

# **Functional Medicine University's Functional Diagnostic Medicine Training Program**

## **Module 3**

### **Immunology and Allergy**

By Wayne L. Sodano, D.C., D.A.B.C.I., & Ron Grisanti, D.C., D.A.B.C.O., M.S.  
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Module 3: Immunology and Allergy  
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Recommended Reading (Article Attached): Anterior Uveitis, Inflammatory Bowel Disease, and Ankylosing Spondylitis in a HLA-B27-positive woman, Publication: Southern Medical Journal, May 1, 2006, Sanford E. Hutson

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The immune system of the body is designed for combating infections and toxic agents. The system is composed of leukocytes (white blood cells) and specific tissue cells that are derived from the white blood cells.

White blood cells are formed partially in the bone marrow and partially in the lymph tissue (especially the lymph glands, spleen, thymus, tonsils, and the Peyer's patches in the gastrointestinal system).

### **Types of White Blood Cells**

Neutrophils	}	Collectively known as polymorphonuclear granulocytes
Eosinophils		
Basophils		
Monocytes		
Lymphocytes		
Plasma cells		

The granulocytes and monocytes are formed in the bone marrow and protect the body from invaders by using a process called phagocytosis. The lymphocytes and plasma cells are formed in various lymphogenous tissues and are part of the adaptive (Specific) immune system.

### **Neutrophils and Monocyte-Macrophage**

Both neutrophils and macrophages can attack and destroy bacteria, viruses, and other toxic agents by a process called phagocytosis, which means ingesting the toxic agents. Monocytes are essentially inactive in the blood, however, once they leave the blood stream, they mature into macrophages, which are formidable warriors against invaders.

White blood cells enter the tissue spaces of the body by squeezing through the capillaries in a process known as diapedesis. They are attracted to inflamed/injured tissue by a phenomenon known as chemotaxis. Chemotaxis is a process by which the injured/inflamed tissue produce substances that attract the neutrophils and macrophages found in the inflamed area. Examples of chemotaxis substances are bacterial toxins, viral toxins, degenerative tissue products, and cytokines.

### **Tissue Macrophage System**

Monocytes, once in the tissue, grow and become macrophages. They can move through and become attached to the tissues. The combination of mobile and fixed macrophages is collectively called the Reticuloendothelial System.

- Kupffer cells (liver)
- Reticulum cells (lymph nodes, spleen, bone)
- Microglia (brain)
- Alveolar (lung)
- Histiocytes (subcutaneous)
- Type A lining (synovium)
- Osteoclasts (bone)

### **Eosinophils**

Eosinophils are polymorphonuclear granulocytes that have weak phagocytic capability. They normally account for about 2% of the white blood cell count and have 2 main functions:

1. They attach themselves to parasites and release substances that kills them
  - Hydrolytic enzymes
  - Reactive oxygen species
  - Polypeptide called 'major basic protein'
2. They are involved in allergic reactions. Mast cells and basophils release a substance called 'eosinophil chemotactic factor' which causes the eosinophils to move toward the allergic area. Eosinophils are thought to detoxify substances released by the mast cells and basophils.

### **Basophils**

Basophils are polymorphonuclear granulocytes that release heparin into the blood. Tissue mast cells are similar to basophils and have similar functions. Both cells also release histamine, bradykinin, and serotonin, and play a role in Type I Hypersensitivity reactions (IgE).

### **Dendritic Cells –Antigen- presenting Cell**

“.....although Monocytes-macrophages were originally thought to be the major antigen-presenting cells of the immune system, it is now clear that dendritic cells are the most potent and effective APC in the body.”

-As quoted from Harrison's Principles of Internal Medicine; 16<sup>th</sup> edition

- An antigen-presenting cell is a cell that displays a foreign antigen complexed with MHC (major histocompatibility complex) on its surface for T-cell recognition.
- They are important for adaptive immunity
- Dendritic cells are bone marrow derived APCs that come from both lymphoid and myeloid lineages
  - Plasmacytoid (lymphoid)
  - Langerhans (myeloid)
  - Interstitial (myeloid)

### **Spleen**

Similar to lymph nodes, except that blood, instead of lymph, flows through the substance of the spleen.

- Old RBCs
- Abnormal platelets
- Blood parasites
- Any bacteria in circulating blood

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**White Blood Cell Count**

Reference range:	3.8 – 10.8	$10^3/\text{ul}$
Optimal range:	5.0 – 7.5	$10^3/\text{ul}$

The life span of leukocytes varies from 13 to 20 days.

High count

Childhood diseases  
Acute viral/bacterial infection  
Stress  
Neoplasm  
Steroid use

Low Count

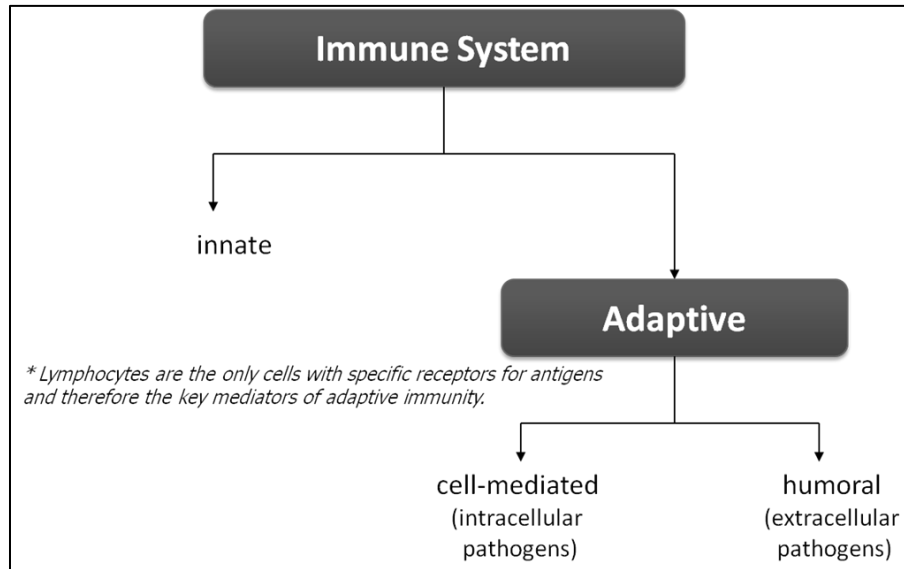
Nutritional deficiencies  
Drugs/Chemotherapy  
Autoimmune disease  
Overwhelming infection

