

Autoimmune Diseases

Dr. Gary Mumaugh



The immune system represents an interface between a constant everchanging external environment and an internal system that is striving to maintain homeostasis and defend its boundaries from harmful foreign invaders

Primary Roles of the Immune System

- Identify potentially infectious or injurious substances
- Distinguish self antigens from non-self antigens
- Assess the potential level of threat posed by infectious, toxic or non-self adherents
- Mount an appropriate response
- Repair any damage that ensues

NORMAL IMMUNE RESPONSE

Antigens invade



Antibodies form

Antibodies remove invading antigens



Antibodies remain and protect



AUTOIMMUNE DISEASE

Immune system forms antibodies to self-antigens



Antibodies attack self-antigens



Inflammation and tissue damage



Macrophages

- First cell type to act as a sentinel to detect and report about what it finds in the environment around it.
- Macrophage means "big eater."
- Constantly eating up a little bit of whatever surrounds it, cutting the ingested proteins up into small pieces (the antigens mentioned above), and then displaying these pieces of protein on its surface.

T Cells

- Macrophage presents these antigens to the T cell
- Primary decision maker in the immune process
- Highly specialized • Each are different from every other one.
- On their surface, T cells express a protein called the T cell receptor, which will bind to only one or a few antigens out of the thousands that are possible.

T Cells

- When a macrophage and a T cell encounter one another, they see whether any of the antigens on the surface of the macrophage fit into the T cell receptor.
- Most of the time the antigens don't fit.
- If the antigens do match the T cell receptor, then the cells stick to one another.
- Through the action of chemical messengers, the T cell becomes turned on, or activated.

B Cells

- Each B cell is unique
- Instead of making specific surface proteins, B cells make proteins called antibodies that are released in the bloodstream
- These antibodies travel until they bind to the antigen that fits
- After an antigen is coated with antibodies, it is tagged for destruction

- Whether autoimmune disease will follow an autoimmune response depends upon both the quality of the immune response and the availability of the corresponding antigen.
- Antigens on the surface of circulating cells such as blood cells are readily available to circulating antibody, and therefore such cells may be damaged or eliminated by autoantibody acting with complement, killer T cells, or phagocytes.

- The receptors on cell surfaces such as the TSH receptor on the thyroid cell or on the acetylcholine receptor at neuromuscular junctions may also be directly attacked by autoantibody.
- This interaction may result in stimulating the receptor in Graves' disease or in blocking the neuromuscular transmission as observed in myasthenia gravis.

Other Causes of Autoimmunity

- Other autoimmune diseases are not due to the direct effects of autoantibody
- They are associated with T-cell-mediated immune responses
- Cytotoxic T cells may be generated that can damage their respective target cell.
- In other cases, cytokines are produced that are harmful to surrounding tissue cells.

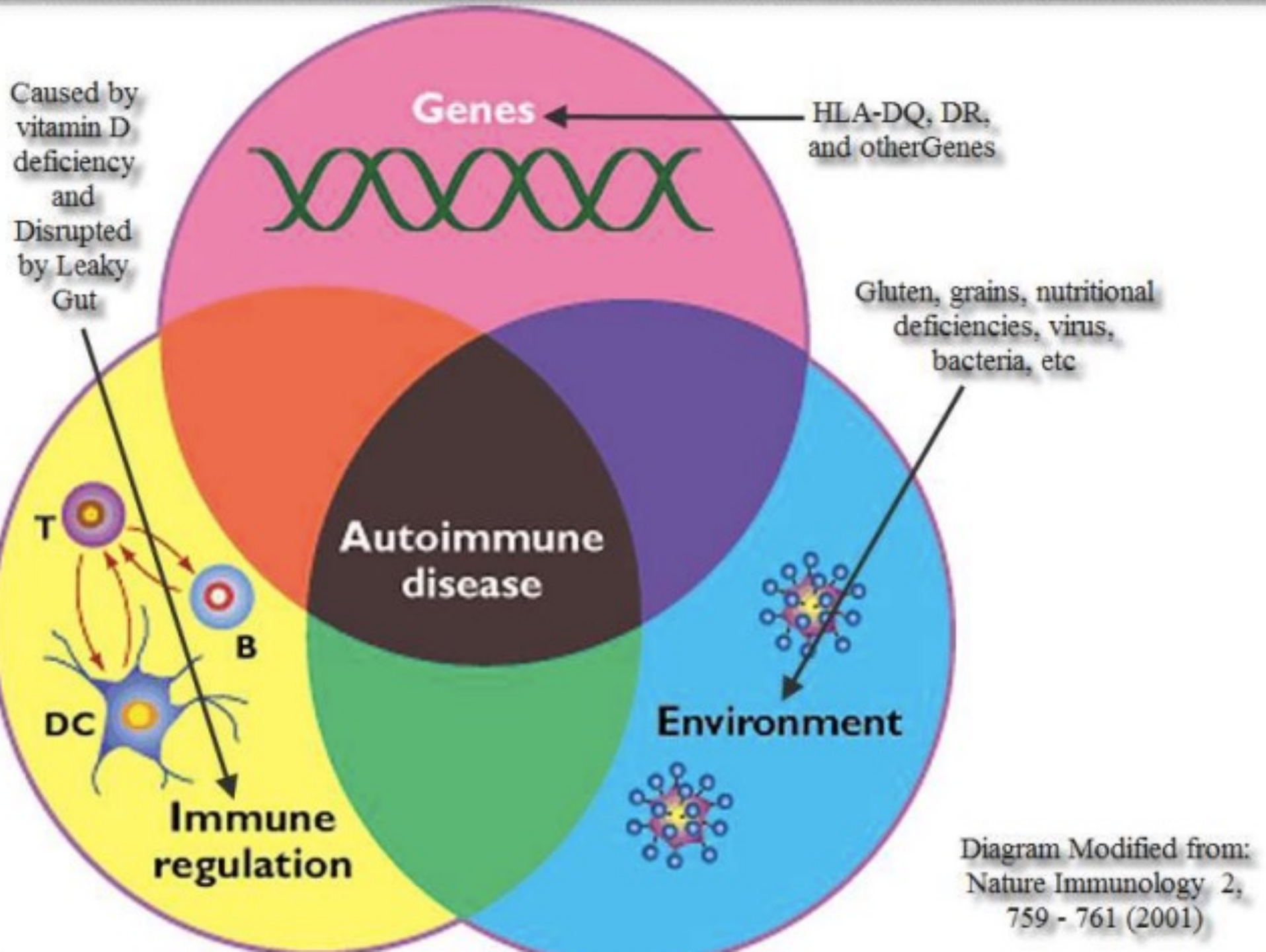


Diagram Modified from:
Nature Immunology 2,
759 - 761 (2001)

How Common Are Autoimmune Diseases

- Affect more than 23.5 million Americans
 - 1:7 Americans incidence
- Autoimmune diseases constitute a leading cause of death among young and middle-aged women per NIH.
- Some autoimmune diseases are rare, while others, such as Hashimoto's thyroiditis, affect many people.

How Common Are Autoimmune Diseases

- Some estimate that >50 million people have autoimmune disease as many cases are undiagnosed.
- According to the AADRA (American Autoimmune Disease Related Association), there are @ 80-100 conditions that are autoimmune related.

Who Gets Autoimmune Disease?

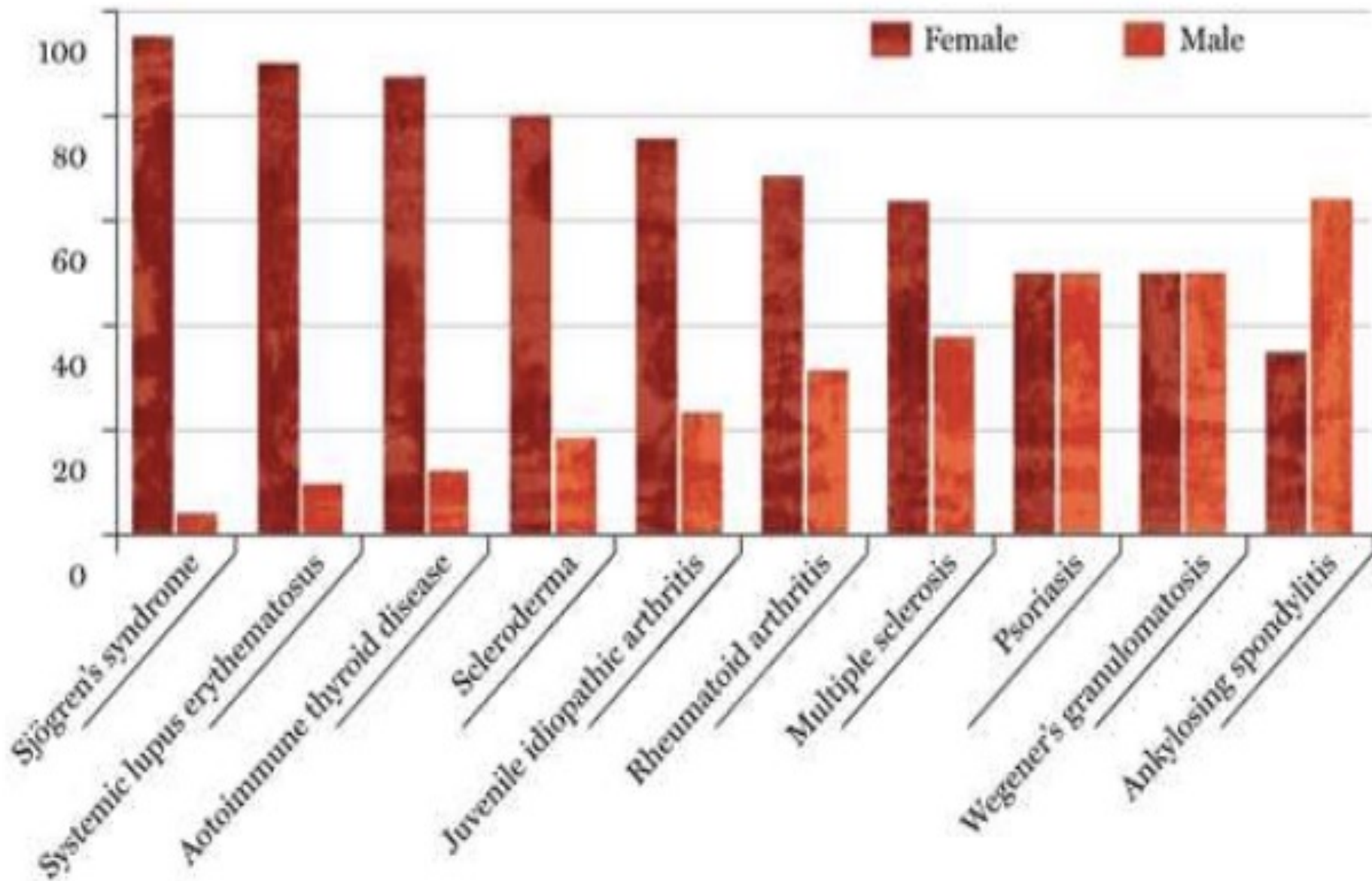
- It is also common for different types of autoimmune diseases to affect different members of a single family.
- Inheriting certain genes can make it more likely to get an autoimmune disease.
- A combination of genes and other factors may trigger the disease to start.

