Immunopathology: The Immune System Going Wrong

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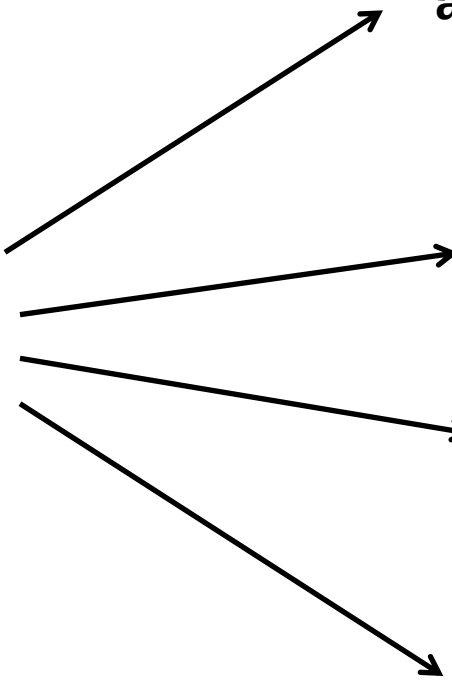
Immunopathology



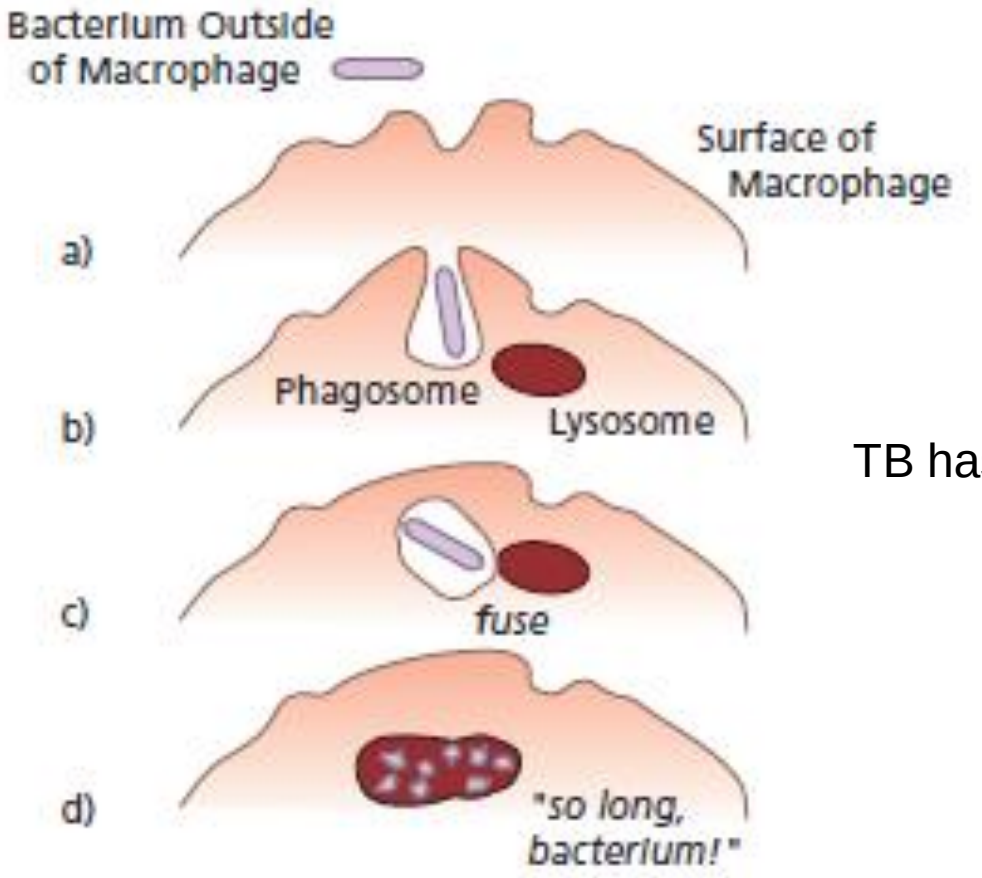
Pathological conditions caused by a normal immune response
Ex: TB, sepsis

