 6 weeks of treatment
  - Improvement sustained for 24 weeks
  - Can decrease number of tender joints by 36%, swollen joints by 28%
  - Dose: 1300 mg of oil daily

Evening primrose (*Onangraceae)*

- A wildflower
- Has 7 -10% GLA
  - Same fatty acid in borage oil
- Side effects: nausea, diarrhea, rashes
- Do not take if have epilepsy
- **Rheumatoid Arthritis**
  - Arthritis Research UK validated the effectiveness of evening primrose for RA
  - Helps the immune system and joint function
  - Dosage: 540 mg of the oil twice daily
    - May take 6 months for clinical efficacy

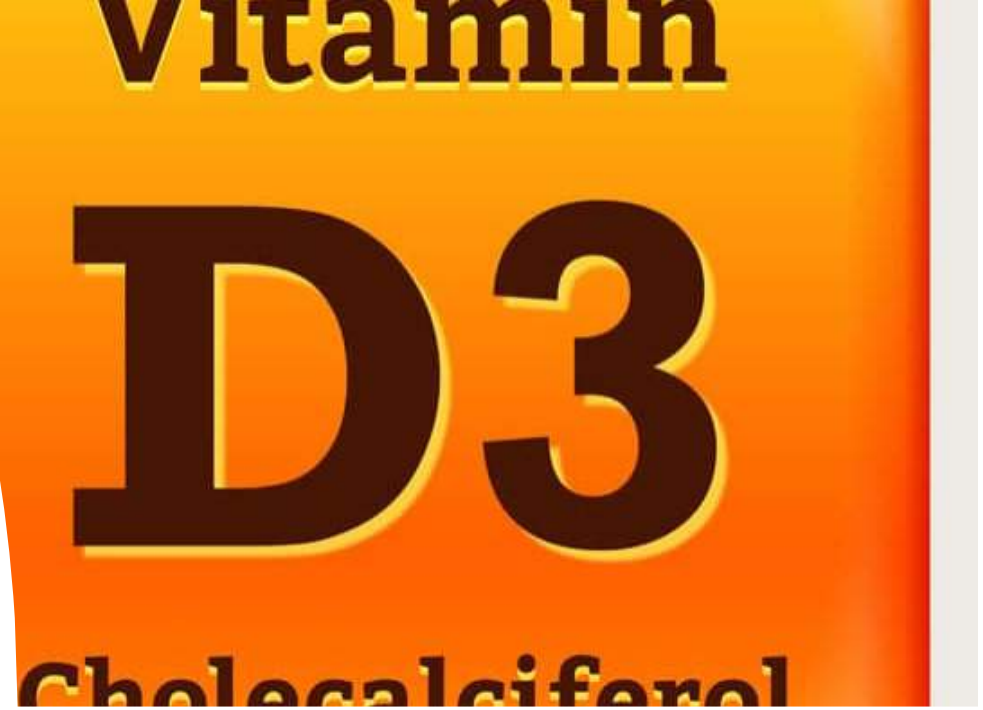
Vitamin D3

- **Mechanism of Action**
  - Immunologic effect
  - May inhibit autoimmune reactions that target cells in the body
  - Modulates the activity of immune cells



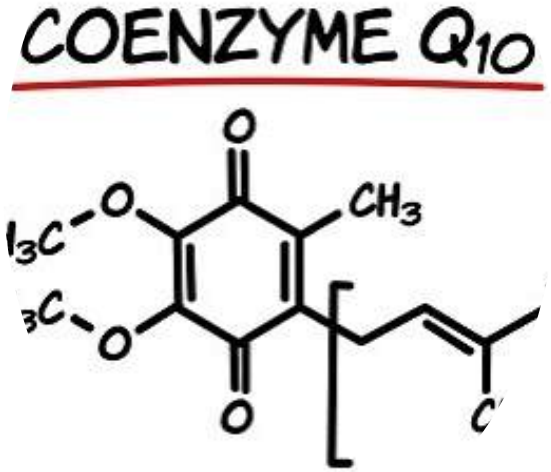
Vitamin D3

- **Plaque Psoriasis**
  - Used topically
  - Can be used in combination with corticosteroids such as betamethasone
- **Multiple Sclerosis**
  - Decreases risk of MS in women by up to 40% (dose-dependent, 400 IU daily)
- **Rheumatoid Arthritis**
  - Increased vitamin D intake associated with lower risk of RA
- **Systemic Lupus Erythematosus**
  - Lower vitamin D levels are linked to more aggressive lupus autoimmunity
  - Supplement with vitamin D to lessen symptoms
- **Diabetes Mellitus Type 1**
  - Helps prevent incidence and associated complications