Who Gets Autoimmune Disease?

- Certain events or environmental exposures may cause some autoimmune diseases, or make them worse.
- Sunlight, chemicals called solvents, and viral and bacterial infections are linked to many autoimmune diseases.

- People of certain races or ethnic backgrounds.
 - For instance, type 1 diabetes is more common in white people.
 - Lupus is most severe for African-American and Hispanic people.
- More women than men have autoimmune diseases, which often start during their childbearing years.
 - The statistics are that women are more prone to autoimmune disease X16 more than men!

Autoimmune Diseases: Gender Percentage



Systematic autoimmune diseases

- Rheumatoid arthritis (RA)
- Systemic lupus erythematosus (SLE)
- Anti-phospholipid antibody syndrome (APS)
- Systemic sclerosis (SSc)
- Polymyositis and dermatomyositis (PM/DM)
- Mixed connective tissue disease (MCTD)
- Sjogren's syndrome (SS)
- Microscopic polyangiitis (MPA)
- Granulomatosis with polyangiitis (GPA)
(Wegener's granulomatosis (WG))
- Eosinophilic Granulomatosis with Polyangiitis (EGPA)
(Allergic granulomatous angitis (AGA),
Churg-Strauss syndrome)

General symptom

Fever
Malaise
Weight loss
Joint pain and swelling
Muscular pain and weakness
Skin manifestation
Organ dysfunction

Organ-specific autoimmune diseases

Thyroid

- Autoimmune thyroiditis
- Basedow's disease

Liver

- Autoimmune hepatitis (AIH)
- Primary biliary cirrhosis (PBC)

Neuron /Muscle

- Myasthenia gravis
- Multiple sclerosis

GI tract

- Ulcerative colitis
- Crohn's disease

Pancreas

- Autoimmune pancreatitis (AIP)

Kidney

- Goodpasture syndrome
- Crescentic glomerulonephritis

Skin

- Pemphigus vulgaris (PV)
- Pemphigus foliaceus (PF)
- Bullous pemphigoid (BP)
- Epidermolysis bullosa acquisita (EBA)

Autoimmune (AI) Disorders

- Immune system recognizes and reacts to all foreign substances in the body and tries to destroy them by forming antibodies
 - The average adult has specific antibodies to up to 10 million antigens
 - Sometimes the immune system works too hard and can attack its own cells thinking they are foreign.

- The immune system is composed of two major parts.
- One component, B lymphocytes, produces antibodies, proteins that attack "foreign" substances and cause them to be removed from the body; this is sometimes called the humoral immune system.
- The other component consists of special white blood cells called T lymphocytes, which can attack "foreign" substances directly; this is sometimes called the cellular immune system.

- Over a lifetime, the immune system develops an extensive library of identified substances and microorganisms that are cataloged as “threat” or “not threat.”
- Vaccinations utilize this process to add to the library.
- Normally, the immune system can distinguish between “self” and “not self” and only attacks those tissues that it recognizes as “not self.”
- Autoimmune disorders are diseases caused by the body producing an inappropriate immune response against its own tissues.

- Sometimes the immune system will cease to recognize one or more of the body's normal constituents as "self" and will create antibodies – antibodies that attack its own cells, tissues, and/or organs. This causes inflammation and damage and it leads to autoimmune disorders.
- Causes
 - Normal tissue can be altered by a virus, drug, radiation
 - Defective programmed cell death may malfunction
 - Heredity
 - Hormonal changes
 - Middle age and elderly

What about diet?

- “Single nutritional components have the capability to potently modulate autoimmune responses and inflammation.”
 - *Published in final edited form as:*
 - [Curr Allergy Asthma Rep. 2014 Jan; 14\(1\): 404.](#)
 - NIHMSID: NIHMS549353
- “*Role of ‘Western Diet’ in Inflammatory Autoimmune Diseases*”

What about diet?

- Avoiding foods such as **red meat, eggs, vegetable oils** fried foods, sugar, dairy products, refined carbs, gluten, alcohol, and caffeine might be necessary to limit such flare-ups. Nightshade vegetables, such as tomatoes, potatoes, eggplant, and peppers, can also be problematic.

- Autoimmune disorders fall into two general types:
 - Systemic autoimmune diseases affecting the entire body
 - Localized autoimmune disease affecting a single body system

- Autoimmune disorders fall into two general types:
 - Systemic autoimmune diseases
 - RA
 - JRA
 - SLE
 - Polymyalgia Rheumatica
 - Guillain-Barre syndrome

- Autoimmune disorders fall into two general types:
 - Localized
 - Type 1 Diabetes Mellitus
 - Hashimoto's thyroiditis
 - Graves' disease
 - Celiac disease
 - Crohn's disease
 - Ulcerative colitis
 - Multiple sclerosis
 - Addison's disease

Here are the top 14 AI Diseases

1. Type 1 diabetes - **Pancreas**
2. Rheumatoid arthritis (RA) - **Joints**
3. Psoriasis/psoriatic arthritis - **Skin**
4. Multiple sclerosis - **Nerves**
5. Systemic lupus erythematosus (SLE) - **Skin and internal organs**
6. Inflammatory bowel disease - **Colon**
7. Addison's disease - **Adrenal gland**

Localized

Systemic

Here are the top 14 AI Diseases

8. Graves' disease - **Thyroid**
9. Sjögren's syndrome - **Eyes and mouth**
10. Hashimoto's thyroiditis - **Thyroid**
12. Autoimmune vasculitis - **Blood vessels**
13. Pernicious anemia - **RBC**
14. Celiac disease - **Colon**

Localized

Systemic

- S & S
 - Fever, fatigue, malaise
 - Other symptoms depend on the organ involved
- Diagnosis
 - History
 - Blood tests – ESR, CRP, RF, ANA, ELISA
- Treatment
 - Some drugs suppress the immune system
 - Some drugs reduce the inflammatory response
 - Steroids, NSAIDs
- Prognosis
 - Some AI disorders resolve
 - Most are lifelong chronic diseases needing lifelong care

Type 1 Diabetes Mellitus

- Genetic susceptibility
- Failure of beta cells by autoimmune destruction, requires insulin therapy
- Immunologically mediated destruction of beta cells
- Manifestations:
 - Hyperglycemia
 - Polydipsia
 - Polyuria
 - Polyphagia
 - Weight loss
 - Fatigue



#1 of all Auto Immunes

Pancreatic Islet Cells

- Function: regulate blood glucose levels through the production of insulin and glucagon
- Diabetes Mellitus: most common endocrine disorder
- Two forms, with differing pathogenesis:
 - Juvenile onset DM, type I DM, insulin-dependent DM
 - Maturity onset DM, type II DM, non-insulin-dependent DM

Rheumatoid Arthritis

**#2 Autoimmune and
the #1 you will see**



Rheumatoid Arthritis

- Most common Autoimmune Disorder
- Inflammatory arthritis affecting 1% population
- An autoimmune disease causing chronic joint inflammation
- A progressive illness that has the potential to cause joint destruction and functional disability
- Affecting approximately 1.3 million people in USA

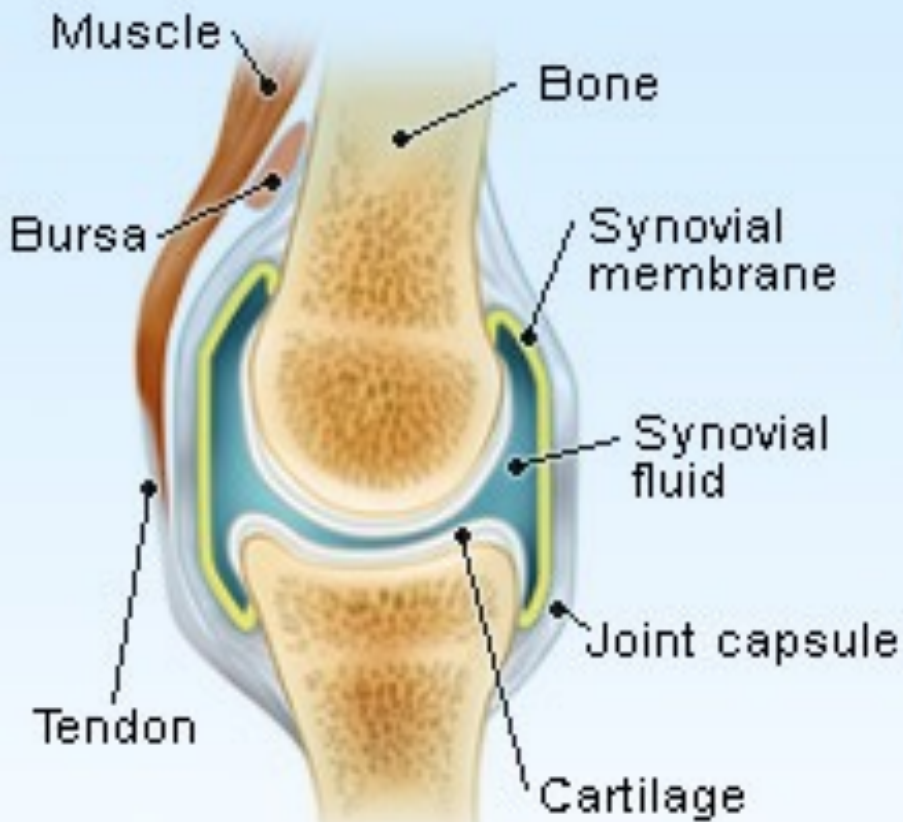
Rheumatoid Arthritis

- Three times more common in women as in men
- It afflicts people of all races equally
- Can begin at any age, but it most often starts after age 40 and before 60
- In some families, multiple members can be affected, suggesting a genetic basis for the disorder

- S & S
 - Symmetrical small joint pain with pronounced morning stiffness (morning gel), low grade fever, joints deformed
- Diagnosis
 - ESR, RF, ASO titer, HLA (human leukocyte antigen)
 - Joint fluid contains WBC, biopsy rheumatoid nodules

- Treatment
 - Supportive – rest, PT, hold and cold packs, DME
 - NSAIDs, Methotrexate, antimalarials
- Prognosis
 - 50-75% remission in a few years, the rest have progressive disease process and dies 10-15 years premature