Diseases caused by defects in immune regulation
Ex: Allergies

Autoimmune diseases

Immunodeficiencies

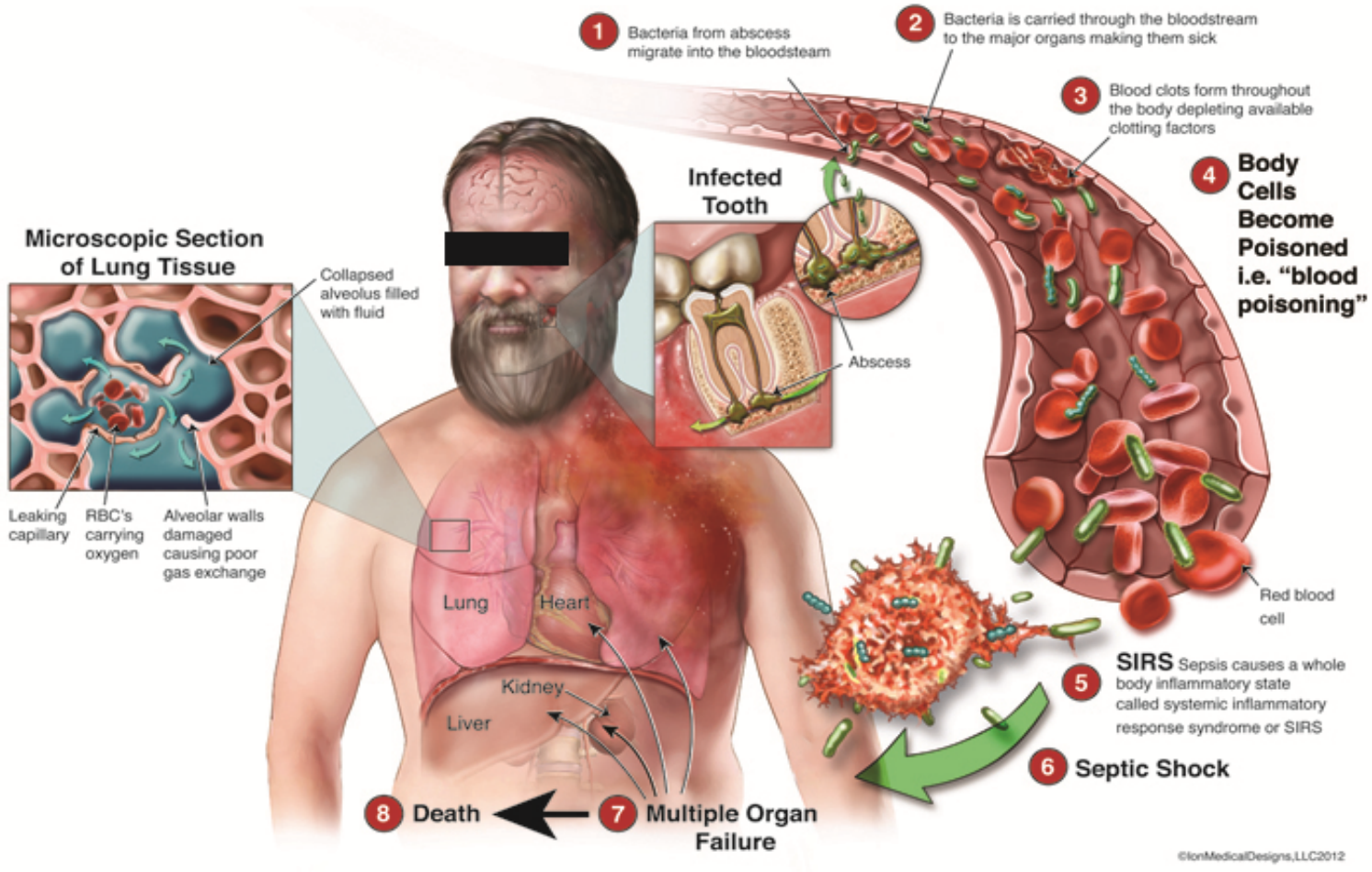
Pathological Conditions Caused by a Normal Immune Response



TB has the ability to block phagosome-lysosome fusion

What happens then?

Sepsis



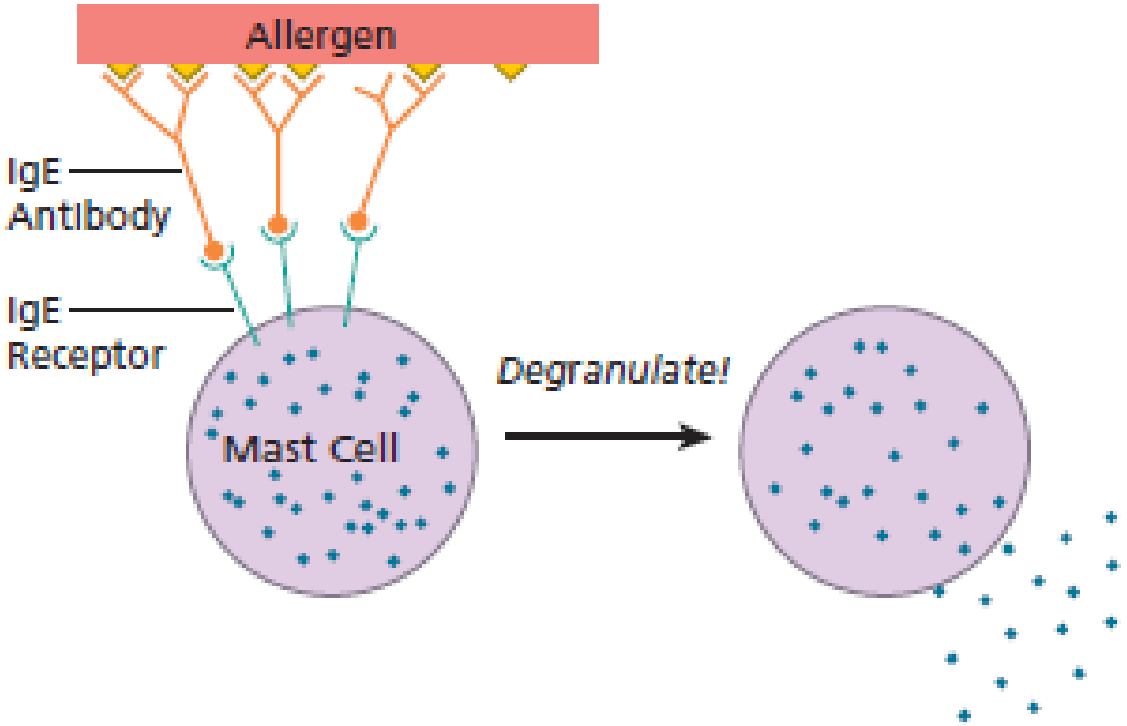
A state of heightened inflammation, TNF produced by Mφ causes leaky blood vessels.

