Casual Friday Presents

Respiratory Function

FM Strategies: Physiology, Pathology, Interventions.

Part II

A BIOGENETIX CLINICAL PRESENTATION

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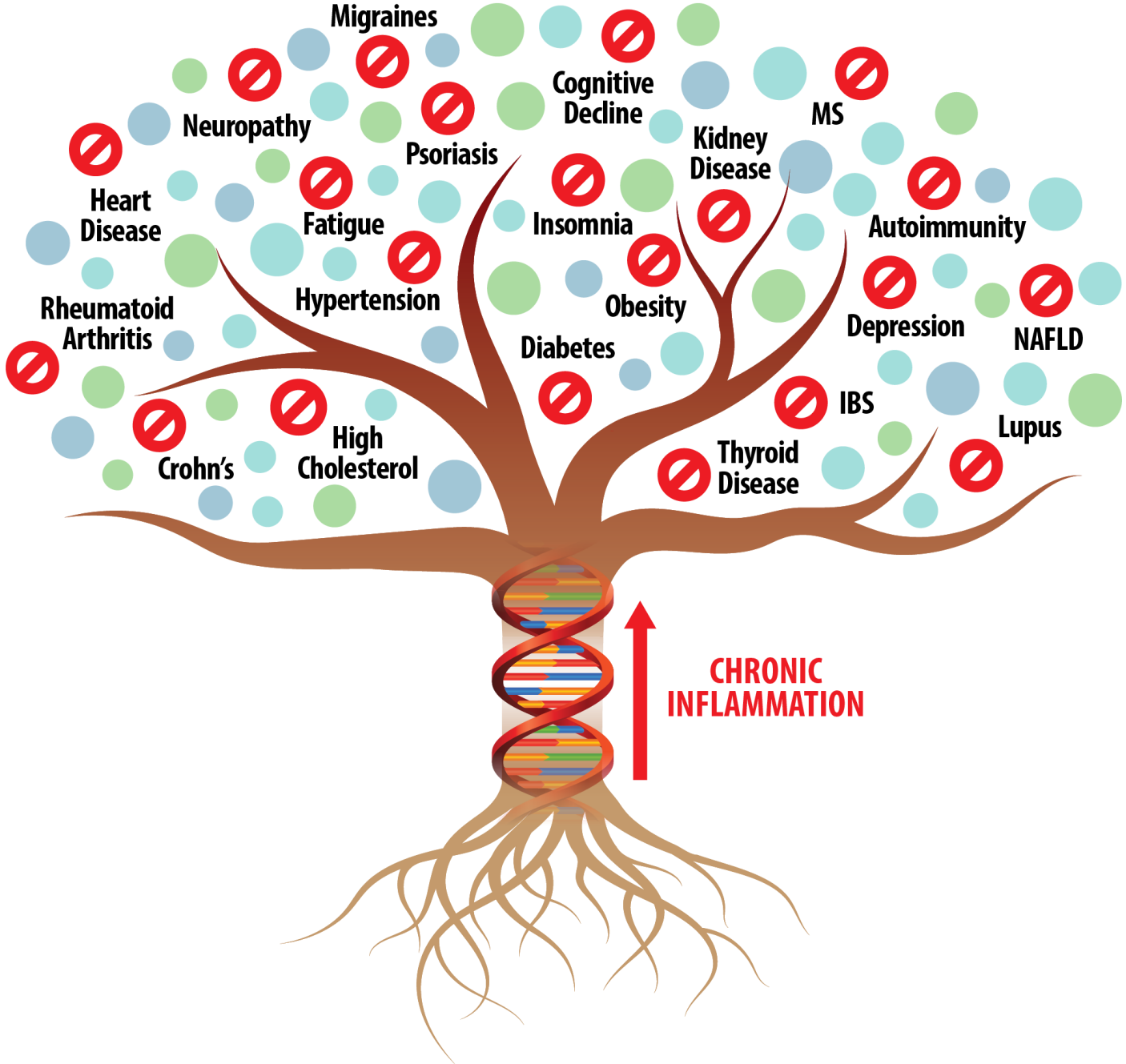
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION

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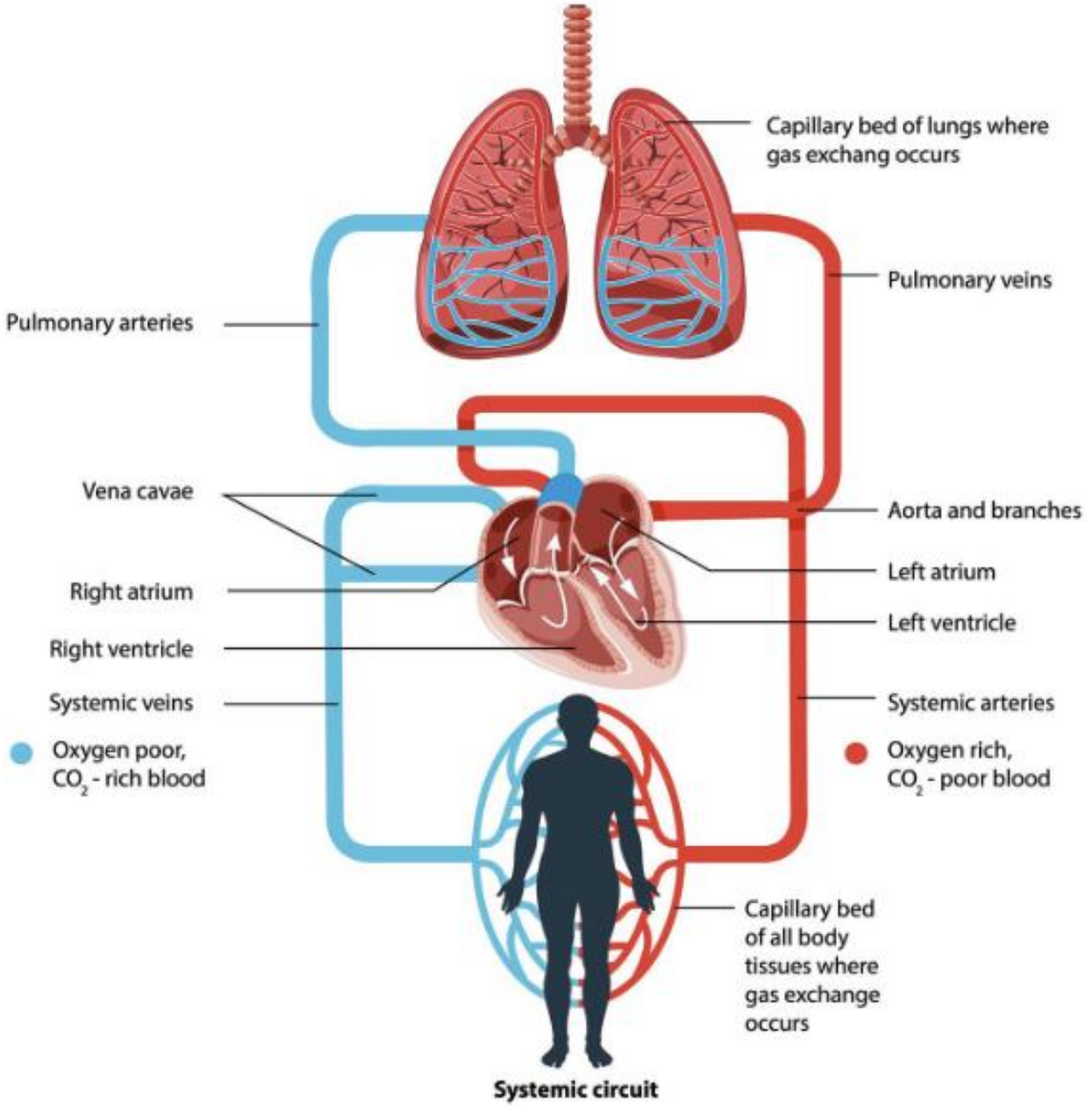
PULMONARY CIRCUIT



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ACE Cycle

1. Liver releases angiotensinogen.
2. Kidney releases renin → converts angiotensinogen to angiotensin I.
3. Lungs (ACE) convert angiotensin I → angiotensin II.
4. Angiotensin II causes vasoconstriction and stimulates aldosterone release.
5. Blood pressure and blood volume increase.