Coenzyme Q-10

- Biosynthesis of CoQ-10 is a 17-step process requiring riboflavin, niacin, pantothenic acid, pyridoxine, b12, folic acid, vitamin C, and other trace elements
- Generates ATP
- Has antioxidant effects
- Has anti-inflammatory effects by attenuating TNF-alpha on peroxisome proliferator-activated receptor gamma (not alpha)
- Immunomodulatory agent
    - Needed for optimal function of the immune system



1

Diabetes Mellitus Type 1

- Q-10 200 mg BID may reduce A1C

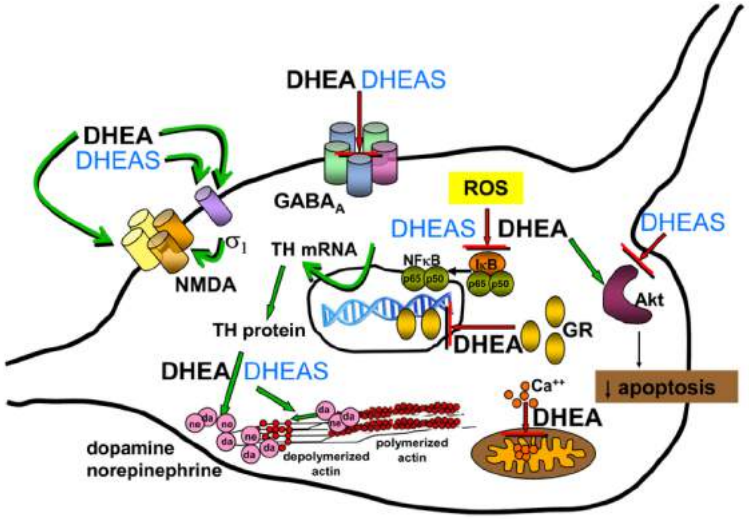
2

Fibromyalgia

- Q-10 200 mg daily for 84 days improves QOL such as physical fitness levels, social activities, overall health, and pain