Diseases Caused by Defects in Immune Regulation

Most common examples: Hay Fever, asthma.

Allergic people over-produce IgE antibodies. Non-allergic people usually respond weakly to allergens by producing IgG antibodies.

Mechanism of allergy



IgE antibodies become more long-lived once attached to surface of mast cells.

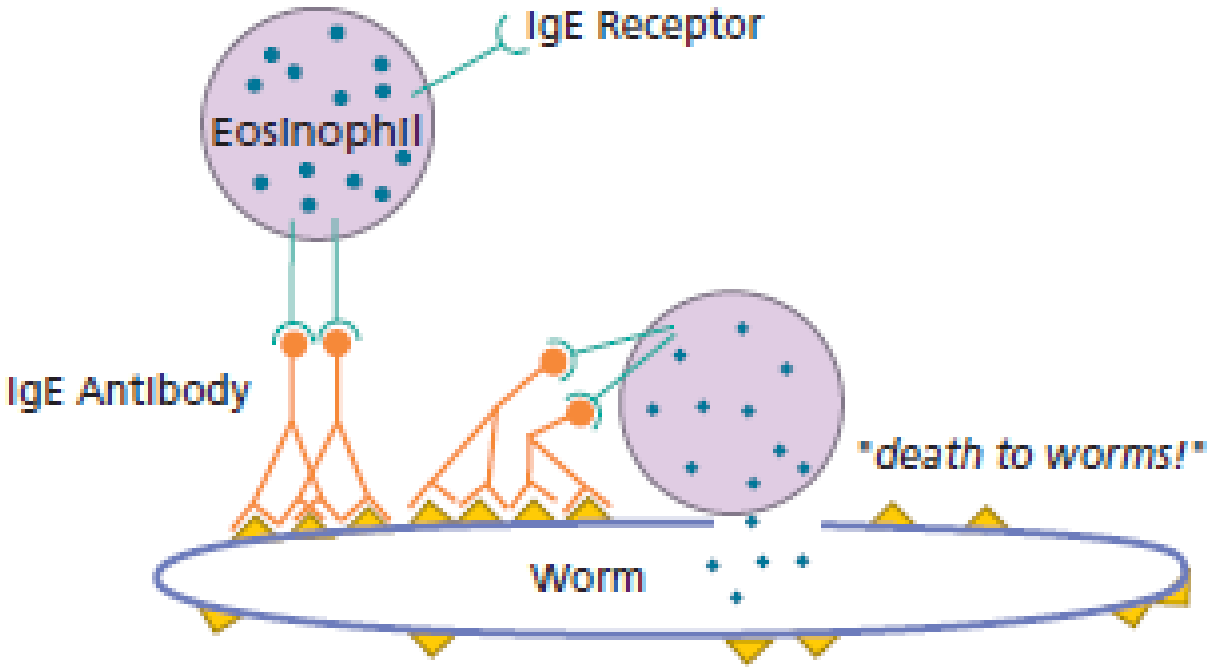
A similar scenario occurs with Basophils. (Immediate allergy).

Delayed Allergic reactions

These are chronic allergic reactions (Ex: Asthma); Eosinophils are involved.

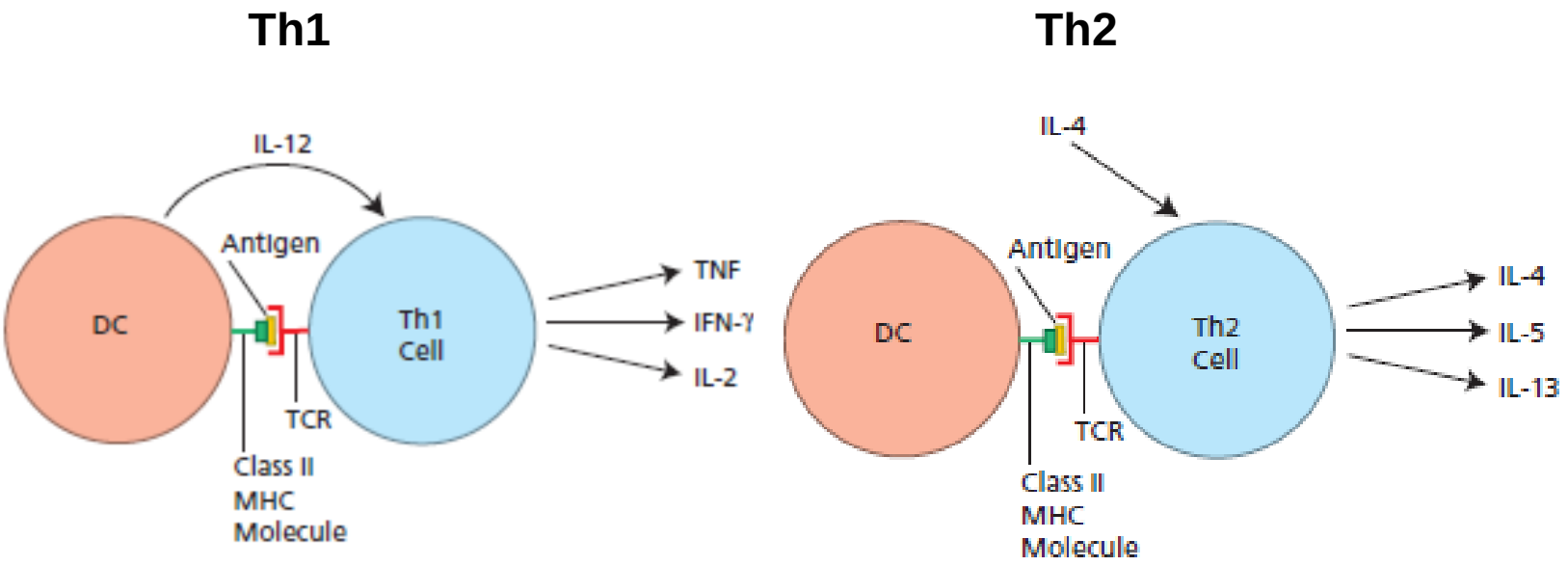
Allergic reactions cause Th cells to produce IL-5 which recruit eosinophils From the BM. = Takes time

What is the biological use of mast cells, basophils, and eosinophils??