Normal Joint

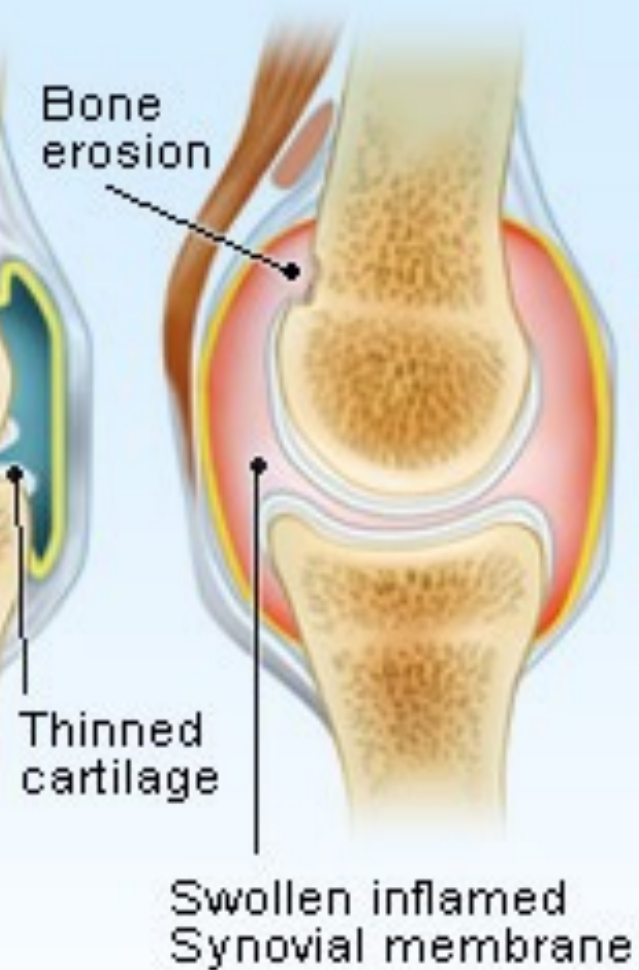


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Osteoarthritis



Rheumatoid Arthritis



Normal and Arthritic Joints

Rheumatoid arthritis

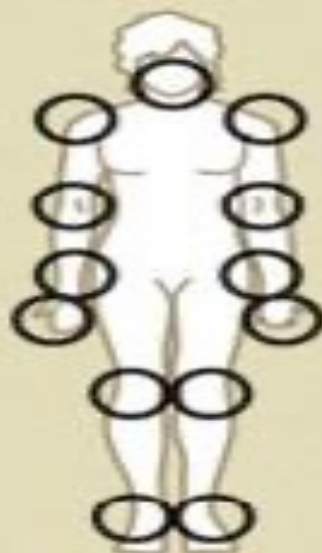
One of the most common and debilitating forms of arthritis, three-quarters of the 2.1 million Americans affected are women.

What is it

- Inflammatory condition; autoimmune disease; body's immune system attacks tissue lining joints; no known cure

Joints that may be affected

- Occurs symmetrically (both sides of body at once)
- Wrist, finger joints closest to hands are often affected



Symptoms, signs

Can vary widely

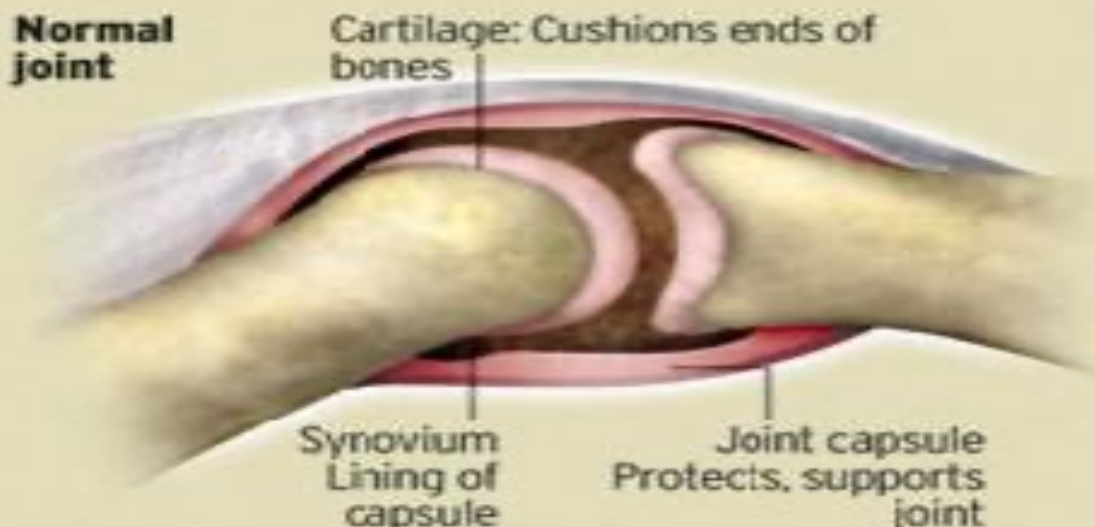
- 30 minutes or more of joint pain, stiffness after long rest
- Fatigue, low fever during flare-ups

Treatment

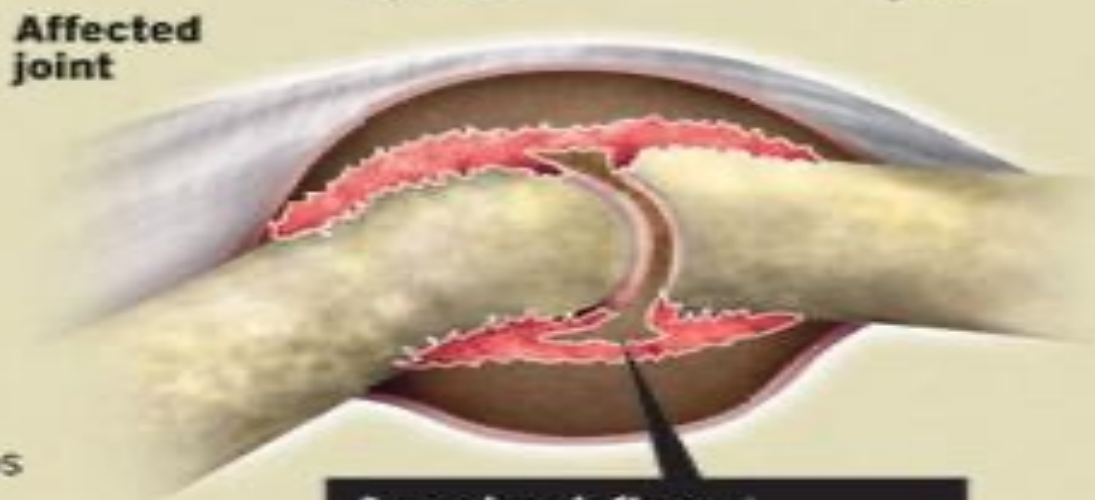
Lifestyle changes, pain and inflammation drugs, surgery, monitoring