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Causes of Abnormalities in White Blood Cell Differential Count		
Type of WBC	Elevated	Decreased
<i>Neutrophils</i>	Neutrophilia Metabolic disorders (e.g. ketadoisis, eclampsia, gout) Inflammatory disorders (e.g. rheumatoid arthritis, Thyroiditis) Cushing's Syndrome Trauma Myelocytic Leukemia Acute or emotional distress	Neutropenia Addison's Disease  Dietary deficiency  Aplastic anemia Radiation therapy Drug therapy-myelotoxic drugs (chemo) Viral infections (e.g. hepatitis, measles, influenza) Addison's Disease
<i>Lymphocytes</i>	Lymphocytosis Infectious hepatitis Infectious mononucleosis Viral infection (e.g. rubella, mumps) Chronic bacterial infection Lymphocytic leukemia Multiple myeloma Radiation	Lymphocytopenia Immunodeficiency diseases Later states of human immunodeficiency virus Sepsis Leukemia Lupus erythematosus Drug therapy: adrenocosteroids, antineoplastics Radiation therapy
<i>Monocytes</i>	Monocytosis Viral infections (e.g. infectious mononucleosis) Chronic inflammatory disorders Tuberculosis Chronic ulcerative colitis Parasites (e.g. Malaria)	Monocytopenia Drug therapy (prednisone)
<i>Eosinophils</i>	Eosinophilia Leukemia Eczema Allergic reactions Autoimmune disease Parasitic infections	Eosinopenia Increased adrenosteriod production
<i>Basophils</i>	Basophilia Myeloproliferative disease (e.g. myelofibrosis, polycythemia, rubra vera) Leukemia	Basopenia Stress reactions  Hyperthyroidism Stress reactions

**There are three types of immunity:**

- Innate
- Humoral
- Cell-mediated



**Innate Immunity**

Innate immunity refers to the general, non-specific protection the body provides against various invaders. The simplest example of innate immunity is the barrier to the outside world known as skin.

The skin is an excellent barrier against the entry of microorganism

- Tears, saliva, and blood contain lysozyme, an enzyme that kills some bacteria by destroying their cell walls.
- The extreme acidity of the stomach destroys many pathogens which are ingested with food or swallowed after being passed out of the respiratory tract.
- Macrophages and neutrophils indiscriminately phagocytize microorganisms
- The complement system is a group of about 30 blood proteins that can nonspecifically bind to the surface of foreign cells, leading to their destruction.

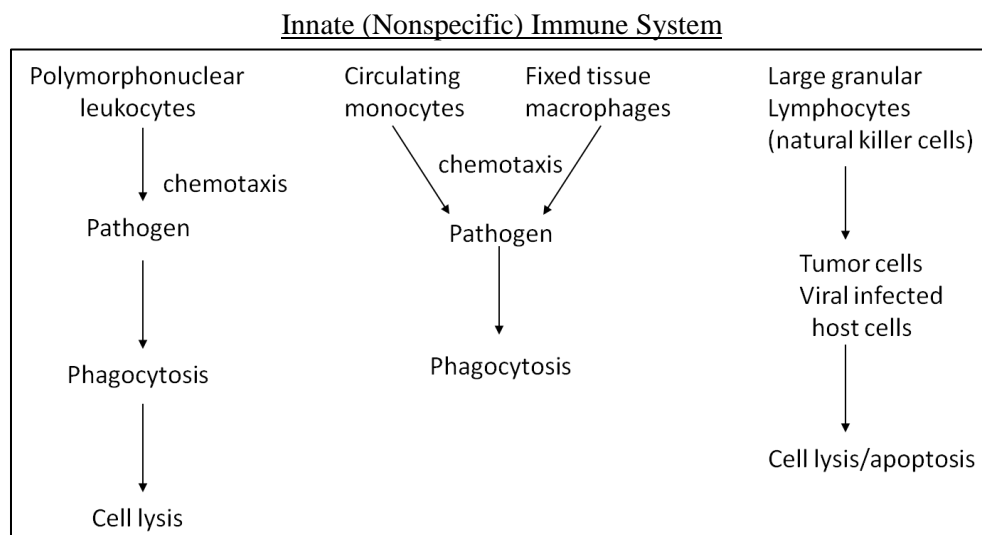
Components of innate immunity

- Neutrophils
- Monocytes
- Macrophages
- Natural Killer Cells
- Eosinophils
- Basophils
- Cytokines
- The Complement System

*Natural Killer Lymphocyte Cells (innate)*

- Specialized to kill
  - Host cells infected with virus
  - Host cells that have become cancerous
  - Foreign cells

Cytokines released by the infected cell can signal the NK cells. The NK cell will bind to a receptor on the target cell and release granules containing perforin and granzymes that kill the infected or foreign cell by a process called exocytosis.



**Acquired (adaptive) Immunity**

Acquired or adaptive immunity is a specific immunity against specific invading substances, such as bacteria, toxins, viruses, and foreign tissues. Acquired immunity forms antibodies and/or activated lymphocytes that attack and destroy invading substances.

There are two basic types of acquired immunity, **cellular** and **humoral**. Cellular or cell-mediated immunity occurs through the formation of 'activated T lymphocytes'. Humoral immunity involves the development of antibodies by the B-lymphocytes. Both activated lymphocytes and antibodies are formed in the lymphoid tissues.

Cell mediated and humoral immunity are initiated by substances called antigens.