Why do some people have allergies?

In order to produce IgE, Th2 cytokines are needed.



The decision to produce IgG or IgE Abs in response to an allergen will depend heavily on the type of Th cell present in the secondary lymphoid organ encountering The antigen.

Hygiene Hypothesis

Cells of the placenta produce large amounts of IL-4 and IL-10, why???

This drives a Th2 response, and blocks activation of CTLs and NK cells

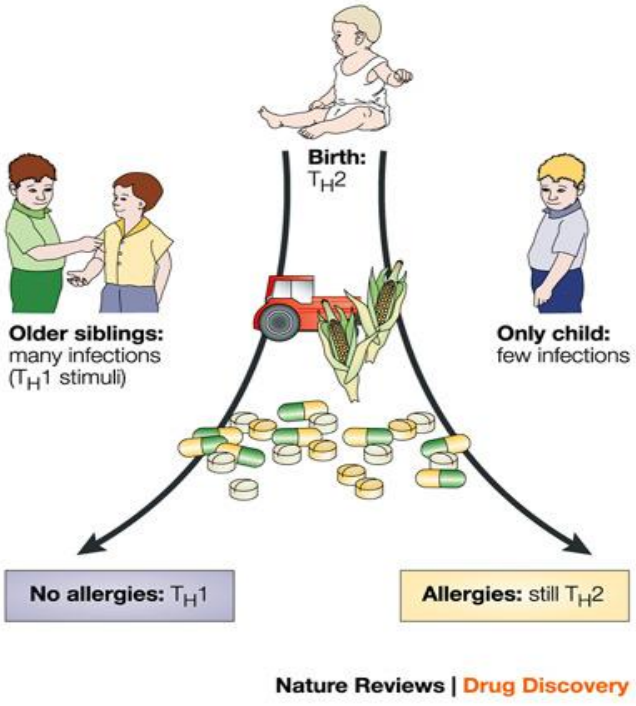
Advantage? Survival of the fetus...

But as a result, fetus has a Th2 bias when born!!!

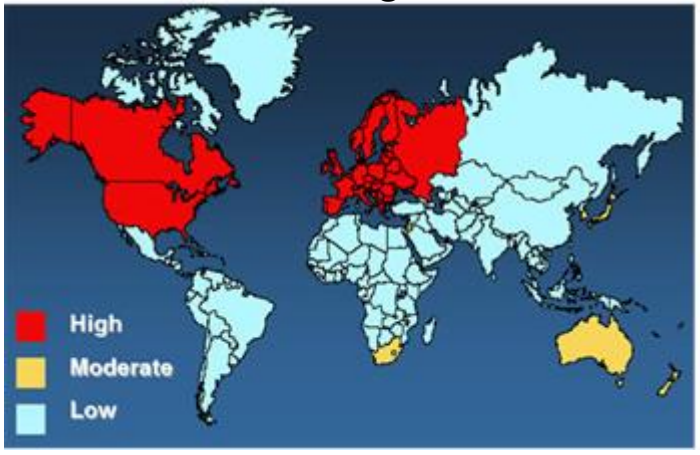
What can balance the bias?

Infections with bacteria and viruses!
The earlier the better= allows a normal response to environmental allergens.

The Hygiene Hypothesis



Allergies



Childhood Infections

Environmental vs. Hereditary causes of allergy

Hygiene Hypothesis= Environmental causes

Hereditary causes exist. If one twin is atopic, other twin has 50% chance

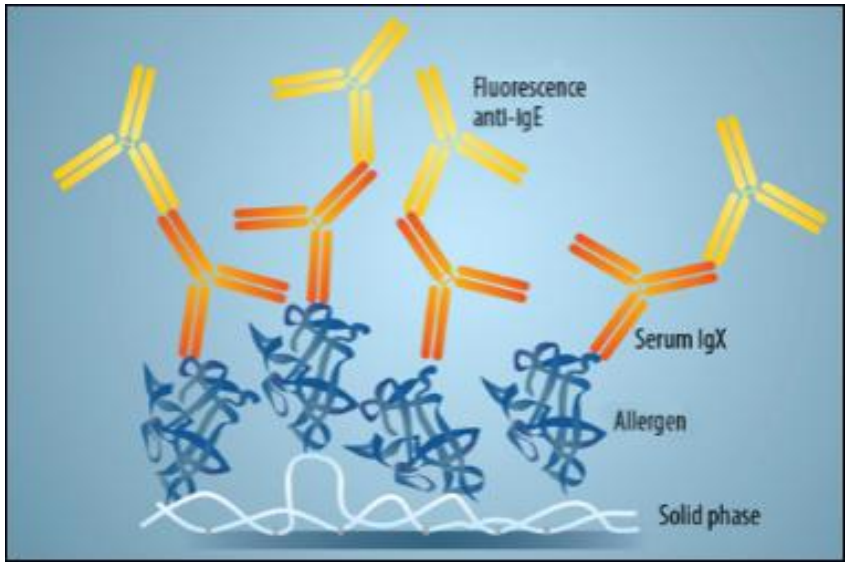
Certain **MHC class II** molecules are more efficient at presenting antigens than others.