Reason for early treatment: Bone damage begins in first year or two of disease

Normal joint



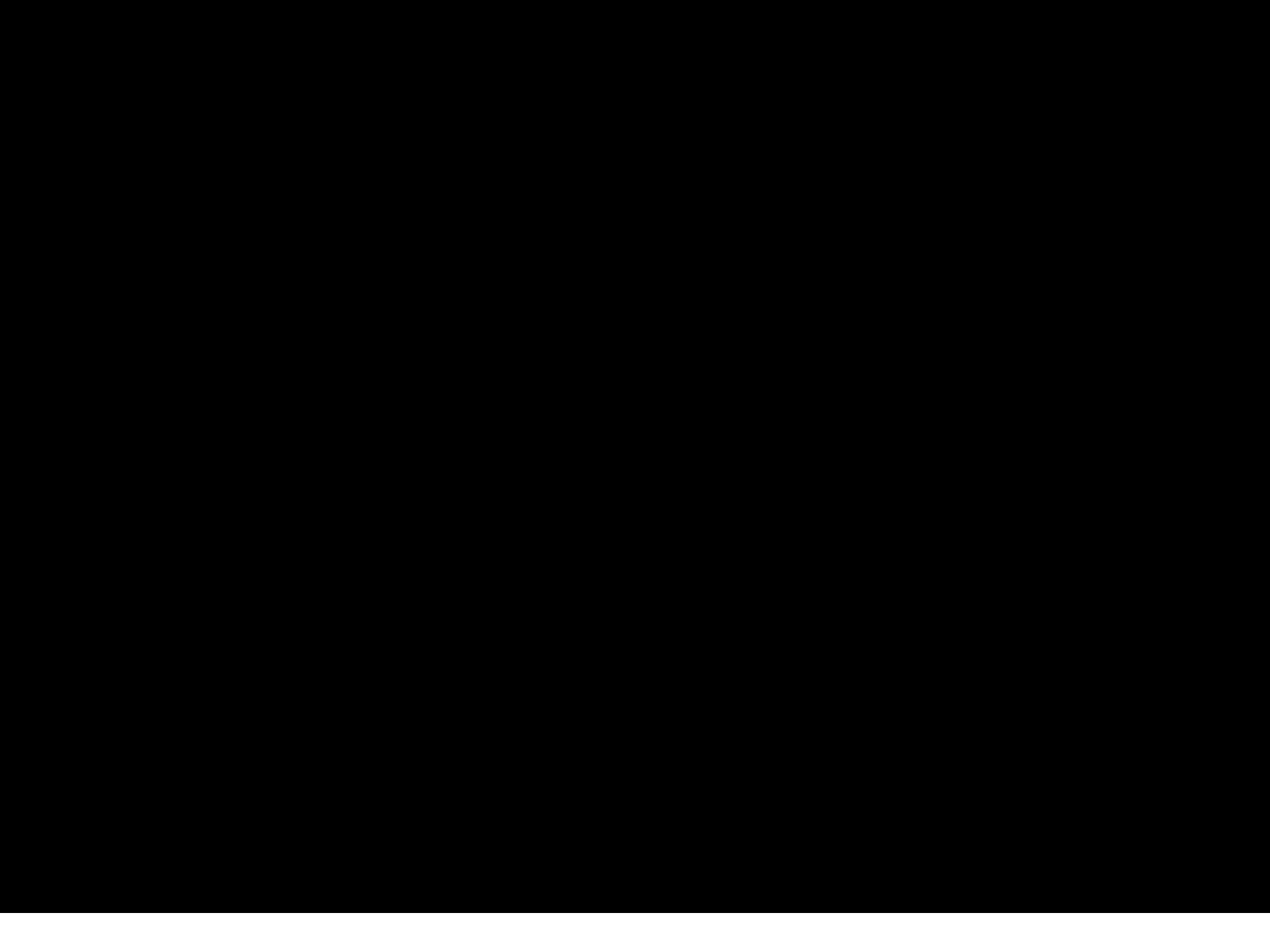
Affected joint



Synovium inflamed by immune system; abnormal cells grow, destroy cartilage, bone

Rheumatoid arthritis - YouTube





Normal



Rheumatoid Arthritis

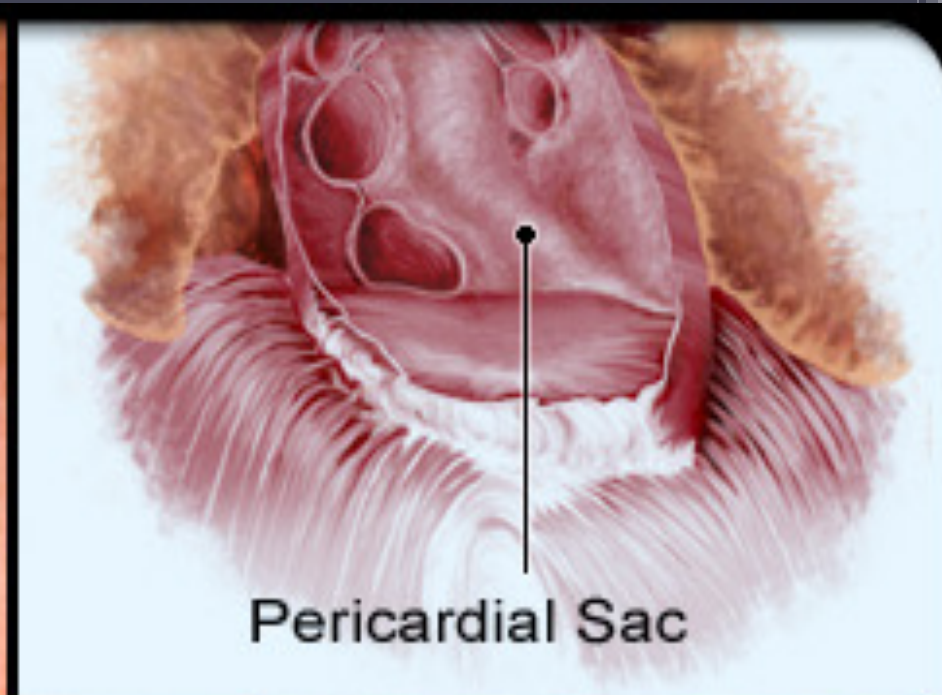


- What causes rheumatoid arthritis?
 - Cause is largely unknown
 - Has a strong genetic link
 - It is suspected that certain infections or factors in the environment might trigger the immune system to attack the body's own tissues

- Symptoms
 - Come and go, depending on the degree of inflammation
 - When body tissues are inflamed, the disease is active
 - The course of rheumatoid arthritis varies from patient to patient, and periods of flares and remissions are typical
 - Inflammation usually symmetrical and of the small joints
 - Pronounced morning stiffness – “morning gel”



- Rheumatoid arthritis and inflammation of organs - can affect organs and areas of the body other than the joints
 - Sjogren's syndrome is inflammation of the glands of the eyes and mouth and causes dryness of these areas
 - Rheumatoid inflammation of the pleura
 - Pericarditis
 - Can have lowered RBC (anemia) and WBC
 - Felty's Syndrome (lowered WBC and splenomegaly)



- Diagnosis
 - Positive RF (rheumatoid factor) and RF titer, ASO titer
 - WBC changes
 - Joint fluid with WBC and proteins
 - X-ray changes
- Treatment
 - Supportive and appliance measures
 - Hot and cold packs, walkers, etc
 - NSAIDs and COX2 inhibitors
 - Steroids are the main treatment
 - Rest and mild ROM exercises

Juvenile rheumatoid arthritis (JRA) causes joint inflammation and stiffness for more than six weeks in a child aged 16 or younger



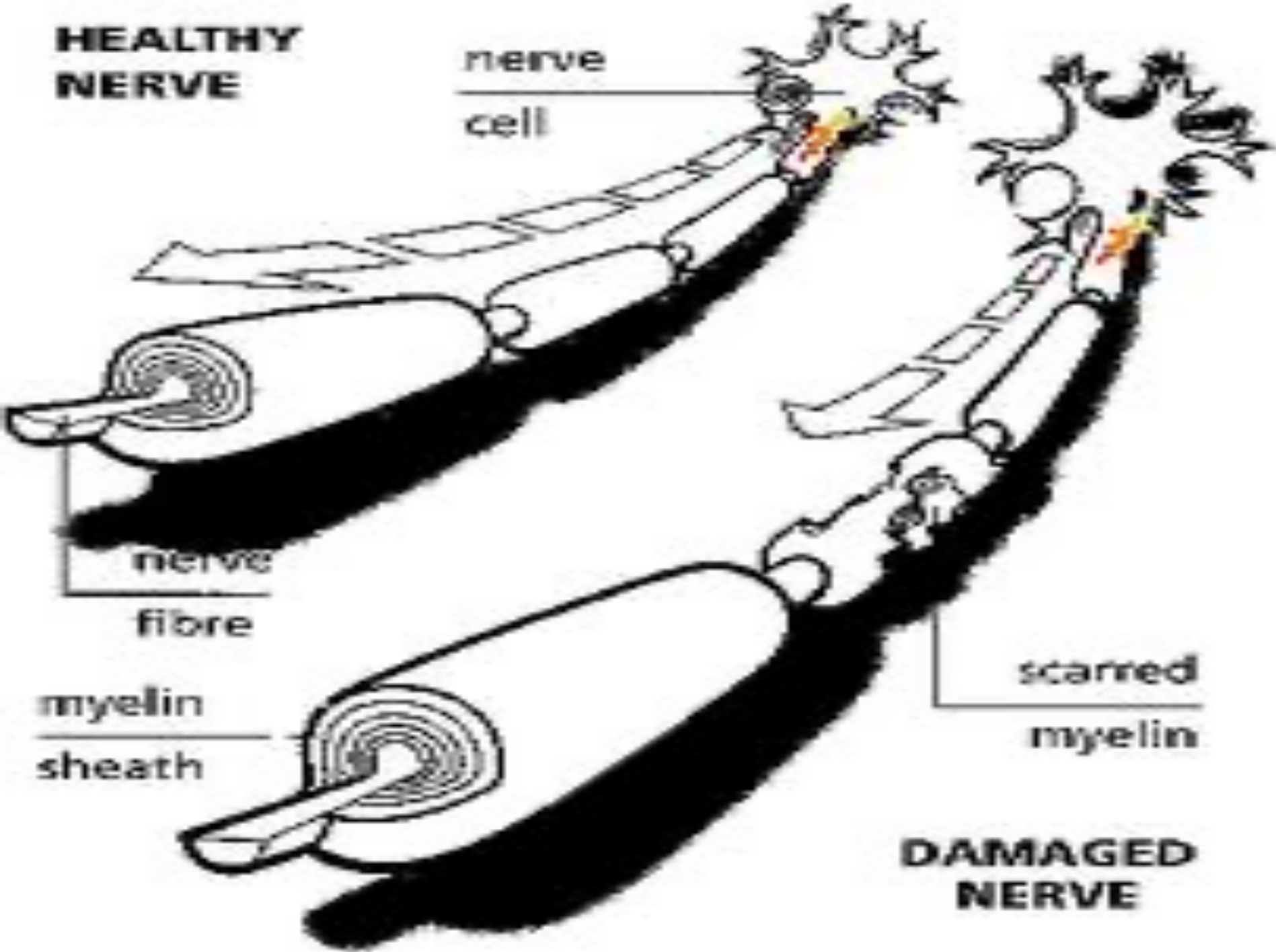
Affects 50,000 children

#4 Multiple Sclerosis (MS)

- Possibly caused by an interaction between a viral illness in teen years and a genetic predisposition
- Arises through a single mechanism of lesion
 - Focal, chronic, progressive
- Areas of demyelination are called plaques
- Optic neuritis is often the first symptom
- Chronic exacerbation and remission
 - Triggers: infection, medication, stress, fatigue