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*Immunogen/Antigen/Hapten*

- Immunogen
  - Antigen that induces an immune response
- Antigen (allergen)
  - Elicits allergic reaction
  - Foreign organism or toxin
  - Proteins
  - Large polysaccharides
  - Large lipoprotein complex
  - Must have a MW of 8000 or greater
- Hapten
  - Antigen that may not stimulate an immune response

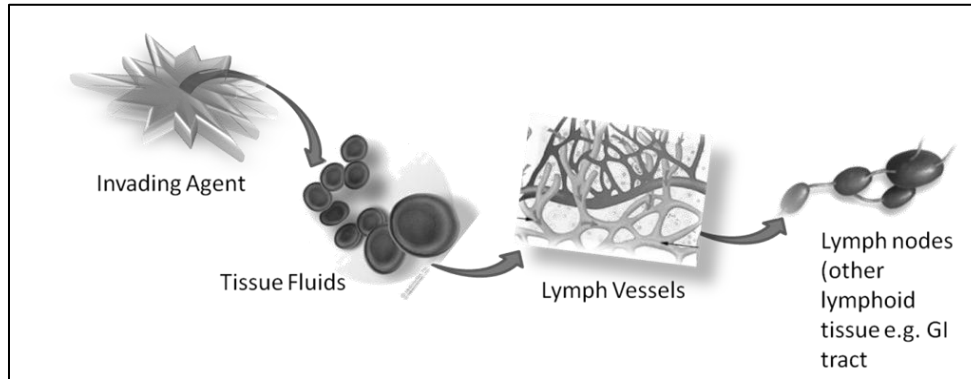
*Note:* Therefore, not all antigens are immunogens

- Haptens: MW less than 8000
  - Does not act as an antigen unless it combines with a substance that is antigenic (such as a protein)
  - Antibody or sensitized lymphocyte that develops against the combination can react either against the protein or against the hapten.
  - On second exposure to the hapten, the antibodies or lymphocytes react with it before it can spread through the body.
  - The haptens that elicit this type of immune response are:
    - Drugs
    - Dust
    - Dander
    - Poison ivy
    - Industrial chemicals

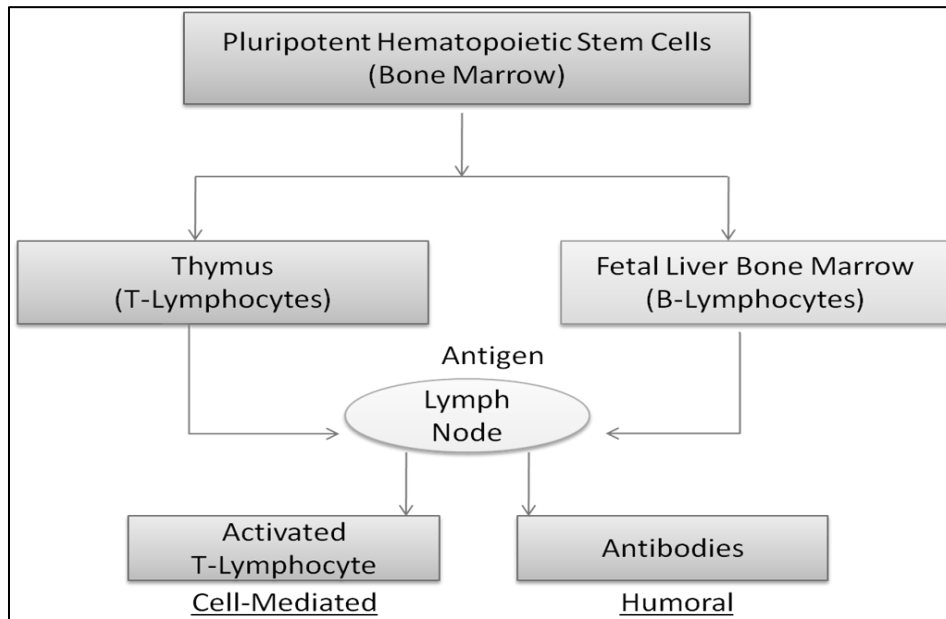
**Location of Lymphocytes**

- Mainly in the lymph nodes
- Spleen
- Gastrointestinal tract (Submucosa)
- Thymus
- Bone marrow

In the lymph node and lymphoid tissue, the invading antigen activates the T-Lymphocytes for a cell-mediated response and the B-Lymphocyte for a humoral response (production of antibody)



### Origins of Lymphocytes



The thymus gland is where the lymphocytes rapidly divide and develop extreme diversity for reacting against specific antigens. The thymus gland also processes the lymphocyte not to react to 'self', that is, not to attack the body's own tissue. Most of the preprocessing of T-Lymphocytes occurs before birth and a few months after birth.

### **Cell-Mediated Immunity and the T-Lymphocyte**

T-Lymphocytes are categorized as T-Lymphocyte helper cells and T-Lymphocyte killer cells (aka Cytotoxic T-cells).

The T-helper cell is the main controller of the whole immune system. Its role is to activate B-cells, T-killer cells and other cells of the immune system. The T-cell communicates with other cells by releasing special chemicals called lymphokines and interleukins.

[The T-helper is the host of HIV]

### **Major Histocompatibility Complex (MHC)**

There are specialized proteins on the surface of the cells in the body. These cell-surface proteins are known as the 'major histocompatibility complex' proteins. These proteins are encoded for by a large group of genes called the MHC.

"Human MHC, commonly called the human Leukocyte Antigen Complex (HLA), is a region on chromosome 6 that is densely packed with expressed genes. The best known of these genes are HLA Class I and HLA Class II, which products are critical for immunologic specificity and transplantation histocompatibility and they play a major role in susceptibility in a number of autoimmune diseases."

*-As quoted from Principles of Internal Medicine; Harrison; 16<sup>th</sup> edition*

The MHC protein picks up proteins and fragments of antigen proteins inside the cells and sends them to the cell-surface to be displayed and examined by the T-cells.

There are two different types of MHC proteins called MHC Class I proteins and MHC Class II proteins. MHC class I proteins are found on all cells of the body and present antigens to the 'cytotoxic T-cells'. MHC Class II proteins are found on what are known as the antigen presenting cells (APCs). There are three major types of antigen-presenting cells: macrophages, B-lymphocytes, and dendritic cells. The dendritic cells are the most powerful. MHC Class II present antigen to the T-helper cells. After the T-helper cells is activated, it activates B-cells which mature into plasma cells that secrete antibodies and T cytotoxic (killer) cells which cause them to proliferate.

### **Type and Functions of T-Cells**

- The Helper T-cells
  - The most numerous of the T-cells
  - Major regulator of all immune functions
  - Regulate the immune system by forming protein mediators called lymphokines. The lymphokines act on other cells of the immune system.

**Type and Functions of T-Cells (T-helper cells) con't**

- Important lymphokines secreted by helper T-cells
  - IL-2
  - IL-3
  - IL-4
  - IL-5
  - IL-6
  - Interferon-gamma
  - Granulocyte-monocyte colony-stimulating factor
- Stimulate the growth and proliferation of cytotoxic T-cells and suppressor T-cells.
- Stimulates B-cell growth and differentiation to form plasma cells and antibodies
- Activates the macrophages
- Feedback stimulatory effect on the helper cells themselves
- Cytotoxic T-cells (killer)
  - Antigens on the surface of cells cause the cytotoxic cells to bind to the surface. The cytotoxic cells secrete proteins called perforins that make a hole in the cell membrane that allows substances to enter the cell and attack it.
- Suppressor T-cells
  - Prevent cytotoxic cells from causing excessive immune reactions which can damage the body's own tissue.