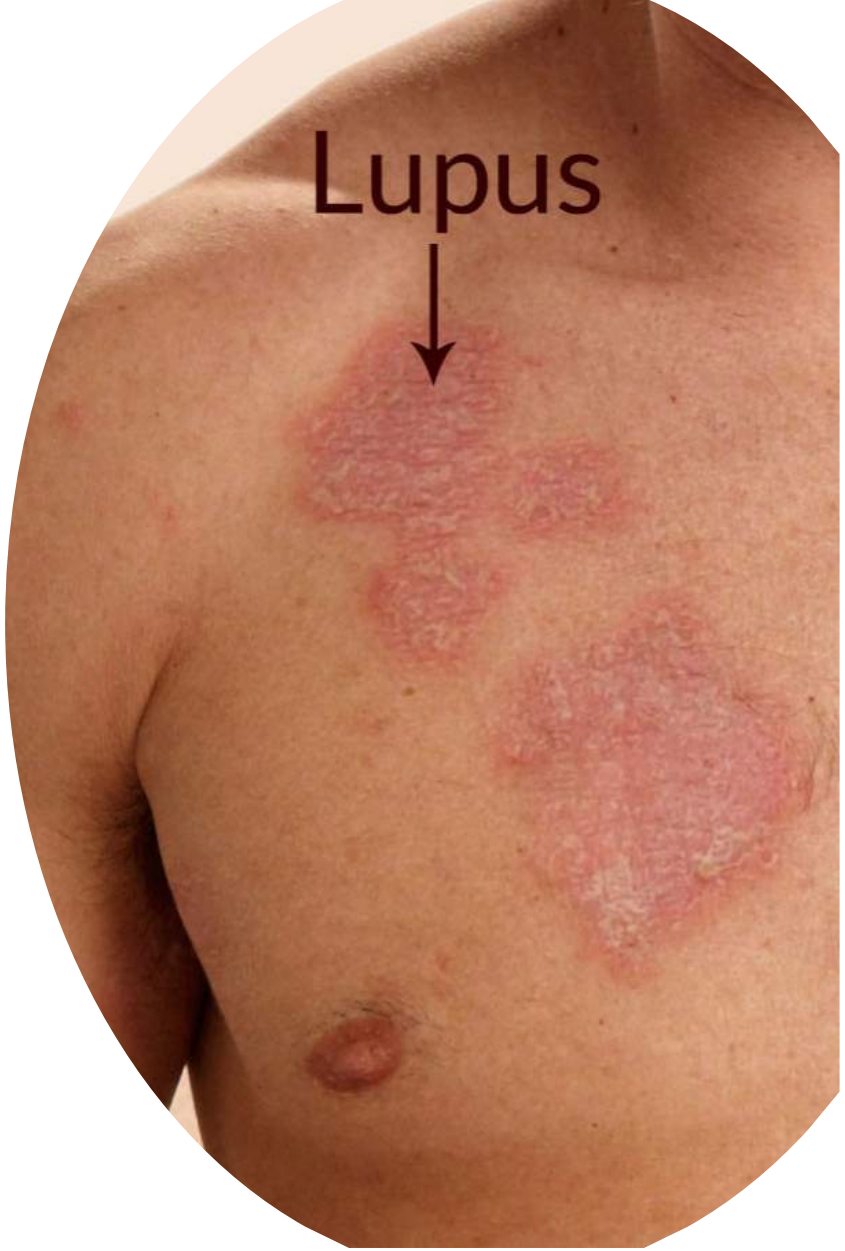
DHEA

- Decreases with age
- Linked to a variety of chronic and degenerative diseases
- As a result of aging, immunity may become compromised due to poor regulation of cellular hormones that govern immune responses
- Has antioxidant effects
- Stimulatory effect on the immune system
- DHEA upregulates various parameters involved in the inflammatory pathway



DHEA

- **Systemic Lupus Erythematosus**
  - Adjunct treatment
    - Help improve SLE disease activity, frequency of flare-ups, muscle aches, oral ulcers, QOL and corticosteroid doses needed
  - More evidence needs to be conducted
- **Inflammatory Bowel Disease**
  - DHEA 200 mg/day orally for 8 weeks reduced symptoms
  - Remission occurred in 6 of 7 Crohn's patients and 6 of 13 UC patients



Acetyl-Glutathione

- Antioxidant that is naturally produced in the body
- **Mechanism:**
  - During chronic inflammation during a period of sustained production of reactive oxygen species, antioxidant defense systems weaken
    - Glutathione stimulates and inhibits immunological response to control inflammation
  - Plays a role in detoxification
    - Deficiency impairs the body's ability to get rid of toxins, so glutathione helps to prevent this

Curcumin

- Also known as turmeric
- **Mechanism**:
  - Anti-inflammatory effects
  - Antioxidant effects
  - Immunomodulatory effects

Curcumin

Side Effects	• Dyspepsia • Nausea • Vomiting • Diarrhea • GI upset
Drug Interactions: use with caution with these medications	• Antiplatelet/anticoagulant drugs • Antidiabetic drugs

Curcumin

- **Multiple Sclerosis**
- **Type 1 Diabetes Mellitus**
- **Rheumatoid Arthritis**
  - May reduce symptoms including morning stiffness, walking time, and joint swelling compared to baseline
  - Curcumin 500 mg BID reduced RA symptoms more than diclofenac sodium 50 mg BID after 8 weeks
- **Systemic lupus erythematosus**
  - Turmeric 1.5 g/day in 3 divided doses for 3 months can reduce systolic BP and improve kidney function compared to baseline in patients with lupus nephritis
- **Inflammatory Bowel Disease**
  - Curcumin 1.1 g/day orally for one month followed by 1.65 g/day for another month reduced symptoms of ulcerative colitis in patients taking 5-ASA and corticosteroids compared to baseline
  - Study showed that taking 2 g/d orally with sulfasalazine or mesalamine for 6 months can reduce the risk of ulcerative colitis recurrence compared to placebo