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Nitric Oxide Cycle

1. eNOS produces NO from L-arginine.
2. NO should cause vasodilation via cGMP.
3. Some NO reacts with oxyhemoglobin (Oxy-Hb).
4. Oxy-Hb is converted to methemoglobin (Met-Hb).
5. NO is consumed/scavenged.
6. Less NO available → vasoconstriction and endothelial dysfunction.

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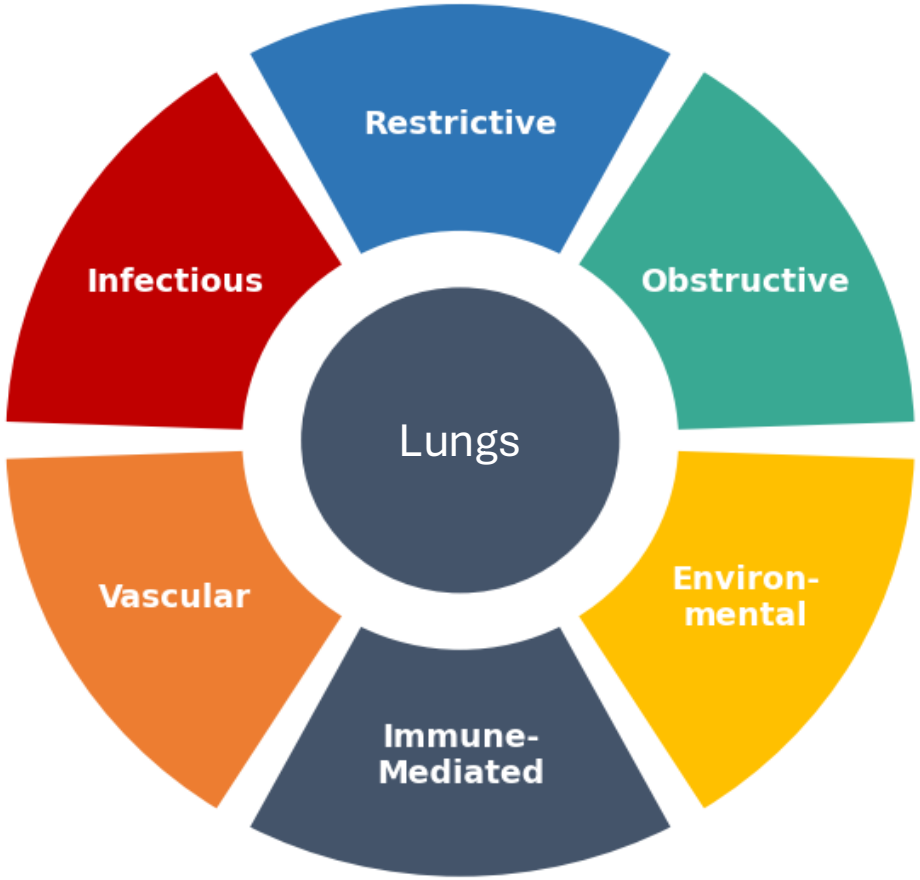
The Big 6 Pathology Categories