Some indiciduals possessing **mutated IgE receptors**= Send stronger signals.

Mutations in the **promoters of IL-4 genes**, can increase its production.

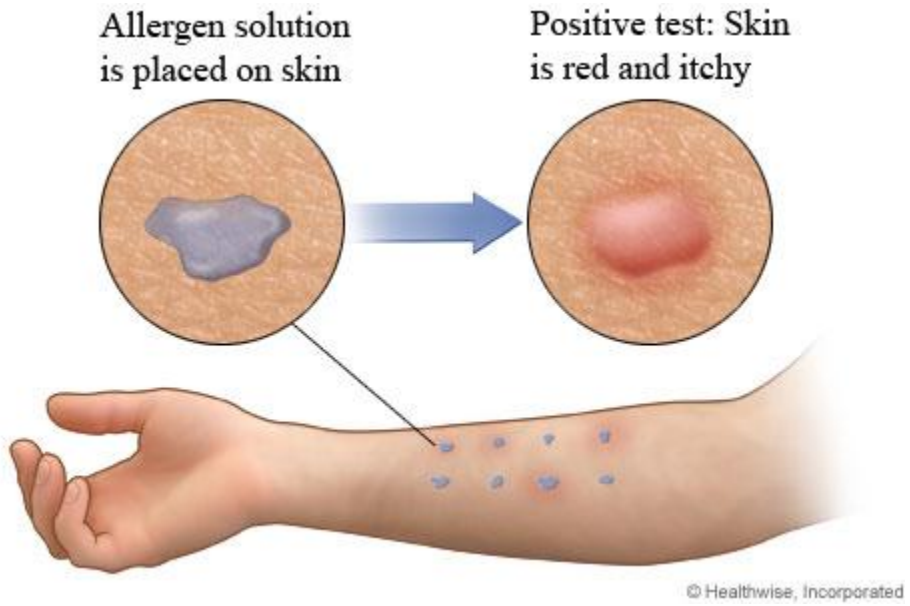
Allergy Diagnosis

1



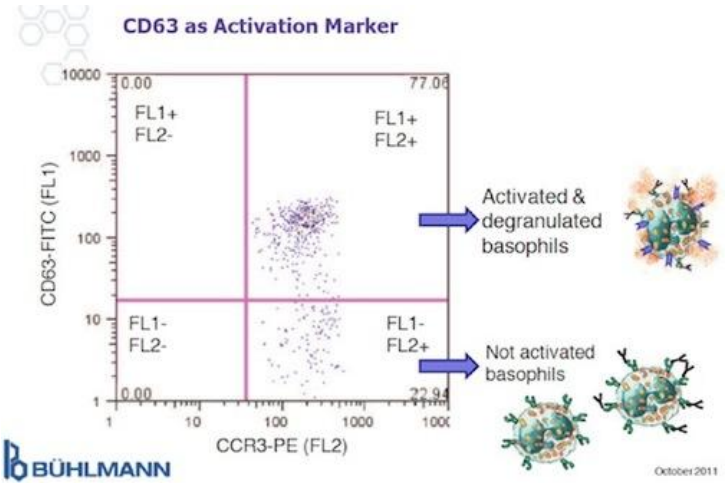
Specific IgE testing

2



Skin prick test

3



Basophil Activation Test (BAT)

Allergy treatment

Anti-histamines

Glucocorticoid steroids (block cytokine production by Th)

Omalizumab (Abs that bind to Fc portion of IgE) Safe, effective, but expensive

Specific Immunotherapy (Cure!): Injection of gradually increasing doses of crude extracts of allergens until a maintenance dose is achieved. (Several years)

Switch from IgE to IgG production. (Regulatory T cells involved?)

Autoimmune Disease

Results when a breakdown occurs in the mechanisms meant to preserve tolerance of self that is severe enough to cause a pathological condition. (~5% of Americans).

Genetic Causes:

Autoimmune lymphoproliferative syndrome (Genetic defect in Fas or FasL)
(Canale-Smith Syndrome)

Non-genetic Causes (Loss of self tolerance):

Failure to eliminate self-reactive cells in genetically normal individuals.

Conditions Needed for Autoimmune Diseases

Three conditions need to be met:

Individual must express an MHC molecule that efficiently presents a self antigen.

Individual must produce T and/or B cells that recognize self antigens.

Environmental factor (trigger) that breaks self tolerance (Viral/bacterial infection).

(Molecular mimicry) ex: rheumatic heart disease

Inflammation and Autoimmune Disease

Even self-reacting lymphocytes entering tissue will die by apoptosis if not continuously activated. What provides the co-stimulation???

Inflammation- Cytokines activate APCs which provide co-stimulation to autoreactive lymphocytes

For autoimmune disease to occur: An inflammatory reaction should take place in the tissues where the self antigen is expressed.

Cause of inflammation: Mimicking microbe, unrelated infection, trauma.