*Note on **Human Leukocyte Antigen***

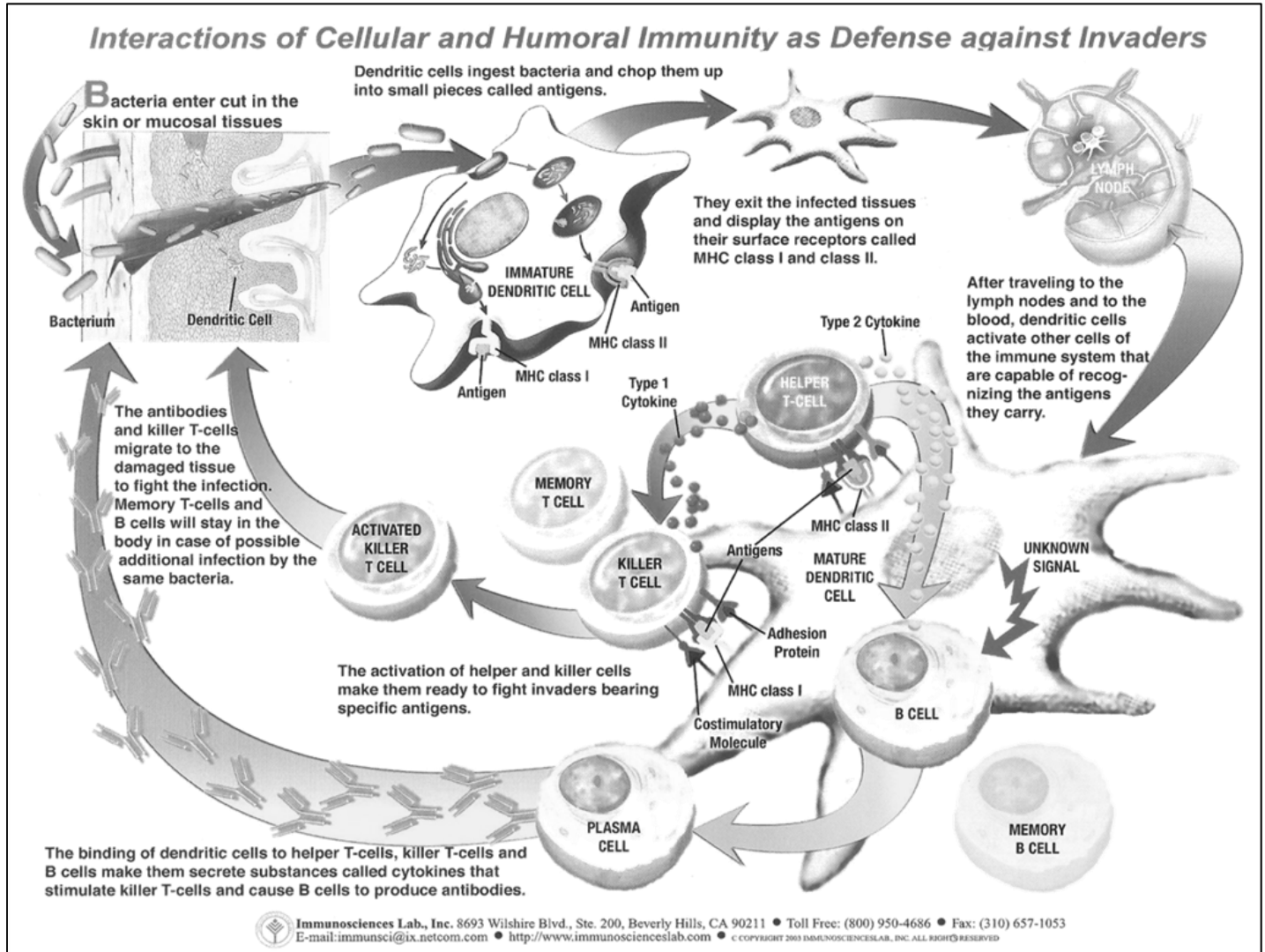
- Encodes for cell surface antigen-presenting proteins
- Proteins encoded by HLA are those on the cell surface that are unique to that person
- The immune system uses HLA to differentiate self cells and non-self cells
- Infectious disease
  - Foreign pathogen is loaded onto HLA and presented
- Graft rejection
  - Other HLA (not self)
- Autoimmunity
  - Person with certain HLA antigens are more likely to develop certain autoimmune disease (See Markers)
- Cancer
  - Some HLA mediated disease are directly involved in promotion of cancer
    - e.g. gluten sensitivity enteropathy increased prevalence of enteropathy-associated T-cell lymphoma

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Significant HLA Class I and Class II Associations with Disease	
	Marker
<b><i>Spondyloarthropathies</i></b>	
Ankylosing spondylitis	B27
Reiter's syndrome	B27
Acute anterior uveitis	B27
Reactive arthritis (Yersinia, Salmonella, Shigella, Chlamydia)	B27
<b><i>Collagen-Vascular Diseases</i></b>	
Rheumatoid arthritis	DR4
Sjogren's syndrome	DR3
Systemic lupus erythematosus Caucasian Japanese	DR3 DR2
<b><i>Autoimmune Gut and Skin</i></b>	
Gluten sensitive enteropathy (celiac disease)	DR3
Chronic active hepatitis	DR3
Dermatitis herpetiformis	DR3
<b><i>Autoimmune Endocrine</i></b>	
Type I Diabetes Mellitus	DR4
	DR3
	DR2
Hyperthyroidism (Graves')	B8
	DR3
Adrenal insufficiency	DR3
<b><i>Autoimmune Neurologic</i></b>	
Multiple sclerosis	DR2

*Note:* Many bacteria share antigens similar to those on some human cells. Continued exposure of these antigens to the immune system can evoke an autoimmune response. An example of this is Klebsiella and its association with Ankylosing spondylitis. Think of Leaky Gut!