1. Obstructive

Asthma, COPD, Bronchiectasis

2. Restrictive

Fibrosis, Sarcoidosis

3. Infectious

Viral/Bacterial Pneumonia, TB

4. Vascular

Pulm. Hypertension, Pulm. Edema

5. Immune-Med.

Eosinophilic, Autoimmune Pneumonitis

6. Environmental

Mold/CIRS, Occupational, VOCs

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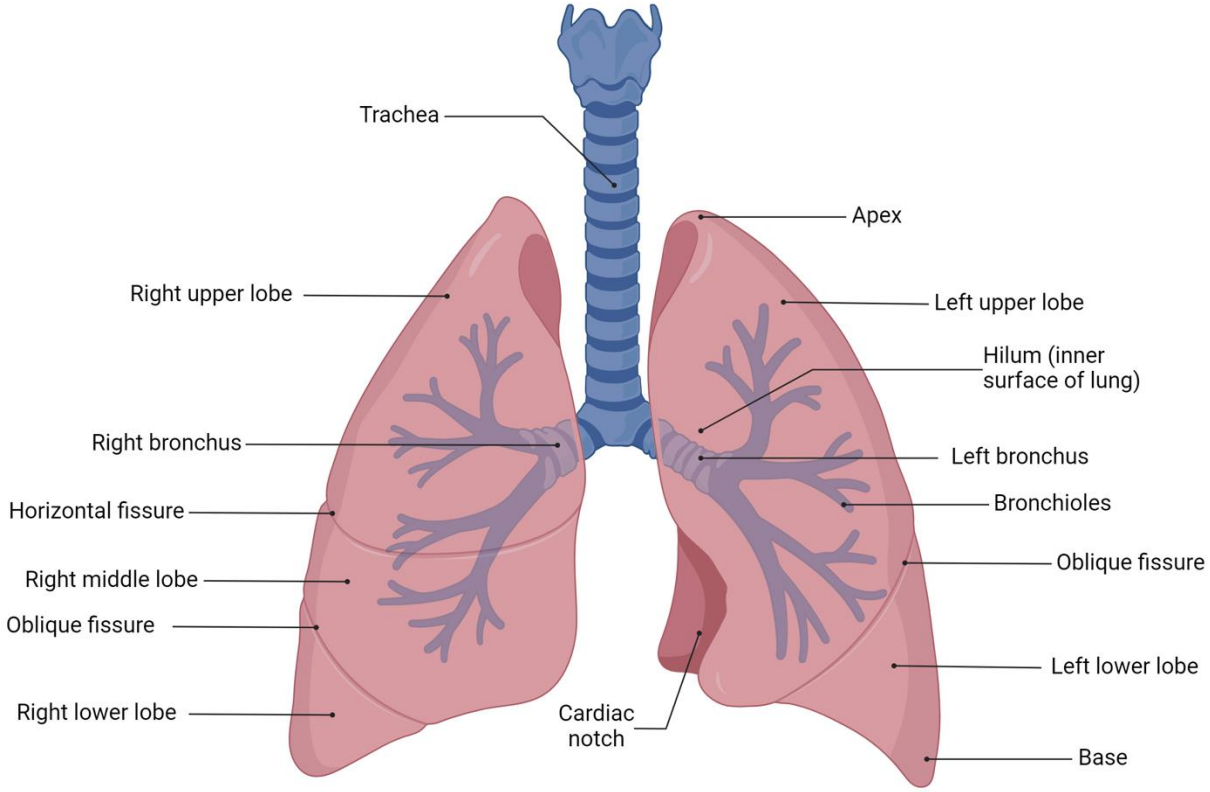
Restrictive Lung Disorders Mechanism

Reduced lung expansion.

Examples
- Pulmonary fibrosis
- Sarcoidosis
- Interstitial lung disease
- Autoimmune lung involvement

Symptoms
- Exertional dyspnea (SOB)
- Dry cough
- Fatigue
- Exercise intolerance

Functional Drivers
- Chronic inflammation
- Autoimmunity
- Oxidative stress
- Mitochondrial dysfunction
- Environmental exposures



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The Measurements

Measurement	Restrictive	Obstructive
TLC	↓	↑
RV	↓	↑
FEV_1	↓	↓
FVC	↓	↓
FEV_1 / FVC (~80%)	WNL - ↑	↓

Definitions
TLC: total lung capacity
RV: residual volume (volume after max exhale)
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity (volume exhaled after TLC)
FEV1 / FVC ratio: % of FVC exhaled in first second

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Pulmonary Fibrosis

Nonidiopathic interstitial pulmonary fibrosis (non-IPF) describes a group of interstitial lung diseases (ILD) that cause inflammation and fibrosis of the lung interstitium, leading to impaired gas exchange due to a known cause. Depending on the specific disorder, it can also affect the trachea, bronchi, bronchioles, alveoli, and pleura. Most of these diseases are characterized by clinical, radiographic, pathologic, and physiologic findings. The classic features often include progressive shortness of breath and cough, chest imaging abnormalities, and inflammatory and fibrotic changes on histology. A restrictive pattern with a decreased diffusing capacity for carbon monoxide (DLCO) is often seen in pulmonary function testing (PFT).[1]