Example of Autoimmune Diseases

Insulin- dependent diabetes mellitus

Organ-specific autoimmune disease. (β-islets of the pancreas)

Genetic component: 50% chance in identical twin

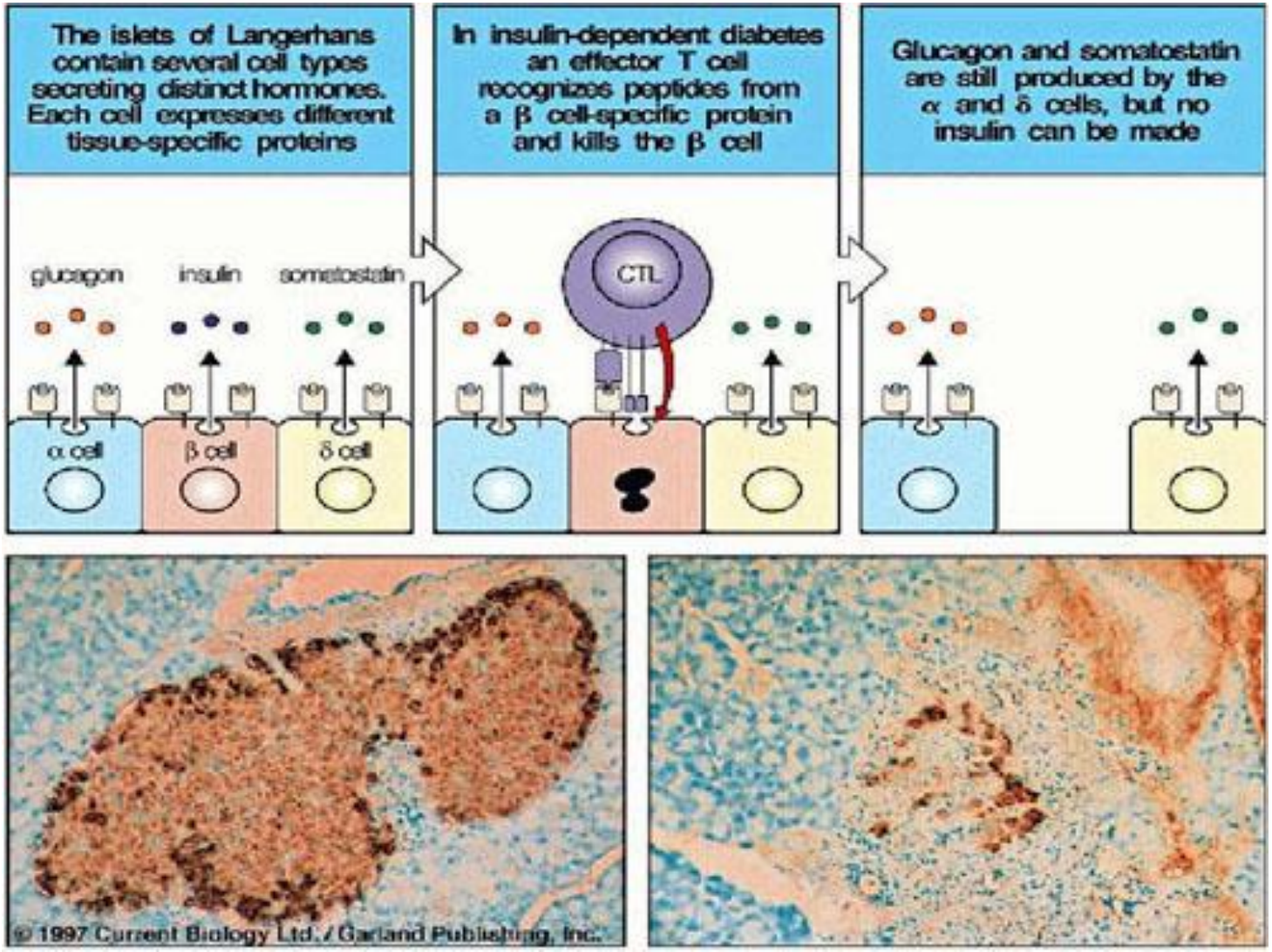
Patients make less CTLA-4 RNA- More activity for self reactive T cells

Defects in naturally occurring Treg functions suspected.

Silent Killer, symptoms appear when more than 90% of islets are destroyed.

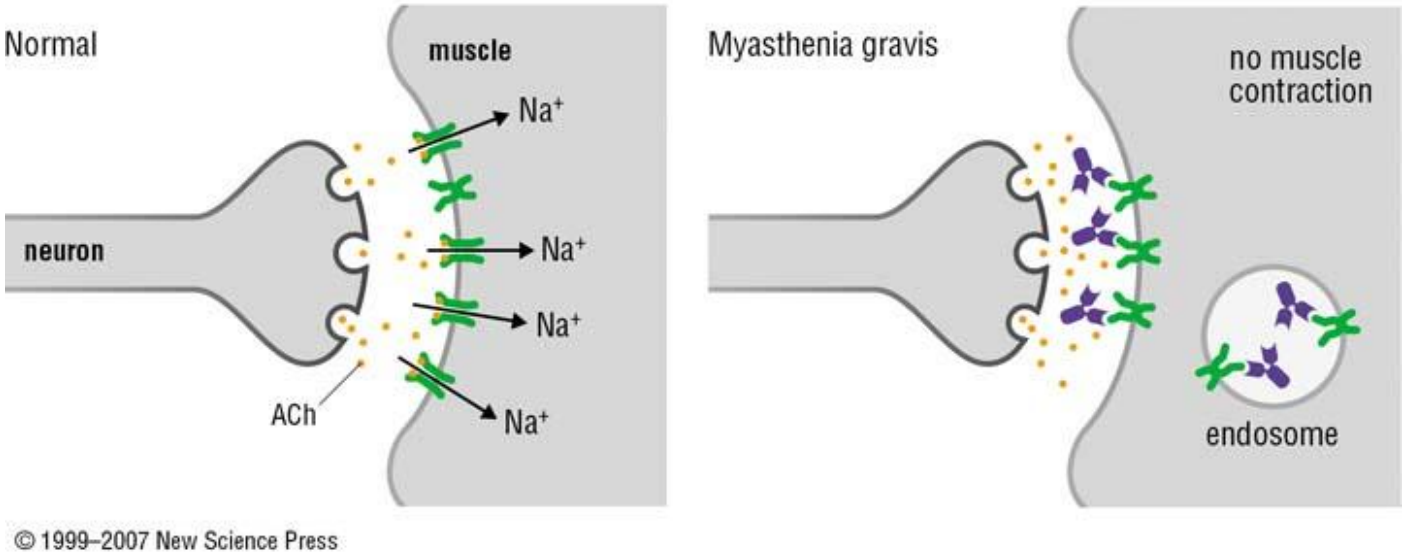
Diagnosis: anti-GAD, anti- islet antibodies