Boswellia

- The applicable part of boswellia is the gum resin
- Gum resin is obtained by pulling away the bark of the boswellia tree
- Gum resin contains up to 16% essential oils including
    - Phenyl propanoids, terpenoids, flavonoids, and other phenolics
- Has immunomodulatory effects and may inhibit mediators of autoimmune disorders
    - Reduce production of antibodies and cell-mediated immunity

5 – Loxin (Boswellia Serratia Extract)

- Mechanism of Action
  - Inhibit 5-lipoxygenase and reduces leukotriene synthesis
  - Inhibits leukocyte elastase
- Dose
  - 100-250mg daily by mouth
- Safety
  - Often used to treat pain and inflammation usually associated with arthritis
  - Well-tolerated orally

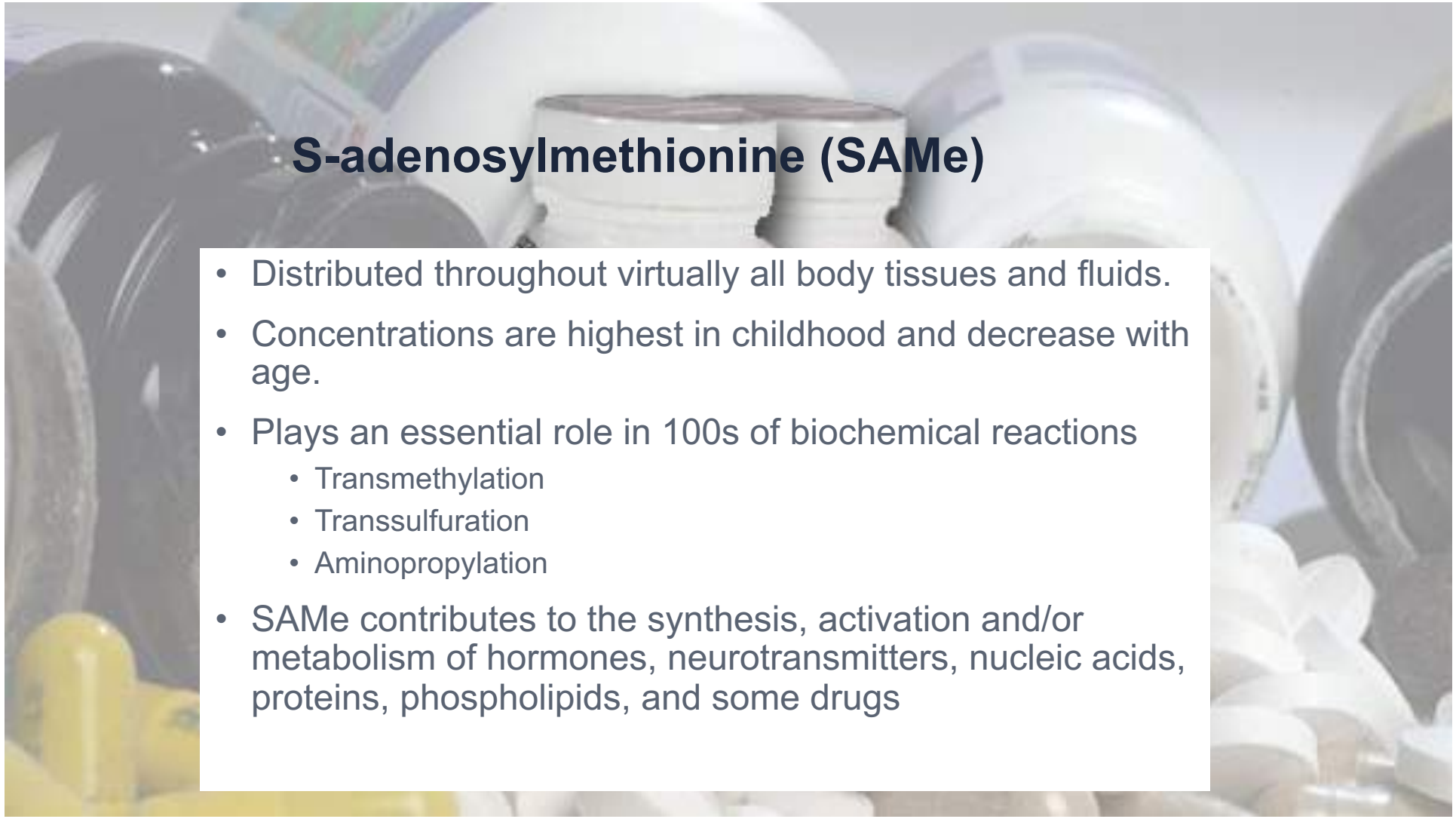
5 – Loxin (Boswellia Serratia Extract)