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Pulmonary Fibrosis

Occupational and environmental exposures:

- Pneumoconiosis due to inorganic substances and associated occupations
  - Asbestos: Plumbers, shipyard and construction workers
  - Beryllium: Aerospace workers and those involved in mining
  - Carbon dust: Coal miners
  - Silica: Silica mining and sandblasting
  - Chromium: Metal and chemical manufacturing
- Organic substances causing hypersensitivity pneumonitis
  - Thermophilic fungi
  - Avian droppings
  - Bacterial species (ie, *B. subtilis*, *B. cereus*)

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Pulmonary Fibrosis

Drug-induced lung toxicity

- Numerous drugs can cause interstitial pulmonary fibrosis.
    - Common drugs include amiodarone, antineoplastic agents, beta-blockers, nitrofurantoin, statins, and radiation therapy.

Connective tissue diseases (CTD):

- Systemic lupus erythematosus (SLE)
- Systemic sclerosis
- Rheumatoid arthritis
- Antisynthetase syndrome
- Polymyositis/dermatomyositis
- Mixed connective tissue disease

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Pulmonary Fibrosis

Systemic Illnesses:

- Sarcoidosis
- Pulmonary Langerhans cell histiocytosis
- Lymphangiomyomatosis
- Granulomatosis with polyangiitis
- Anti-glomerular basement membrane antibody disease
- Chronic aspiration
- Alveolar proteinosis

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Pulmonary Fibrosis

Although there are numerous known causes of non-IPF, the pathogenesis is similar to most diseases. The process involves phases of injury, inflammation, and repair. There is recurrent and direct epithelial/endothelial injury to the distal air spaces due to various causes (e.g., drug toxicity, environmental exposure, autoimmune reactions). Destruction of the alveolar-capillary basement membrane leads to platelet activation and fibrin-rich clot formation. Macrophages release proinflammatory cytokines and chemokines, resulting in the chemotaxis of neutrophils. The release of cytokines, reactive oxygen species, proteases, and transforming growth factor-beta (TGF-β) amplifies the inflammatory process. TGF-β released by macrophages and damaged tissue promotes fibroblast proliferation, resulting in myofibroblast formation and secretion of fibrous proteins and ground substance, which form the extracellular matrix (ECM). Chronic inflammation from repetitive injury over time leads to continued thickening and fibrosis of the lung parenchyma. This process ultimately results in irreversible fibrosis and impaired gas exchange.[4][5][6]

→ Injury and healing never complete their cycles.

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Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that primarily affects the lungs and lymphoid organs. Additional organs may become involved over time. Sarcoidosis was first reported in 1877 and remains a concern for clinicians and pathologists. The disease may remain silent, and most patients remain asymptomatic for a prolonged period. Patients may later present with nonspecific symptoms or organ failure. Sarcoidosis is a challenging diagnosis for clinicians, and histopathology remains the gold standard for diagnosis.

*Granulomatous inflammation is a specialized, long-lasting type of chronic inflammation. It occurs when your immune system attempts to "wall off" and isolate foreign invaders or substances it cannot easily destroy. This process creates tightly clustered microscopic nodules of immune cells, which are known as **granulomas**. (NIH)

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Sarcoidosis

Sarcoidosis is a chronic inflammatory disease of unknown etiology; however, it has been associated with genetic factors, certain antigens, and immune dysregulation, and usually occurs in individuals with genetic susceptibility after exposure to specific environmental agents. Etiologic agents can evoke the histologic hallmarks of sarcoidosis and are responsible for its clinical heterogeneity and immunologic features. Genetic factors that predispose patients to sarcoidosis include the following risk loci: butyrophilin-like 2 (*BTNL2)*, human leukocyte antigen B (*HLA-B)*, human leukocyte antigen DP β1 chain (*HLA-DPB1)*, annexin A11 (*ANXA11)*, interleukin 23 receptor (*IL23R)*, SH2B adaptor protein 3 (*SH2B3)*, ataxin 2 (*ATXN2)*, interleukin 12B p40 subunit (*IL12B)*, nuclear factor κB subunit 1 (*NFKB1)*/ mannosidase β A (*MANBA)*, and family with sequence similarity 177 member B (*FAM177B)*. Environmental agents, such as aluminum, zirconium, talc, pine tree pollen, clay, and insecticides, have been implicated.
Mycobacteria species are the infectious agents most strongly associated with sarcoidosis, followed by *Leptospira* species, *Mycoplasma* species, *Chlamydia pneumoniae*, and *Borrelia burgdorferi*.