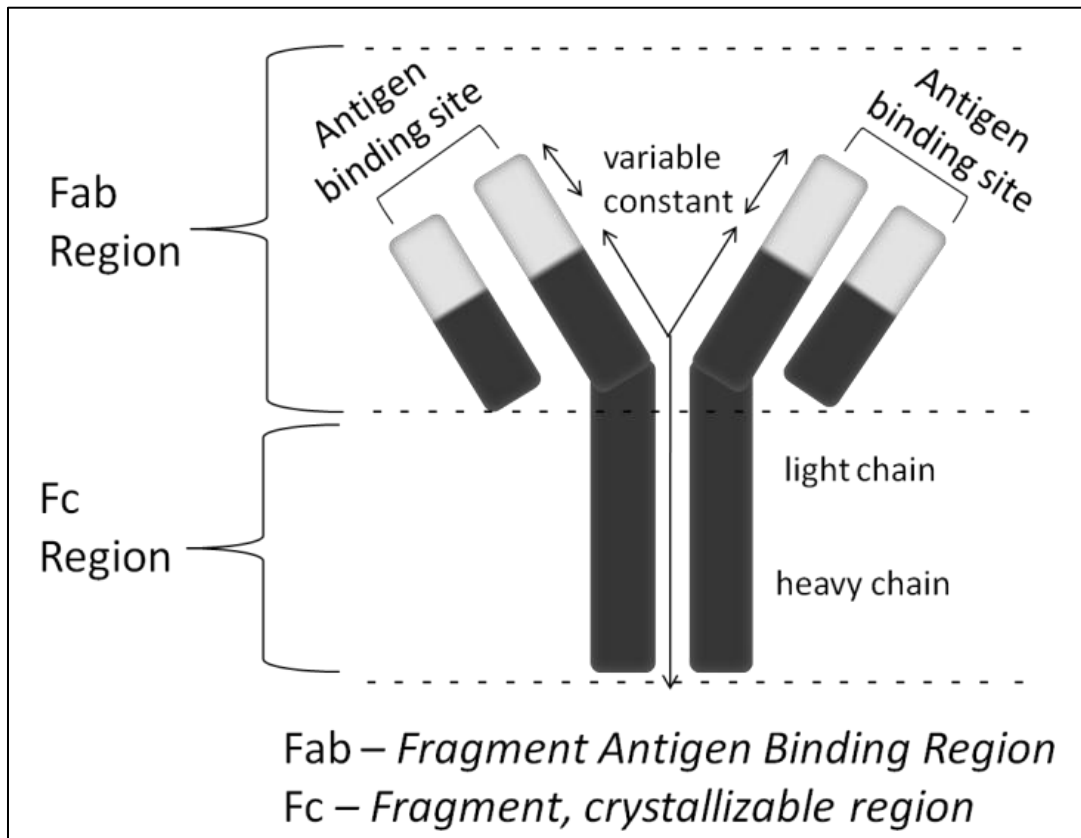
*(Please refer to article at the end of this Insiders Guide)*



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### Humoral Immunity, Antibodies, and B Cells

**Humoral immunity** refers to specific protection by proteins in the plasma called **antibodies (Ab)** or **immunoglobulins (Ig)**. Antibodies specifically recognize and bind to microorganisms (or other foreign particles), leading to their destruction and removal from the body. There are several different classes of immunoglobulins: IgG, IgA, IgM, IgD, and IgE. The classes of immunoglobulins have slightly different functions, with most of the antibody circulating in plasma in the IgG class.



### **Classification of Immunoglobulins**

#### **IgG:**

- Only immunoglobulin able to pass the placental barrier.
- Smallest and most abundant antibody

#### **IgA:**

- Highest concentration in the epithelial surfaces of the eyes, respiratory tract, nose, ears, vagina, and gastrointestinal tract.
- Up to 40% of the IgA in the body is found intravascularly
- Secretory IgA (Extravascular) is found in external secretions such as tears, saliva, intestines, respiratory tract, milk, and colostrum
- Secretory IgA serves as a first line of defense against infection.

#### **IgM:**

- Largest antibody
- Found in blood and lymph fluid
- First antibody in response to an infection
- Related to the rheumatoid factor
- Potent agglutinator and cytolytic agent.

#### **IgE: (Reagenic Antibody)**

- Becomes fixed to mast cells and basophils
- Attachment to the skin permits their demonstration by the skin test
  - Histamine release characterized by a flair and wheal
- IgE also found in the lungs and mucous membranes

#### **IgD:**

- Found in small amounts
- Lines the cavities inside the body
- Role in allergic reactions



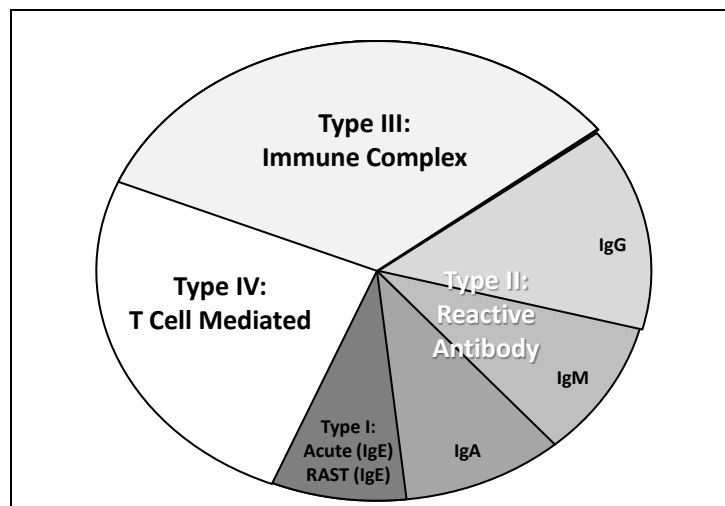
### Mechanisms of Antibodies

- Direct action on invading agent
  - Agglutination (clump antigens)
  - Precipitation (antigens insoluble)
  - Neutralization (cover toxic site)
  - Lysis ( attack membranes)
- Complement system for antibody action
  - System of enzymes and enzyme precursors normally found in plasma and other body fluids
  - Enzymes are normally inactive.
  - When antibody combines with antigen, a reactive site on the antibody turns on the complement system.
  - The activated enzymes then attack the invading agent.