HEALTHY NERVE

nerve
cell



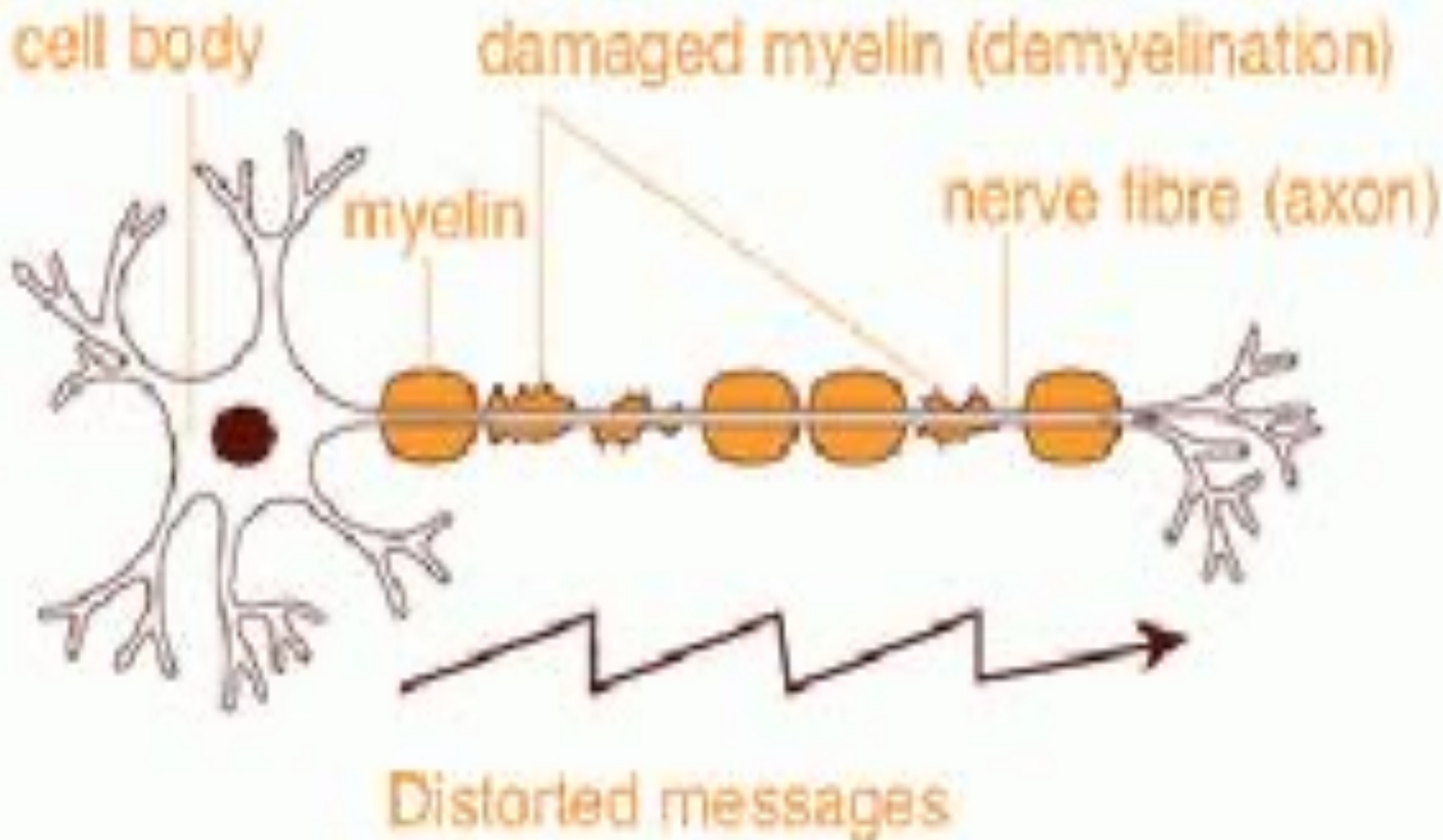
nerve
fibre

myelin
sheath

scarred
myelin

DAMAGED NERVE

Demyelination in MS



SLE – Systemic Lupus Erythematosus

- Generalized Autoimmune involving joints, skin, brain, mucus membranes, kidneys, bone marrow, vessel walls
- 50,000 new cases per year **#5**
- 90% are young women in their late teens to 30s
- Spontaneous remissions & relapses is the typical course

SLE – Systemic Lupus Erythematosus

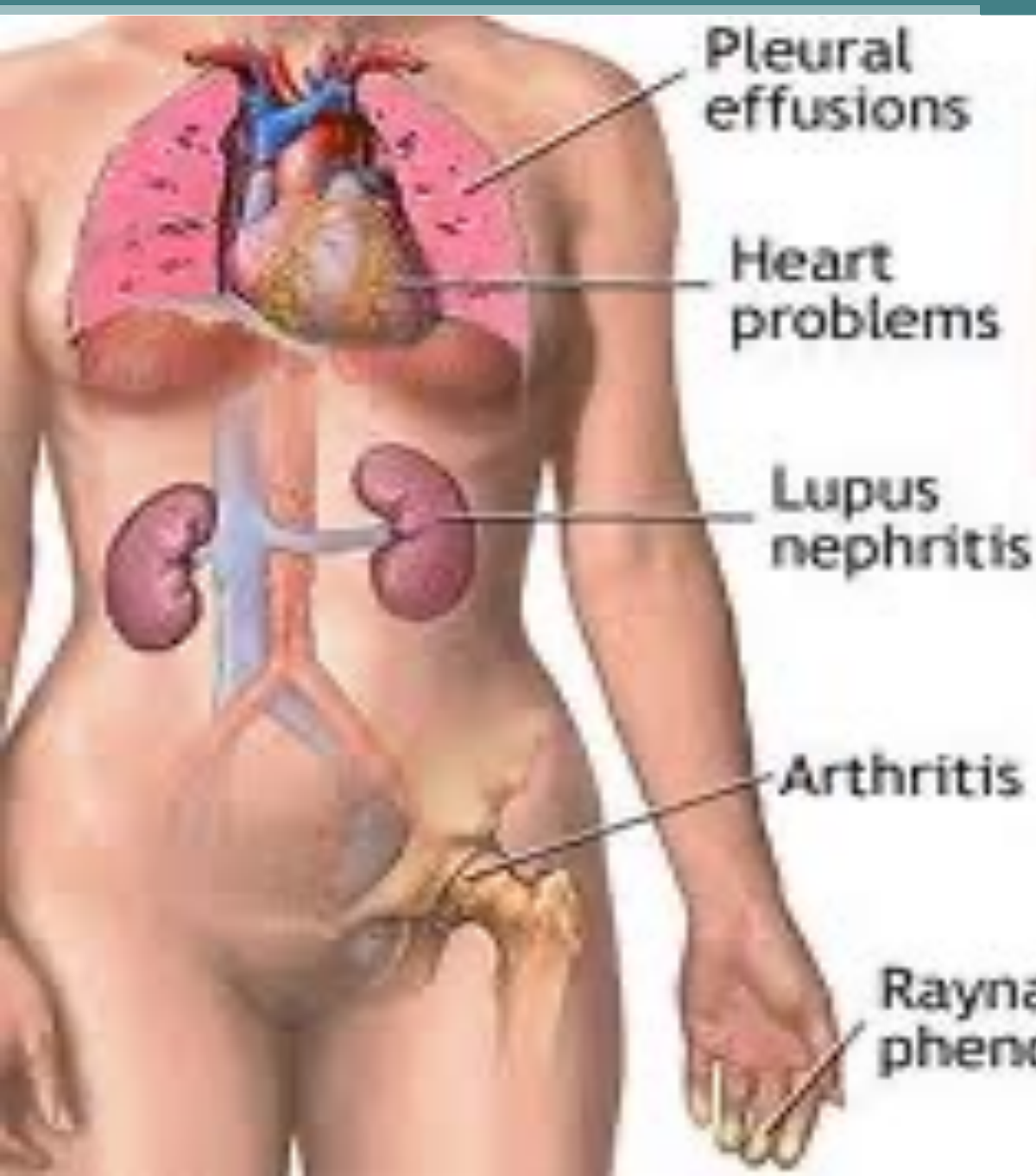
- Four types:
 - Systemic lupus erythematosus – most common
 - Drug-induced lupus – resolves when drug stopped
 - Discoid lupus – affects skin with the classic butterfly rash
 - Neonatal lupus – transmitted to fetus

- S & S

- Arthralgia (95%), inflammatory arthritis (90%)
- Fever (90%), fatigue (81%) rashes (74%)
- Anemia, kidney involvement, chest pain, alopecia
- Cognitive dysfunction, photophobia, headaches
- Blood clotting problems, Raynaud's
- Mucosal ulcers, pericarditis, vasculitis
- Seizures, psychosis, peripheral neuropathy

- Diagnosis
 - Confirmed by four or more of the above symptoms
- Lab tests
 - ANA (95%), RF usually negative, antibodies (40%)
 - Anemia (60%), proteinuria, hematuria
 - Tissue biopsy of rash

- Treatment
 - Very little treatment effective – supportive care is best
 - Avoid sun exposure with rash
 - NSAIDs
 - Hemodialysis is needed
 - Other meds
 - Hydroxycortisone, prednisone, Medrol
 - Decadron
 - Topical corticosteroid creams and ointments
 - Cytoxin, Imuran, Methotrexate
 - Antimalarials
 - DHEA



Pleural effusions

Heart problems

Lupus nephritis

Arthritis

Raynaud's phenomenon

Butterfly rash



Symptoms of systemic lupus erythematosus may vary widely with the individual



• Scleroderma

- Inflammation and fibroids in connective tissue, skin and supporting tissues around joints
- More in women
- Signs and Symptoms
 - Skin hardening, tendon friction rubs, migratory polyarthrititis (90%), low grade fever, spider veins, calcified lumps, dysphagia, heatburn, GI tract fibrosis, pulmonary fibrosis
 - Usually starts with Raynaud's, finger swelling and tightness

Scleroderma

- CREST syndrome – less severe form
- C – calcium deposits
- R – Raynaud’s of fingers and toes
- E – Esophageal dysfunction
- S – Sclerodactyly –finger hardening
- T – Telangiectasia – spider veins

The limited symptoms of scleroderma are referred to as **CREST**

Calcinosis- calcium deposits in the skin



Raynaud's phenomenon- spasm of blood vessels in response to cold or stress



Esophageal dysfunction- acid reflux and decrease in motility of esophagus



Sclerodactyly- thickening and tightening of the skin on the fingers and hands



Telangiectasias- dilation of capillaries causing red marks on surface of skin



- Diagnosis
 - Suggestive history and physical
 - Positive ANA, ELISA, skin biopsy thickened skin
- Treatment
 - No current effective western care
 - Supportive treatment
 - NSAIDs, corticosteroids
- Prognosis
 - Course varies widely and progresses to rapid decline and death
 - Survival rate averages 9 years

Telangiectasia



Dilation of small vessels and capillaries cause flat red marks to appear on the skin



Other AI Diseases

- Crohn's disease
- Ulcerative colitis #6
- Fibromyalgia
- Chronic Fatigue Syndrome
- Graves' Disease #8
- Thyroid storm

Crohn's disease

- Chronic lifelong illness thought to be an autoimmune inflammatory disease
- S & S
 - Pain, cramping, fever, malaise, weight loss, frequent bowel movements
 - 50% involve small & large intestine, 35% involve small intestine only, 15% involve only large bowel

Crohn's disease

- Diagnosis
 - Clinical history with x-ray findings
- Treatment
 - Strict nutritional program with low lactose, low fiber, vitamin and mineral supplements
 - Corticosteroids (Prednisone)
 - Antibiotics (Flagyl)
 - Immunosuppressant drugs (Imuran)