Diabetes- Type 1



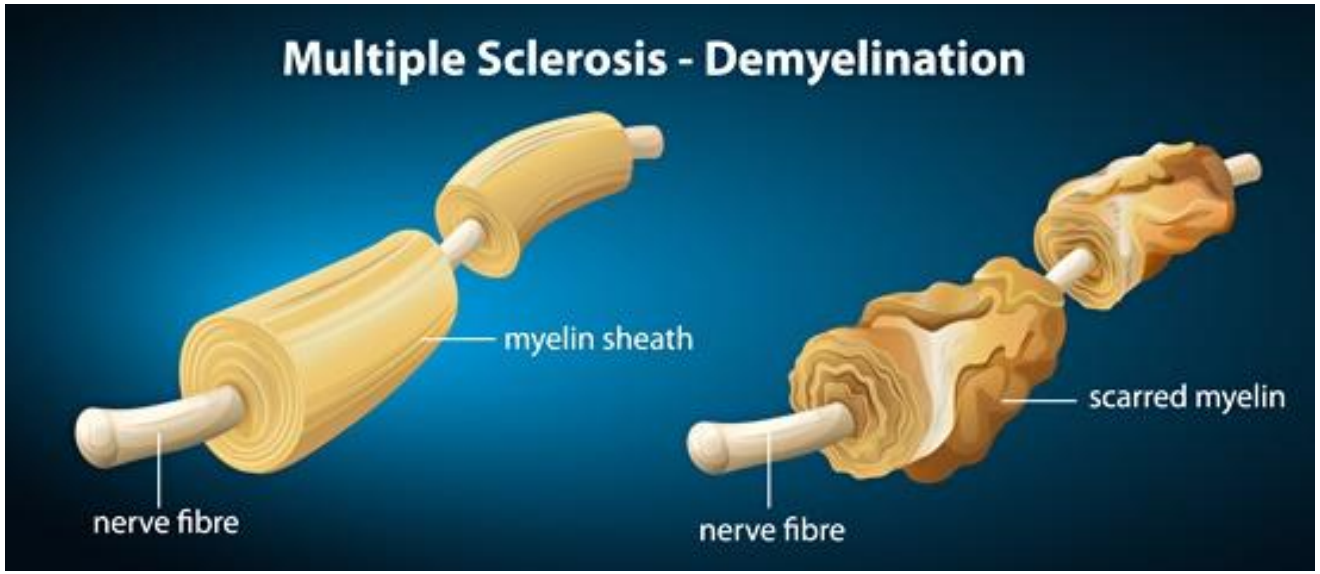
Myasthenia gravis (Case study)

From **Immunity: The Immune Response in Infectious and Inflammatory Disease**
by DeFranco, Locksley and Robertson



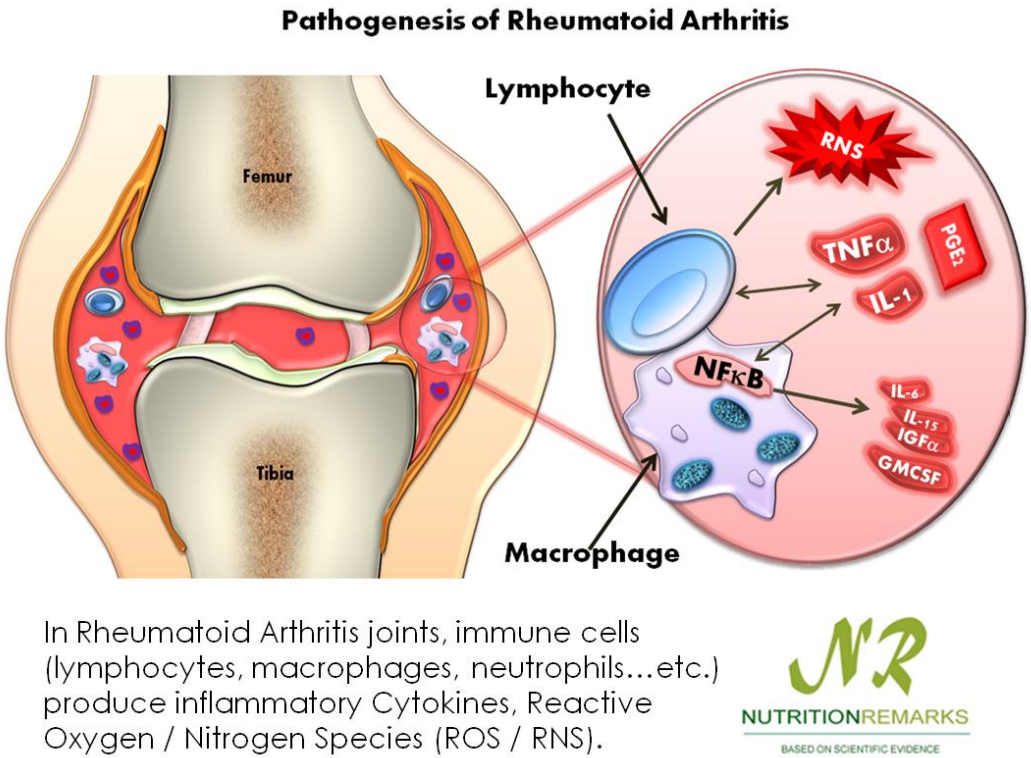
Possible trigger: **Poliovirus**- homologies to ACR