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Sarcoidosis

The pathogenesis of sarcoidosis is poorly understood. Environmental exposures, genetic factors, and dysregulated immune systems have been associated with an exaggerated T helper 1 cell immune response, which contributes to the pathogenesis of sarcoidosis. T cells are often associated with an inverted CD4/CD8 ratio and play a key role in the development of sarcoidosis by promoting cellular immune responses. The noncaseating granuloma characterizes Sarcoidosis. Tumor necrosis factor is elevated in this disease.

In addition to the role of T cells, polymorphisms in human leukocyte antigen genes and the butyrophilin-like 2 receptor gene (*BTNL2*, a costimulatory molecule within the MHC locus) have been associated with sarcoidosis. There is an association of the annexin A11 gene on chromosome 10q22.3. The function of annexin is to regulate calcium signaling, cell division, and apoptosis.[2] Sarcoidosis is also associated with the DR subtypes of class II antigens. *HLA-DRB1**03, *HLA-DRB1**11, *HLA-DRB1**12, *HLA-DRB1**14, and *HLA-DRB1**15 increase the risk of sarcoidosis. Lofgren syndrome is an acute form of sarcoidosis that is self-limited and shows a triad of lymphadenopathy, erythema nodosum, and arthritis. *HLA-DRB1**03 is associated with sarcoidosis.[3]

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Sarcoidosis

Symptoms are variable; typically, patients present with a persistent dry cough, fatigue, and shortness of breath. Other manifestations include painful, red lumps on the skin; uveitis with blurred vision; hoarseness; palpable lymph nodes at multiple sites (including the axilla and neck); painful, swollen joints; hearing loss; seizures; and psychiatric disorders. Cardiomyopathy, conduction defects, nephrolithiasis, and hepatomegaly are observed in a few cases.

A wide range of cutaneous manifestations may be observed, including papular, maculopapular, nodular, subcutaneous, hypopigmented, and plaque sarcoidosis. The most common lesions in cutaneous sarcoidosis are papular nodules on the upper half of the face, the back of the neck, and at sites of previous trauma, including scars and tattoos. Lupus pernio is a cutaneous sarcoidosis variant that mainly involves the central facial skin and presents with violaceous or erythematous papules, plaques, or nodules.

Other well-described skin manifestations of sarcoidosis include nodular sarcoidosis. Plaque-like lesions and subcutaneous nontender nodules are also commonly observed. Erythema nodosum is seen in a variety of other conditions, including sarcoidosis, and usually presents with painful nodules on the shins. This panniculitis is a characteristic feature of Löfgren syndrome. Skin lesions can appear up to 10 or more years after the initial injury or tattoo.[5]

Ocular manifestations are observed in approximately 50% of patients, with uveitis being the most common clinical feature. The CD4:CD8 ratio of vitreous lymphocytes has prognostic value in this condition. Additionally, conductive heart block and sudden cardiac death have also been reported in patients with sarcoidosis. Prophylactic insertion of an implantable cardioverter-defibrillator is recommended in patients with cardiac sarcoidosis. Furthermore, central nervous system manifestations include diabetes insipidus followed by hyperprolactinemia. Patients with central nervous system symptoms often have a poor quality of life and may present with psychiatric disorders such as anxiety and depression.[6]

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Pulmonary Fibrosis

→ Injury and healing never complete their cycles.

Sarcoidosis

→ immune system ”walls off" something it perceives as foreign, even when no infectious organism can be identified.