< Normal ileum

Source: L. Bailen



Ulcerative colitis

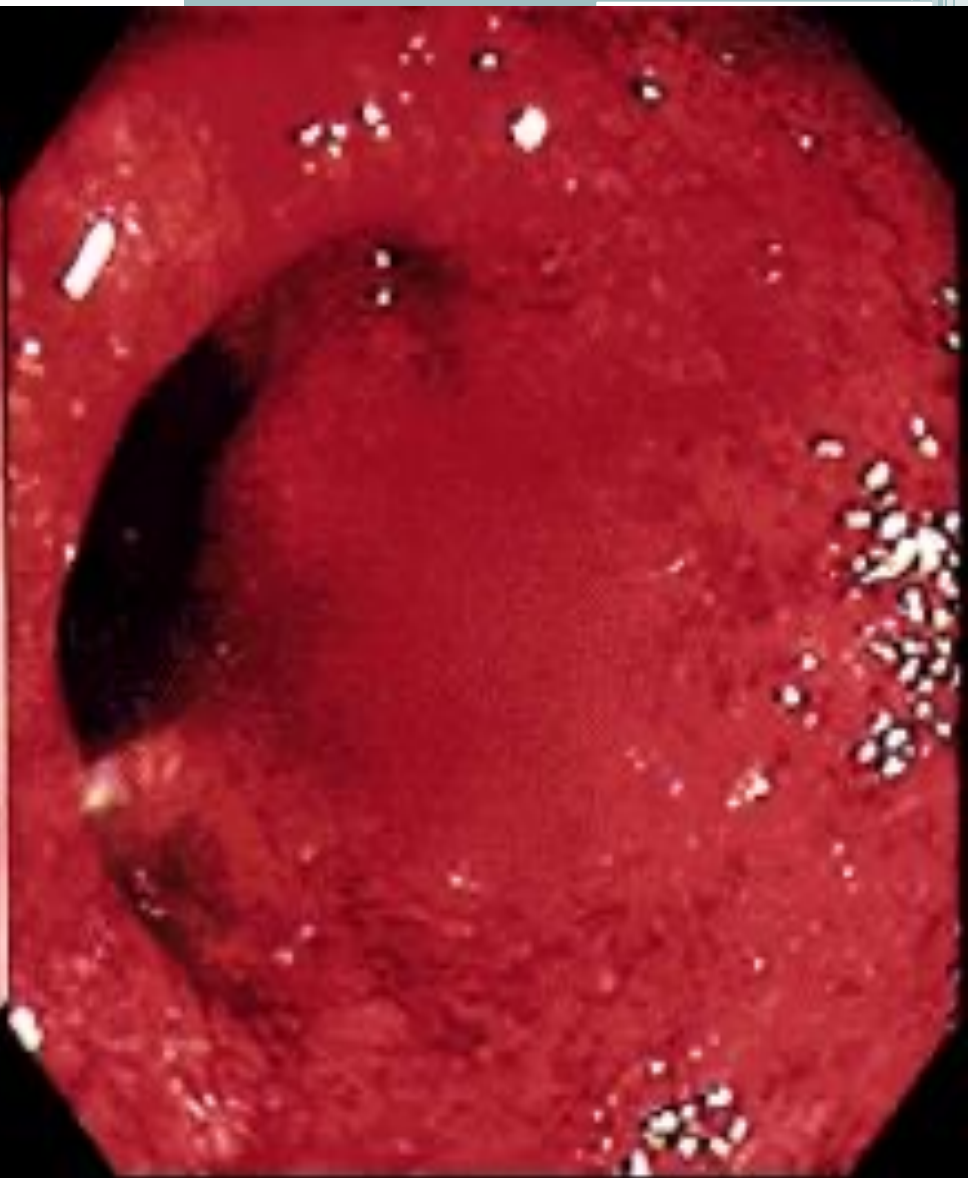
- Lifetime inflammatory auto-immune disorder
- Confined to the colon only
- S & S
 - Severe disorder with bloody diarrhea, cramping, and abdominal pain
 - Fecal urgency 5-10 x per day, with blood & mucus
 - Weight loss, anemia, low-grade fever
- Diagnosis
 - Sigmoidoscopy with mucosal biopsy

Ulcerative colitis

- Treatment
 - High fiber diet
 - Imodium
 - Corticosteroids
 - Suppositories
- Prognosis
 - High risk of colon cancer



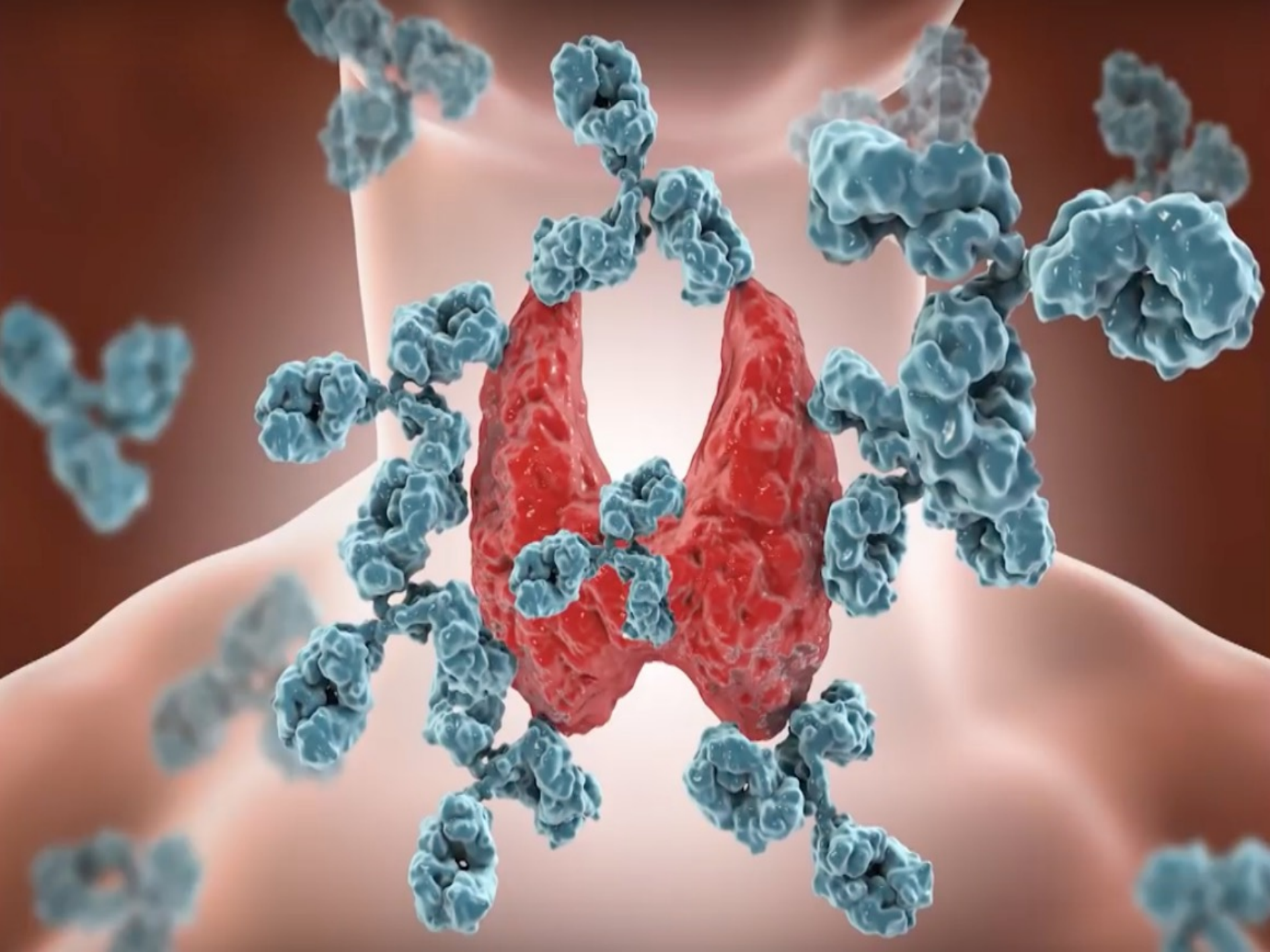
Healthy Colon



Ulcerative Colon

#8 Hyperthyroidism

- Thyroid gland produces thyroxine hormone
- An **autoimmune disorder**
- Significantly accelerates metabolism
 - Sudden weight loss, a rapid or irregular heartbeat, sweating, nervousness or irritability
 - Fatigue, muscle weakness, difficulty sleeping
 - Tremor, sweating
 - Changes in menstrual patterns
 - Increased sensitivity to heat
- 8 times more common in women



Hyperthyroidism symptoms



Hand tremors



Difficulty in sleeping



Hair loss



Menstrual problems



Swollen eyes



Weight loss



Irregular heart rate



Elevated blood pressure



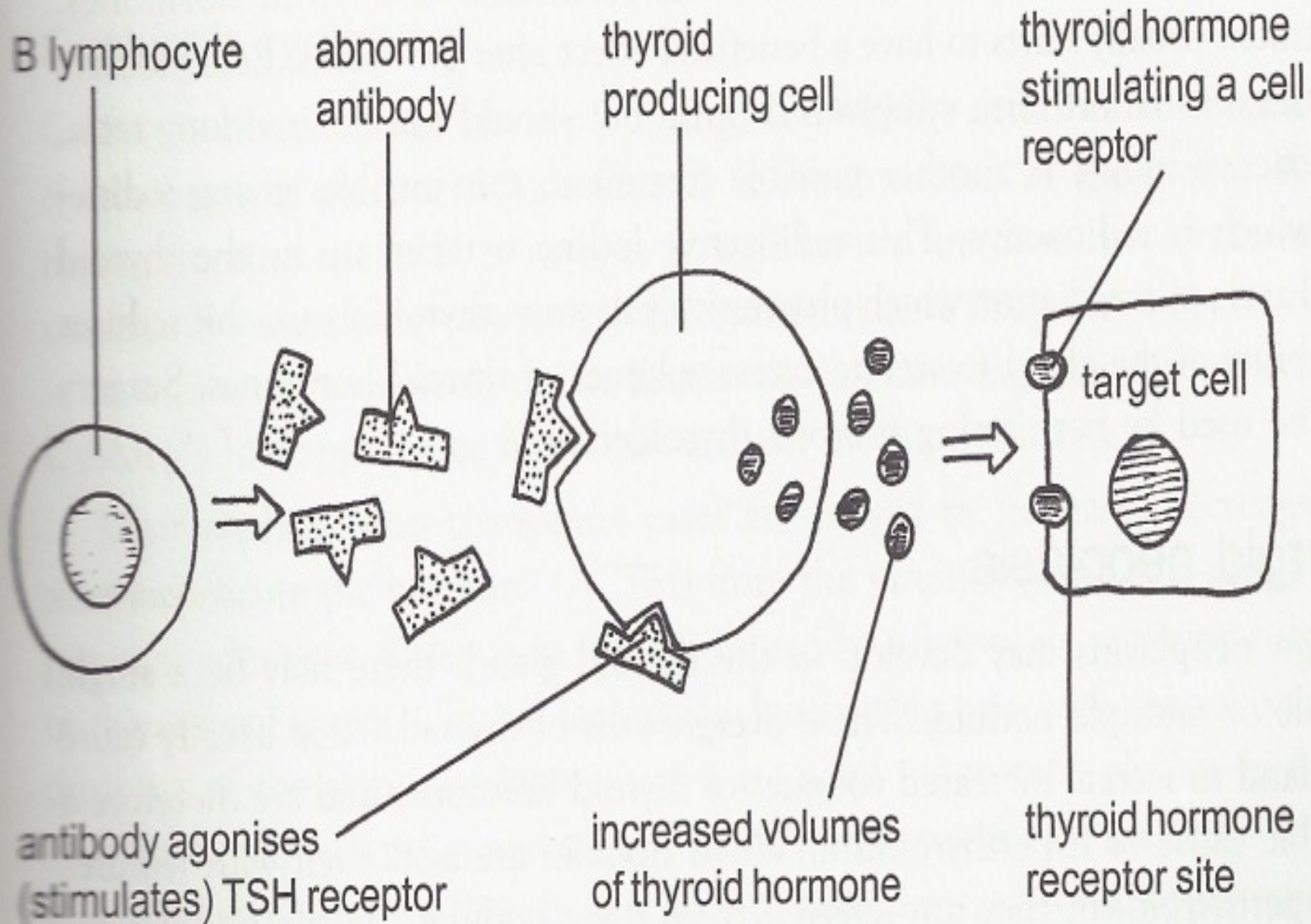
Nervousness



Feeling hungry

- **Etiology of Grave's Disease**

- For autoimmune reasons, a group of B lymphocytes secrete IgG which fits into and stimulates the TSH receptors present on cell membranes which increases the production of thyroid hormone.