### Activation of Anaphylactic System by Antibody

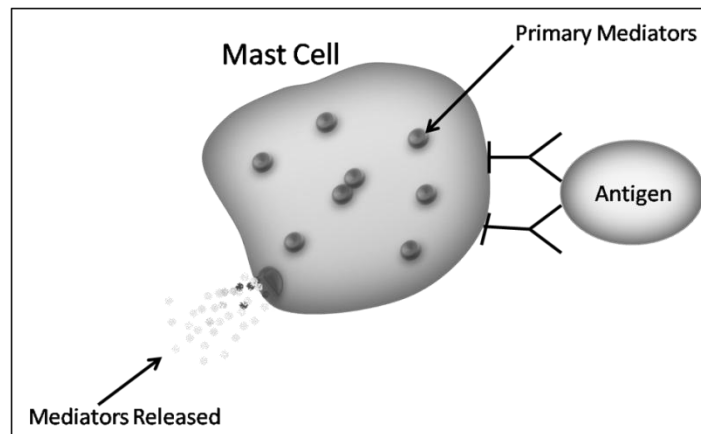
- IgE attach to mast cells and basophils
- When an antigen reacts with one of the antibody molecules attached to the cell, there is immediate swelling and rupture of the cell.
  - Histamine
  - Slow-Reacting Substance A
  - Chemotactic factor
  - Lysosomal enzymes

### Hypersensitivity Reaction



Type I Hypersensitivity 'Allergic' Person

- Immediate
- IgE mediated
- Symptoms are produced upon exposure of a sensitized person
- Host has pre-existing IgE antibodies found on the mast cells and basophils
- Mast cells and basophils are activated when the antigen cross-links with the fixed antibodies



- Cross-linking causes rapid degranulation releasing primary mediators in stored granules.
- Cross-linking also causes the production of secondary mediators which are made inside the cells.
- Examples of Type I Hypersensitivity include Hay Fever (allergic rhinitis), eczema, asthma, and Urticaria.

Primary Mediators	
<i>Histamine</i>	Vascular permeability, sm contraction
<i>Serotonin</i>	Vascular permeability, sm contraction
<i>ECF-A</i>	Eosinophil chemotaxis
<i>NCF-A</i>	Neutrophil chemotaxis
<i>Proteases</i>	Mucus secretion, connective tissue degradation

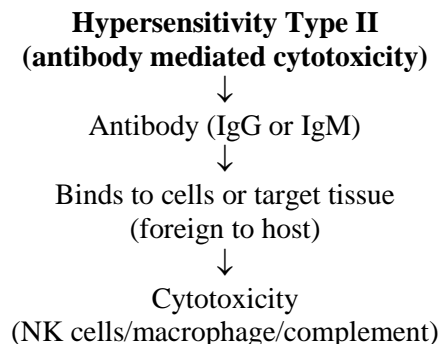
<b>Secondary Mediators (synthesized de novo)</b>	
<i>Leukotrienes</i>	Vascular permeability, sm contraction
<i>Prostaglandins</i>	Vasodilation, sm contraction, platelet activation
<i>Bradykinn</i>	Vascular permeability, sm contraction
<i>Cytokines</i>	Numerous effects inc. activation of vascular endothelium, eosinophil recruitment and activation

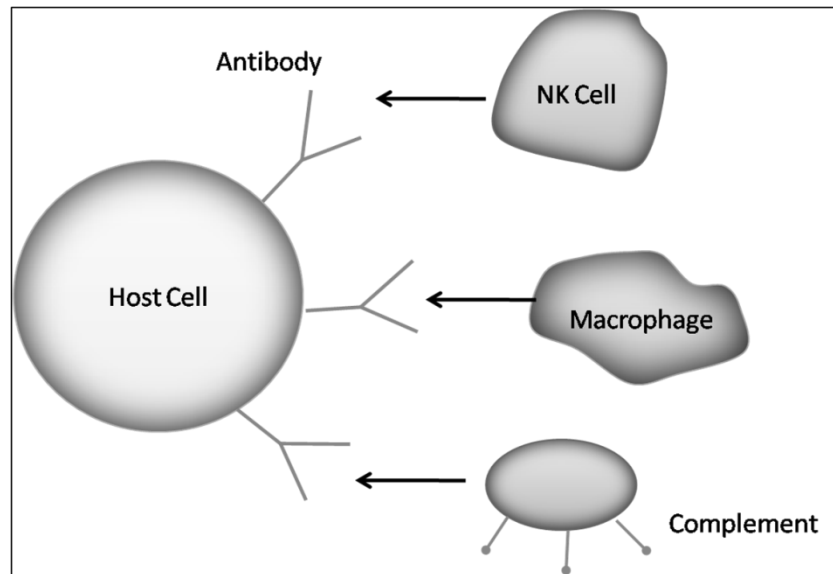
*Common Antigens Which Cause Type I Hypersensitivity Reactions*

- Pollens
  - Birch tree, Ragweed, Oil Seed Rape
- Drugs
  - Penicillin, Salicylates (aspirin)
- Food
  - Nuts (e.g., peanuts), Eggs, Seafood
- Insect Products
  - Bee Venom, House Dust Mite
- Animal Hair
  - Cat Hair and Dander

*Type II Hypersensitivity (Antibody mediated cytotoxic hypersensitivity)*

- Specific antibodies bond to cell surface antigens
- This binding causes cell destruction by antibody dependent cellular toxicity (NK cells/macrophages/complement)
- Usually seen in blood transfusion recipients and certain autoimmune diseases
- Classic ABO incapability (IgM)
- Rh (hemolytic disease) IgG



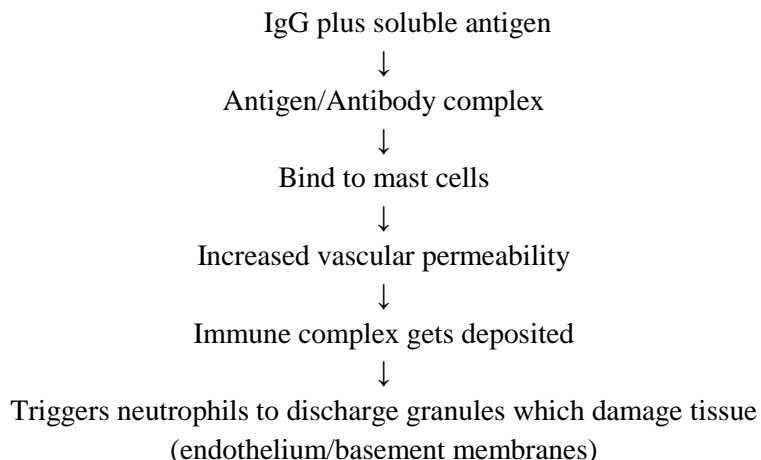


Type III Hypersensitivity (immune complex mediated)