- Side Effects
  - Diarrhea
  - Nausea
  - Abdominal pain
  - Heartburn
  - Itching
  - Headache
  - Edema
  - General Weakness

- Drug Interactions: dose adjustment might need to be made
  - CYP1A2 substrates
  - CYP2C19 substrates
  - CYP2C9 substrates
  - CYP2D6 substrates
  - CYP3A4 substrates
  - Immunosuppresants

Boswellia: Uses

- **Inflammatory Bowel Disease**
  - Improve symptoms in ulcerative colitis
  - Boswellia gum resin 350 mg TID significantly improved symptoms and disease markers of UC
  - 82% of subjects achieved remission compared to 75% taking sulfasalazine
  - Another study boswellial gum resin 300 mg TID improved symptoms and measures of disease pathology in about 90% of patients
    - 70% achieved remission as compared to 40% in the sulfasalazine group
  - Boswellia extract 1200 mg TID for 6 weeks may reduce symptoms of Crohn's disease

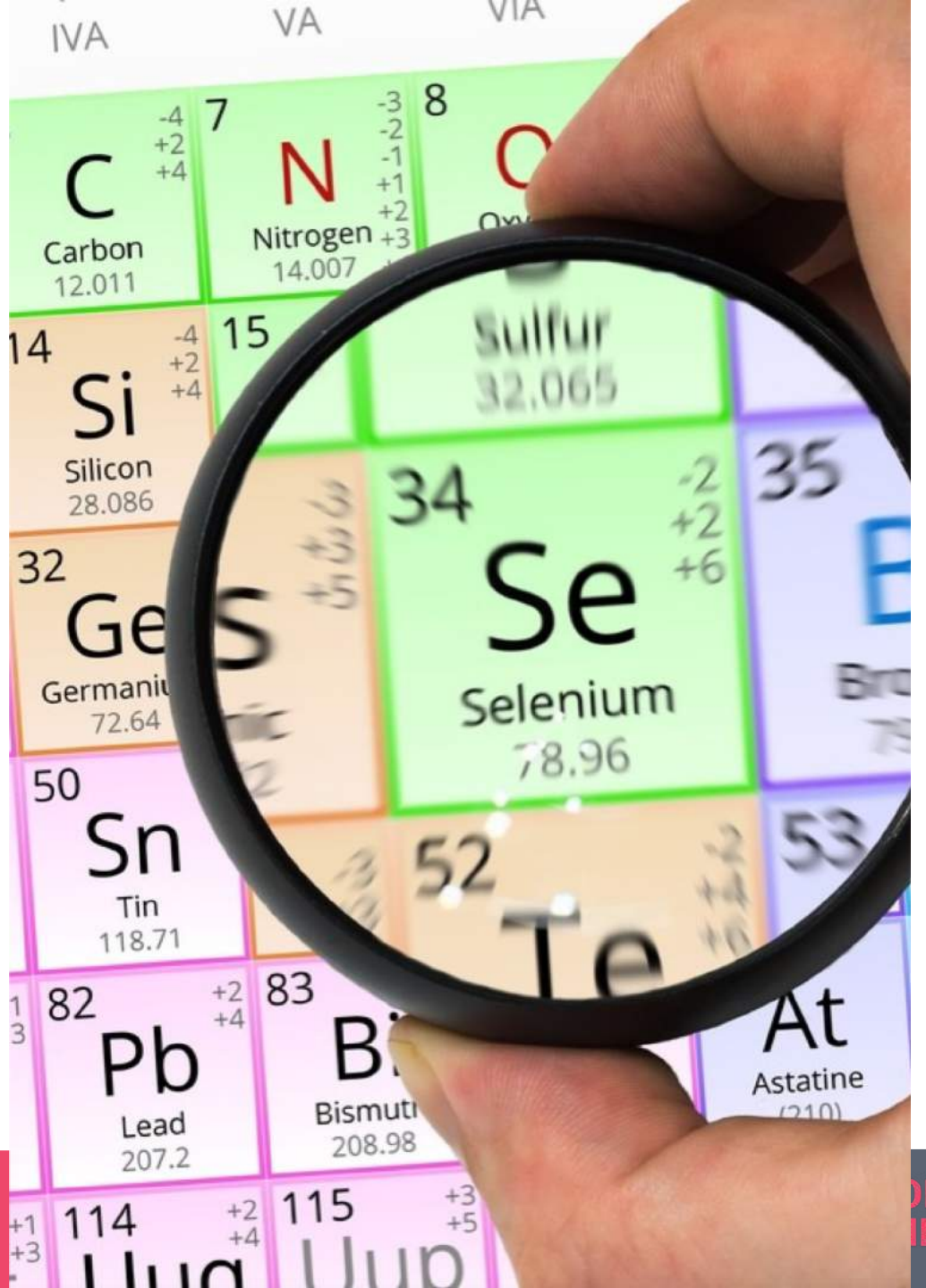


S-adenosylmethionine (SAMe)

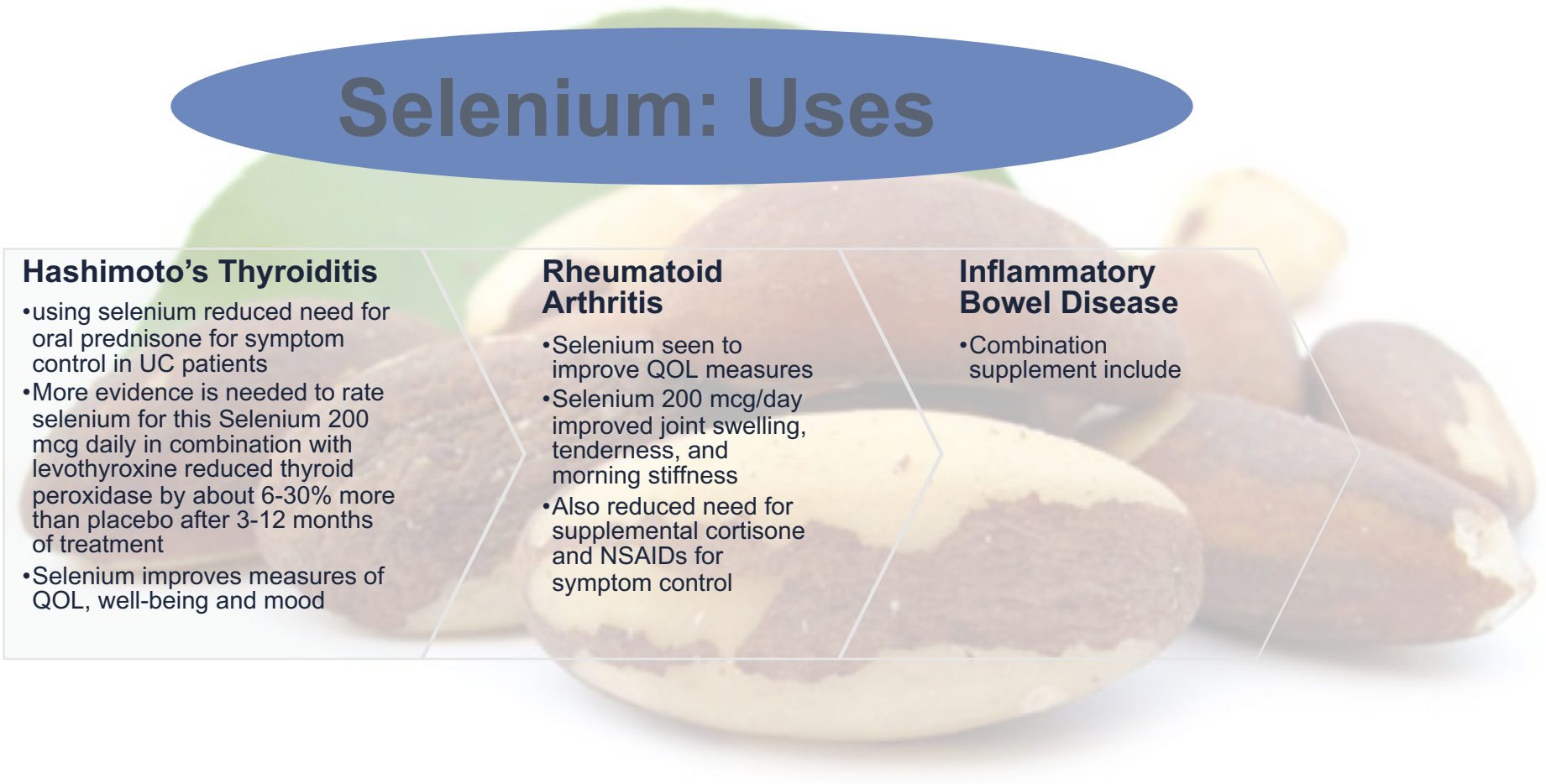
- Distributed throughout virtually all body tissues and fluids.
- Concentrations are highest in childhood and decrease with age.
- Plays an essential role in 100s of biochemical reactions
  - Transmethylation
  - Transsulfuration
  - Aminopropylation
- SAMe contributes to the synthesis, activation and/or metabolism of hormones, neurotransmitters, nucleic acids, proteins, phospholipids, and some drugs