- The characteristic exophthalmus is caused by inflammation of the tissue lining the orbit and extraocular muscles.
 - This causes edema and swelling and fibrosis.
- The increased metabolic rate increases appetite and weight gain.
 - The increased rate increases O₂ consumption and patient is short of breath.
- Increased sympathetic stimulation is present.

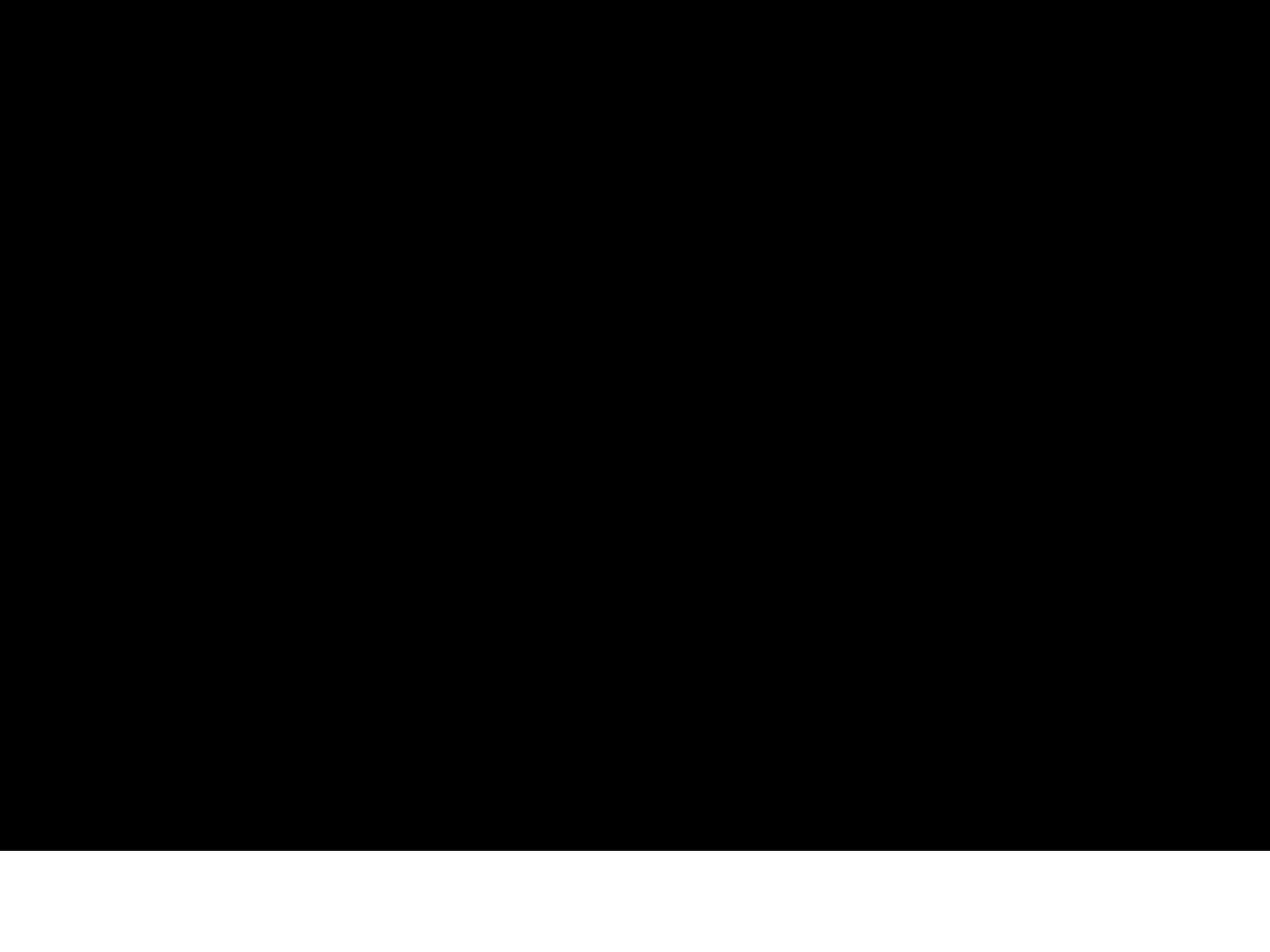
• **Causes of Graves Disease**

- Graves' disease, an autoimmune disorder, is the most common cause of hyperthyroidism
 - Antibodies produced by your immune system stimulate your thyroid to produce too much thyroxine
- Hyperfunctioning thyroid nodules
- Thyroiditis

- **Diagnosis of Graves Disease**
 - Radioactive iodine uptake test
 - Thyroid scan
 - Increased T3 & T4
 - Increased ANA titers

Walk This Way
Abby Normal





Thyrotoxicosis (Graves Disease)



(A from Belchetz P, Hammond P. *Mosby's color atlas and text of diabetes and endocrinology*, Edinburgh, 2003, Mosby.)

It is named Graves Disease after Dr. Robert Graves, who first described it in 1935. It is NOT called this because it takes you to the grave!!

● **Treatment of Graves Disease**

- Beta blockers (atenolol) block increased sympathetic stimulation
- Thioamides – block production of thyroid enzymes
- Increased iodine intake
- Radioactive iodine
- Lifetime thyroxine replacement if surgery utilized
- Graves Disease & Women

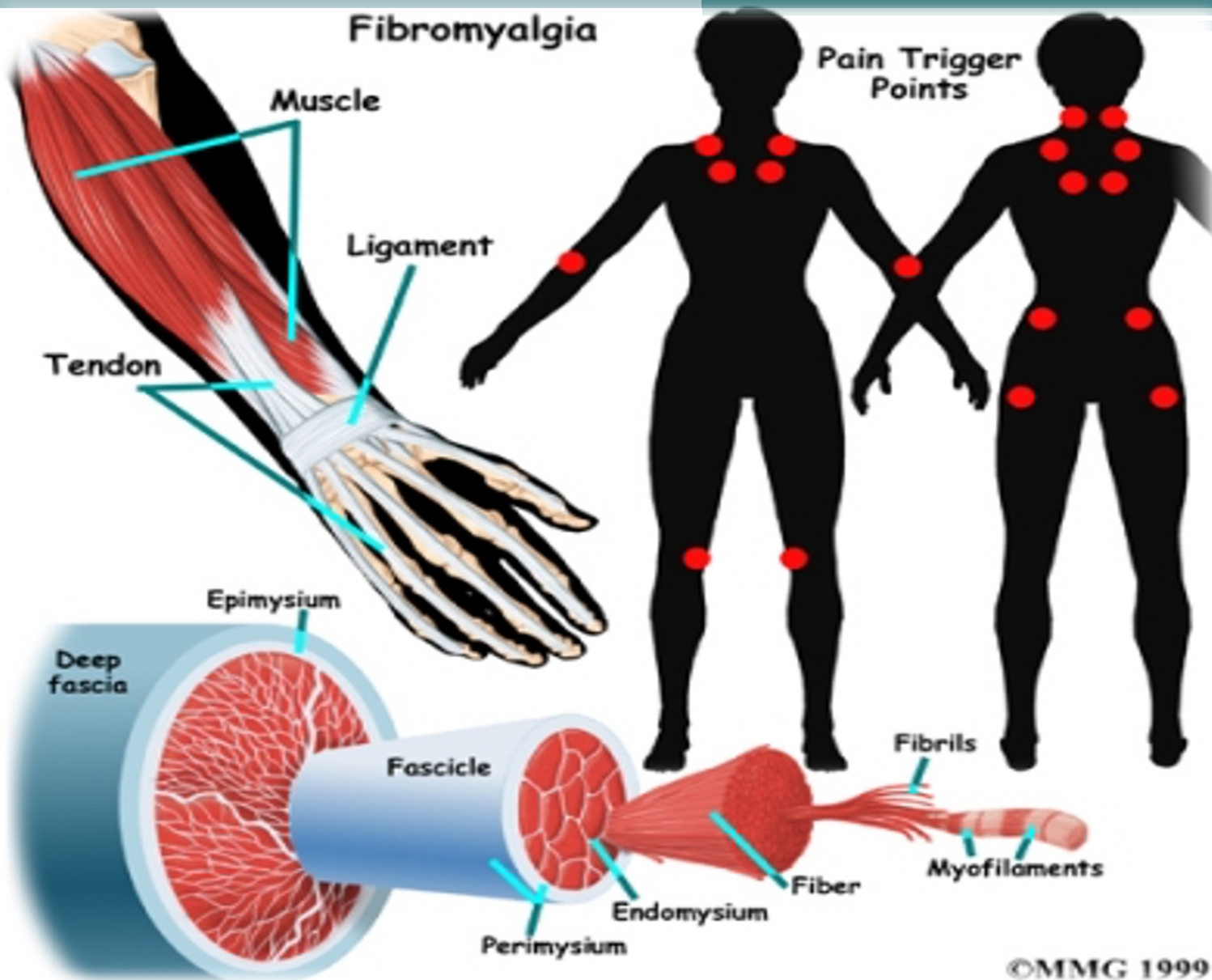




Fibromyalgia

Chronic Fatigue Syndrome

Fibromyalgia



Pathophysiology

- The diagnostic criteria are twofold
 - Widespread pain and tenderness in 11 of 18 defined points
 - PMS Symptoms include non restorative sleep, chronic fatigue, stiffness, and headache, migraine, IBS, TMJ, and mood disorders
- CFS symptoms include
 - Profound fatigue, myalgia, sleep difficulties, low grade fever, pharyngitis, lymphadenopathy



Occiput: at the insertions of one or more of the following muscles: trapezius, sternocleidomastoid, splenius capitis, semispinalis capitis

Low cervical: at the anterior aspect of the interspaces between the transverse processes of C5-C7