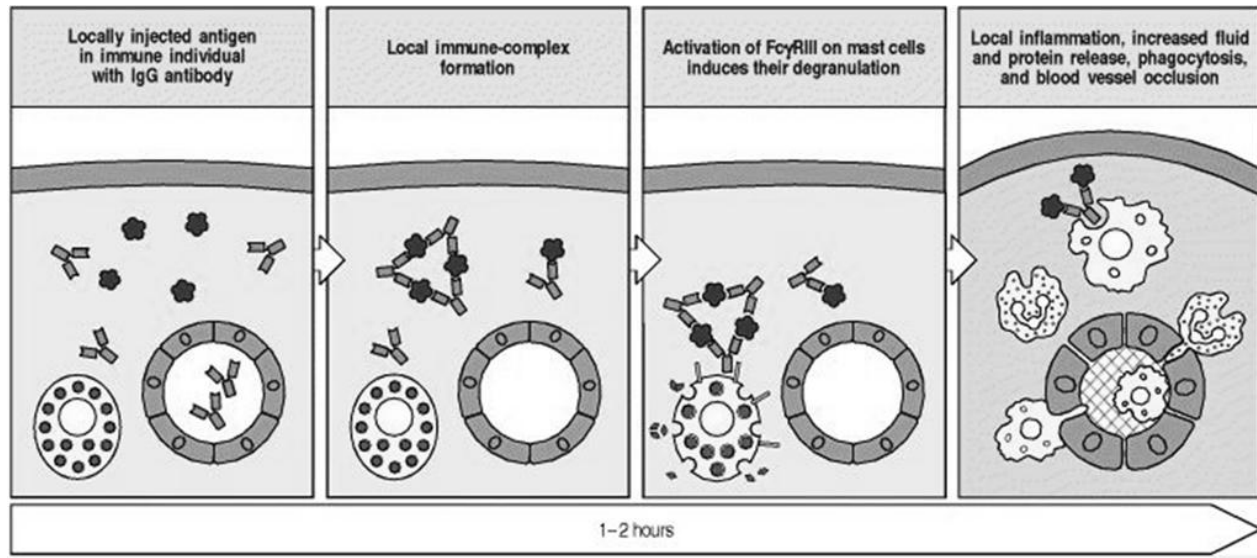
Type III hypersensitivity is mediated by immune complexes essentially of IgG antibodies with soluble antigens. (common to Type I)

- Arthus Reaction
  - Is a type of local Type III hypersensitivity reaction.
  - Type III hypersensitivity reactions are immune complex-mediated, and involve the deposition of antigen/antibody complexes mainly in the vascular walls, serosa (pleura, pericardium, synovium), and glomeruli
  - The Arthus reaction was discovered by Arthus in 1903. Arthus repeatedly injected horse serum subcutaneously into rabbits. After four injections, he found that there was edema and that the serum was absorbed slowly. Further injections eventually led to gangrene.

**Type III (Immune Complex)**



### Type III Hypersensitivity



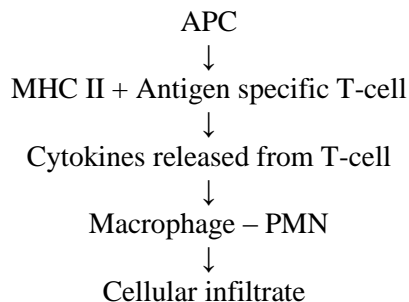
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- Generalized or systemic reactions
  - The presence of sufficient quantities of soluble antigen in circulation to produce a condition of antigen excess leads to the formation of small antigen-antibody complexes which are soluble. The majority pathology is due to complex deposition which seems to be exacerbated by increased vascular permeability caused by mast cell activation. The deposited immune complexes trigger neutrophils to discharge their granule contents damaging the surrounding endothelium and basement membranes. The complexes are deposited in a variety of sites such as skin, kidney, and joints. Common examples of generalized type III reactions are post-infection complications such as arthritis and glomerulonephritis.

### Type IV Hypersensitivity

This is the only class of hypersensitive reactions to be triggered by antigen-specific T cells. Delayed type hypersensitivity results when an antigen presenting cell, typically a tissue dendritic cell which has picked up antigen, processed it and displayed appropriate peptide fragments bound to class II MHC is contacted by an antigen specific  $T_H1$  cell patrolling the tissue. The classical example of delayed type hypersensitivity is in tuberculosis. A more familiar example is contact hypersensitivity.

#### Type IV Hypersensitivity (Antigen-specific T cells)



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Type	Descriptive Name	Initiation Time	Mechanism	Examples
I	IgE-mediated hypersensitivity	2-30 min	Ag induces cross-linking of IgE bound to mast cells with release of vasoactive mediators	Systemic anaphylaxis, Local anaphylaxis, Hay fever, Asthma, Eczema
II	Antibody-mediated cytotoxic hypersensitivity	5-8 hrs	Ab directed against cell-surface antigens mediates cell destruction via ADCC or complement	Blood transfusion reactions, Hemolytic disease of the newborn, Autoimmune anemia
III	Immune-complex mediated hypersensitivity	2-8 hrs	Ag-Ab complexes deposited at various sites induces mast cell degranulation via FcγRIII, PMN degranulation damages tissue	Arthus reaction (Localized); systemic reactions disseminated rash, arthritis, glomerulonephritis
IV	Cell-mediated hypersensitivity	24-72 hrs	Memory TH1 cells release cytokines that recruit and activate macrophages	Contact dermatitis, Tubercular lesions

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Article of Interest: FDM Training Program: Mod 3

**Anterior uveitis, inflammatory bowel disease, and ankylosing spondylitis in a HLA-B27-positive woman.**

*Title Annotation: Case Report*

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**Abstract:** A woman developed anterior uveitis at age 24, inflammatory bowel disease at age 29, and ankylosing spondylitis at age 45 by history. There were frequent recurrences. An HLA-B27 test was positive at age 53. The literature indicates that all of these conditions together in a HLA-B27-positive woman are uncommon. Physicians should be alert to the possibility that a patient might develop another of these associated diseases years after presentation of the first condition and educate their patients accordingly.