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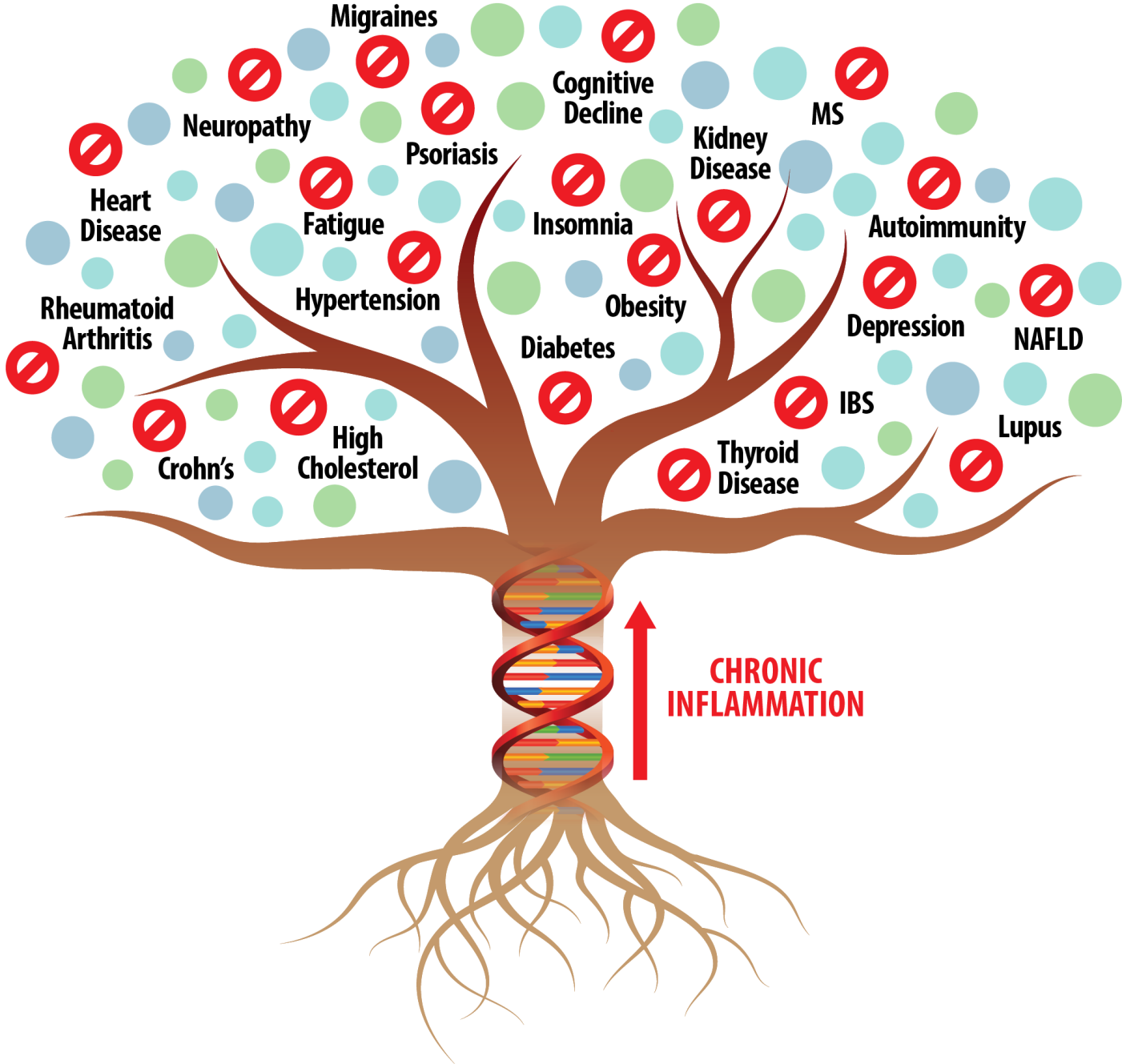
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NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION

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Barrier systems tend to reflect each other.

- If pharma is not stopping the lung barrier from destroying itself, you're unlikely to impact from there.
- Dig in on the other barrier systems.
- Look for the dysbiotic patterns.
- Find the drivers (environmental and lifestyle).
- Focus on systems management rather than organ management.

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We Want to Hear from You!

Give us your Casual Friday feedback
with this short 5-question survey.

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