Selenium

- Organic molecule
- In broccoli, garlic, and other selenium-accumulating plants
- Essential for activity of selenoproteins such as glutathione peroxidase enzyme
- Anti-inflammatory effects by inhibiting ROS and activation of feedback mechanisms
- Antioxidant effects
- Immune system effects
  - Selenium needed for proper functioning of neutrophils, macrophages, NK cells, T lymphocytes, and other immune mechanisms



Selenium: Uses



Hashimoto's Thyroiditis

- using selenium reduced need for oral prednisone for symptom control in UC patients
- More evidence is needed to rate selenium for this Selenium 200 mcg daily in combination with levothyroxine reduced thyroid peroxidase by about 6-30% more than placebo after 3-12 months of treatment
- Selenium improves measures of QOL, well-being and mood

Rheumatoid Arthritis

- Selenium seen to improve QOL measures
- Selenium 200 mcg/day improved joint swelling, tenderness, and morning stiffness
- Also reduced need for supplemental cortisone and NSAIDs for symptom control

Inflammatory Bowel Disease

- Combination supplement include

Resolution of Inflammation

Under normal conditions, neutrophils undergo apoptosis after performing their action at the inflamed site and macrophages ingest apoptotic neutrophils.

Clearance of apoptotic neutrophils prompts a switch from a pro- to an anti-inflammatory macrophage phenotype (M1 to M2), is a prerequisite for macrophage egress via the lymphatic vessels favoring return to tissue homeostasis.

An active phenomenon, aimed at actively suppressing and extinguishing a vibrant inflammatory reaction

Inflammation:
The Clinician's Challenge

What type is it?

General inflammatory
Innate activation
Auto-immune

What part of the immune is the generator?

What is the original cause?

And is it still around?

How do I resolve the inflammation?

What about dysregulation of gene response?

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SUMMARY

Key Takeaways

- Hormones play a role in modulating the immune system, so balance of hormones is a critical component of immunocompetency
- Low Dose Naltrexone have many therapeutic uses in immune system modulation.
- Nutriceuticals can be added for modulation if patient is unable to eat a healthier diet
- Peptide therapies is an emerging field of medicine

FUNCTIONAL MEDICINE
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Questions?

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QUESTIONS

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