**Key Words:** acute anterior uveitis, inflammatory bowel disease, ankylosing spondylitis, HLA-B27  
\*\*\*\*\*

The uncommon presence of anterior uveitis, inflammatory bowel disease, ankylosing spondylitis, and positive HLA-B27 serology in a single patient will be discussed with reference to the disparate specialty literature.

Case Report

A 36-year-old woman was seen with acute onset headache, photophobia, and a red right eye. There was a history of 6 previous episodes of acute anterior uveitis (AAU), or iritis, in one or the other eye since the age of 24. She had a past history of "ulcerative colitis" since the age of 29 that seemed to recur in winter parallel with recurrent anterior uveitis. She stated there had been only one or two Christmases without a simultaneous flare-up of anterior uveitis and inflammatory bowel disease (IBD).

She had 14 episodes of recurrent anterior uveitis over the next 22 years. During these episodes of AAU her visual acuity dropped as low as 6/15 but always recovered to 6/6 after appropriate treatment. Intraocular pressure was always normal except for brief elevations as a steroid responder.

Her anterior uveitis was characterized by +1 to +2 circulating microcells and +2 flare. Twice a heavy fibrin clot filled the pupil. There were no keratic precipitates. Iris adhesions to the lens were broken with vigorous cycloplegia. Episcleritis and/or scleritis were described on occasion. Dilated fundus examinations were always normal.

Her inflammatory bowel disease had periodic flare-ups. It was characterized by right upper quadrant pain, cramping, and diarrhea.



At age 53, she presented to her family practice physician with a 10-year history of chiropractic treatment for low back pain and a 1 1/2-year history of hip pain. She had morning stiffness and pain in her back and both hips. Plain film x-rays showed extensive sclerosis of sacroiliac joints with obliteration of the joint line consistent with ankylosing spondylitis (AS) in this clinical context. (Fig.). A human leukocyte antigen (HLA-B27) test was positive.

### Discussion

Uveitis is inflammation of ocular uveal tissue, the pigmented and vascular tissue in the choroid and ciliary body. Anterior uveitis is the common form, originating in the ciliary body with inflammatory cells carried by aqueous humor circulation into the anterior chamber that are visible with a slit lamp. Acute and recurrent anterior uveitis is potentially vision-threatening because of adhesions of the iris to the lens (posterior synechiae), secondary glaucoma, cataract after multiple recurrences, and rarely cystoid macular edema.

[FIGURE OMITTED]

Acute anterior uveitis is associated with both AS, and to a lesser extent, IBD. Differences in presenting symptoms, rate of onset and duration, gender, and HLA-B27 reaction have been described in AAU patients to differentiate between IBD and AS associated with AAU. (1)

Inflammatory bowel disease includes disease in the small intestine (Crohn disease) and the colon (ulcerative colitis), with occasional overlap. Genetic linkages associated with IBD have been described, but they are neither diagnostic, nor consistent. Current knowledge of IBD pathogenesis requires a genetic propensity and an abnormal immune response to enteric Gram negative bacterial flora, resulting in damage to intestinal epithelial mucosal barrier. Enteric mucosal receptors for bacterial antigens and immune modulators, both up- and down-regulatory, are subjects of research. (2)

Seronegative spondyloarthritis involves the vertebral column and is seronegative for rheumatoid factor. Depending on the rigidity of criteria (eg, European Spondyloarthropathy Study Group), spondyloarthropathy includes varying proportions of patients with ankylosing spondylitis, Reiter's syndrome or reactive arthritis, psoriatic arthritis, arthritis associated with IBD, pauciarticular juvenile rheumatoid arthritis, and undifferentiated spondyloarthritis.

The major histocompatibility complex on the short arm of chromosome 6 contains some 220 genes in 3 gene clusters. Within the first cluster are >500 human leukocyte antigens type B. There are at least 24 HLA-B27 subtypes. Class I molecules, including HLA-B types, present endogenous/intracellular antigen peptides to cytotoxic (CD8+) T-lymphocytes. The three-dimensional structure of HLA-B27 has a unique stereospecific antigen-binding site. (3) There is a strong statistical interrelationship between AAU, IBD, AS, and HLA-B27 depicted in the Table. HLA-B27 is thought to be a marker for an immune abnormality, rather than an etiologic factor.

Current knowledge of all three entities found in this patient, AAU, IBD, and AS, requires a genetic predisposition and an abnormal immune response that damages the respective tissues. A wide variety of abnormal inflammatory mediators have been identified in these diseases: cytokines, chemokines, growth factors, tissue necrosis factors, interferon, interleukins, leukotrienes, nitrous oxides, and prostaglandins. Intestinal abnormalities may be related in AAU and AS, as Reiter's syndrome is known to be precipitated by Gram negative intestinal flora bacteria, as well as genitourinary tract flora. Some two-thirds of AAU patients without gastrointestinal symptoms had microscopic inflammation of blind intestinal biopsies. (4)

This patient developed AAU before IBD and AS, as often occurs. (1) If 3% of AAU patients develop IBD, and 56% of female HLA-B27-positive AAU patients develop AS, (5) the product of their probabilities is 0.0168, or less than 1/50 chance of a woman with anterior uveitis having all three conditions and a positive HLA-B27 serology. Chance favors a prepared mind informed by a thorough past medical history.

### Conclusion

This case illustrates the need for all physicians to be aware of multi-system disease. All patients diagnosed with AAU, IBD, or AS should be questioned specifically if they or their relatives have symptoms of eye, gut, or joint inflammation. They should be educated that these other systems might be involved in the future, if not present initially, and that they have a familial tendency. (6) It may not be cost-effective to test for HLA-B27 if any single disease complex initially responds to treatment. However, if there are recurrences or more than one organ system involved, the HLA-B27 test might contribute to prognosis or treatment. All physicians, and especially specialists, should remember they were trained initially as "head to toe" doctors and not lose sight of the whole patient.

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RELATED ARTICLE: Key Points

\* Statistics from the literature indicate that the presence of all three conditions in a HLA-B27-positive woman is uncommon.

\* Anyone presenting with any of these entities should be questioned specifically and warned about the possibility of the other associated conditions they or their family may experience in future years.

Table. HLA-B27 and Associated Inflammatory Diseases (1,3,7)

Inflammatory disease	HLA-B27 % prevalence	% presenting disease developing AAU	% AAU patients developing specific systemic disease
Inflammatory bowel disease	46	2-9	2-3
Ankylosing spondylitis	90	20-30	* 84-90 if + HLA-B27 * 30-55 if - HLA-B27

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