Multiple Sclerosis (Case study)



Defects in sensory inputs and paralysis.
Target: Myelin basic protein in myelin sheath.
Possible triggers: **HSV**, **EBV** infections
Genetic components: Twin studies, race studies (resistant groups: Hispanic, asian, Native Americans).

Rheumatoid arthritis

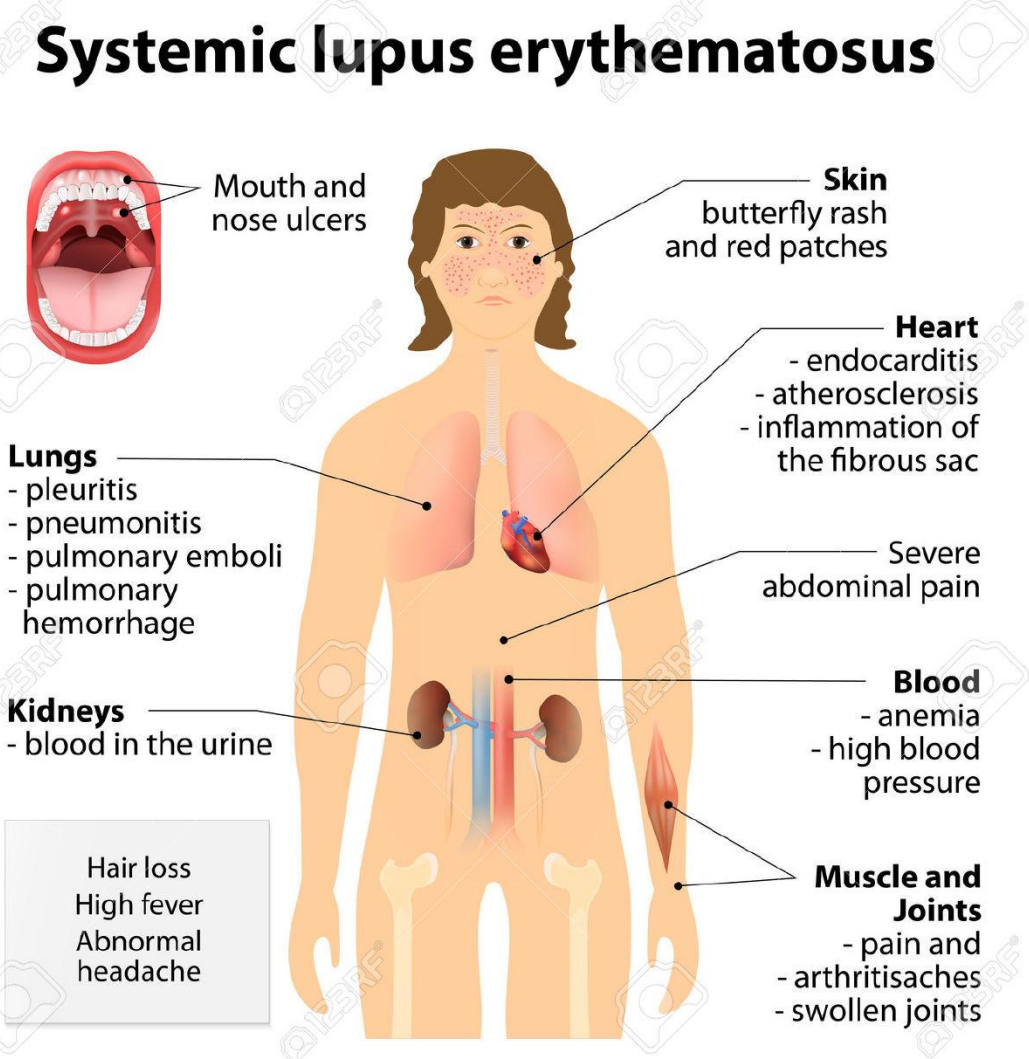


In Rheumatoid Arthritis joints, immune cells (lymphocytes, macrophages, neutrophils…etc.) produce inflammatory Cytokines, Reactive Oxygen / Nitrogen Species (ROS / RNS).

NUTRITIONREMARKS
BASED ON SCIENTIFIC EVIDENCE

Systemic autoimmune disease: joint inflammation, lung, kidney, spleen, muscles, etc.
Autoimmune reaction against a **cartilage protein**
Genetic Predisposition: HLA-DRB1
Environmental triggers: *Mycobacterium tuberculosis*, EBV, smoking

Systemic Lupus Erythematosus (SLE) Case study



Systemic disease

Female bias

Abs against DNA/histones

Genetic factors: Twin studies

Fas-FasL defects involved?

Questions?????