Second rib: just lateral to the second costochondral junctions

Trapezius: at the midpoint of the upper border

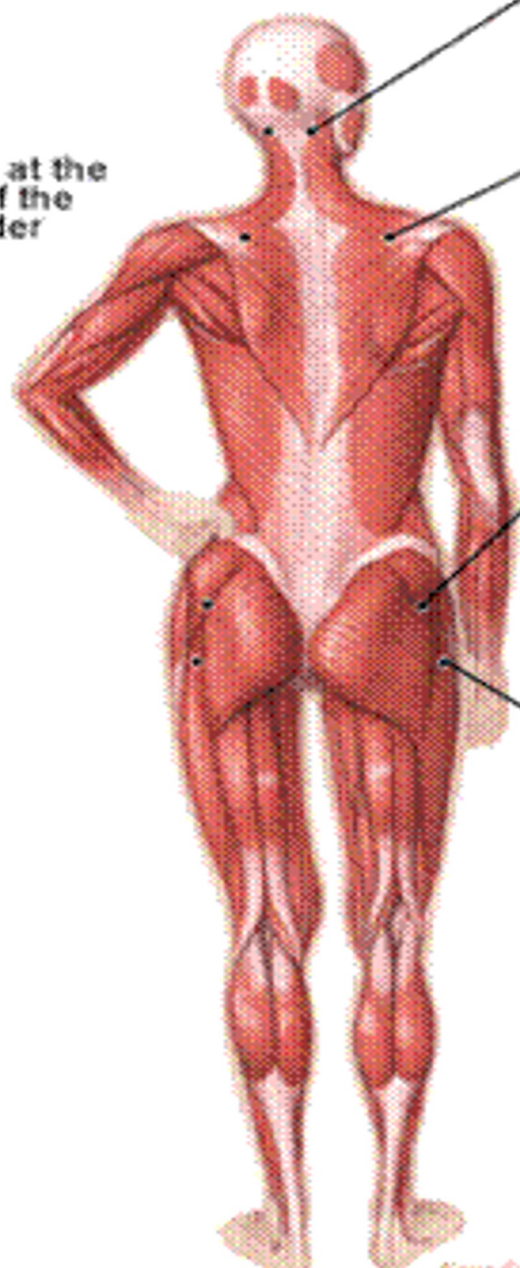
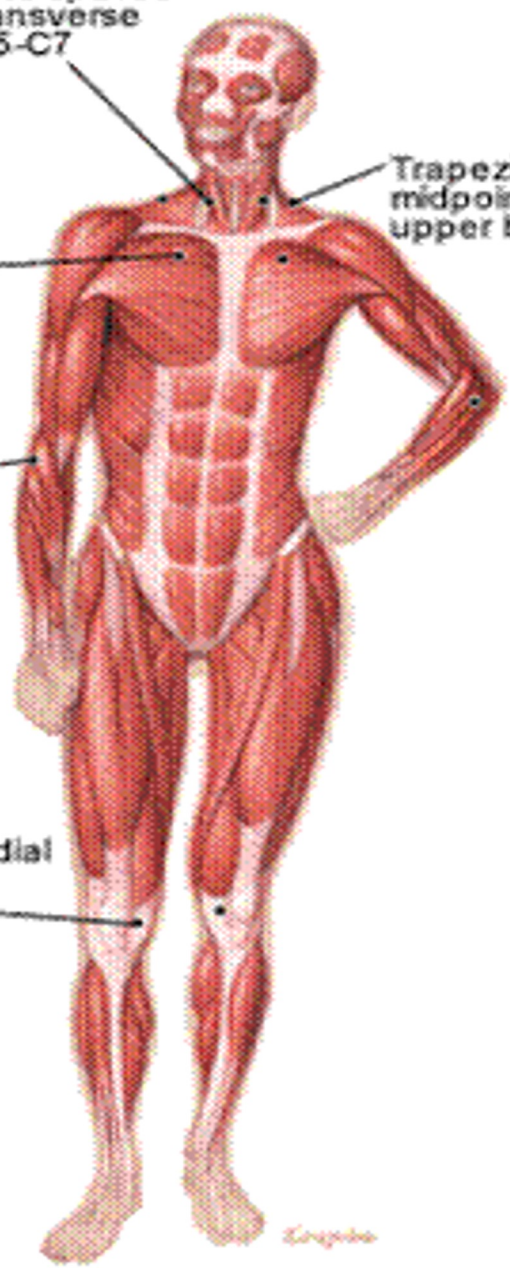
Supraspinatus: above the scapular spine near the medial border

Lateral epicondyle: 2 cm distal to the lateral epicondyle

Gluteal: at the upper outer quadrant of the buttocks at the anterior edge of the gluteus maximus

Knee: at the medial fat pad proximal to the joint line

Greater trochanter: posterior to the greater trochanteric prominence



Anterior view

Posterior view

- Exercise decreases symptoms, overuse increases symptoms
- Consider PT with TENS and massage therapy
- Tai chi – ROM Dance

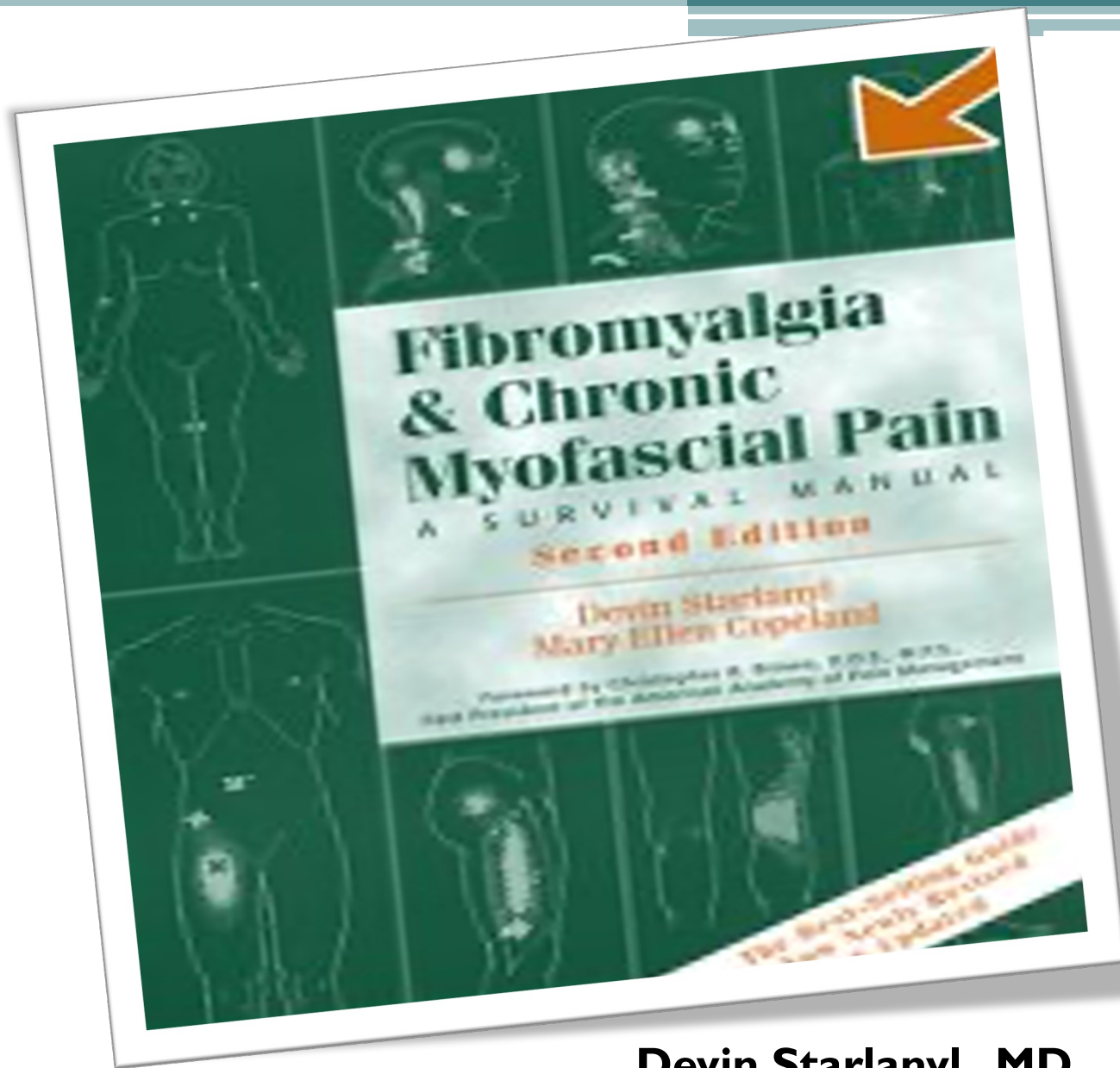


Lifestyle Changes

- Eliminate consumption of coffee, smoking, and alcohol
- Consider aggravating factors of body mechanics at work and home

Fibromyalgia treatment

- In western care, it is best to treat softly and tenderly
- Remember to not aggravate
- Treat with mild Chiropractic adjusting
- TCM, IHH and CAM have been helpful



Fibromyalgia & Chronic Myofascial Pain

A SURVIVAL MANUAL
Second Edition

Devin Starlanyl
Mary Ellen Copeland

Foreword by Christopher W. Brown, F.D.S., M.D.,
Past President of the American Academy of Pain Management

The Best-Selling Guide
Now Newly Revised
& Updated

Devin Starlanyl, MD

Polymyositis & Dermatomyositis

- Polymyositis – disabling muscle weakness
- Dermatomyositis – hyper-pigmentation rashes
- Both occur in 40-60 year olds
- S & S
 - Affects large muscles in shoulders and hips
- Diagnosis
 - Muscle weakness of shoulders and hips in middle age is suggestive, characteristic skin rash
 - EMG, muscle biopsy
- Treatment
 - Steroids and immunosuppressive drugs



Vasculitis – Polyarteritis Nodosa

- Inflammation of the walls of blood and lymph vessels
 - Damaged wall, resulting in either
 - aneurysm: thin and weak wall
 - stenosis and occlusion: thickened wall
 - Vasculitis in general
 - there are 20 different types of Vasculitis
 - Vessels can be in any organ; isolated in one (generally the skin) or systemic (multiple organs)

Vasculitis – Polyarteritis Nodosa

- Pathophysiology
 - AI of blood vessel walls, disrupting blood supply to the organ, starts at 40-50, more in women
 - Often triggered by hepatitis, streptococcus

- S & S

- Gradual onset often associated with joint and connective tissue inflammation
- Fever, paresthesias, weakness, weight loss, extremity pain
- Kidney damage (75%), liver arteries
- Mesenteric vessels, coronary arteries
- Peripheral nerves, rashes and ulcers common

- Diagnosis
 - Typical picture with elevated ESR, antibodies (75%)
 - Biopsy of involved vessels and nerves
 - Angiography occlusion
- Treatment
 - Corticosteroids
 - Immunosuppressive drugs
 - BP meds

- Prognosis

- Very fatal Autoimmune disease
- Without treatment – 67% die with 1 year, 88% in 5 years
 - Worse if renal involvement
- With treatment – 5-year survival to 60%

