Immune-Mediated Diseases

i.e. let's talk about a small subset auto-immune diseases.

In a Nutshell

His general style was to have relatively sparse slides but to cover everything on them. Thus, all the bullet points on all of the slides (unless otherwise noted) are probably fair game IMO.
Objectives

Describe the epidemiology, clinical presentation, pathogenesis and pathologic changes of autoimmune diseases, including lupus erythematosis, rheumatoid arthritis, vasculitis, temporal arteritis and Wegener's granulomatosis.
Hah!

Witch doctor waiting rooms

Immune system has access to many organ systems so there usually is involvement of multiple tissues in these diseases.
Systemic Lupus Erythematosus
Systemic lupus erythematosus: clinical features

Febrile, multisystem inflammatory disease

Variably affects wide range of organs and tissues, especially skin, kidneys, serosal surfaces, joints, heart

Clinical course highly variable, often with multiple exacerbations and remissions

Especially prevalent in young women, black Americans

Prevalence: up to 1 to 2,500 persons

"not common" but "not rare"
Systemic lupus erythematosus: pathogenesis

Autoantibodies develop against a variety of antigens:

- Nucleoproteins / nucleic acids
  - DNA
  - histones
  - nonhistone RNA-binding proteins
- Blood cells
  - erythrocytes
  - platelets
  - lymphocytes and other leukocytes.
- Phospholipids (e.g., “lupus anticoagulant”)
Systemic lupus erythematous: pathogenesis

**Antigen-antibody immune complexes form**

- Complexes deposit in numerous sites, initiate complement cascade, and trigger inflammation
- Antibody bound to cells leads to lysis via complement-mediated cytotoxicity or ADCC

**Type III Hypersensitivity**

- Brief intro to the 4 different types of hypersensitivity:
  1. Anaphylactic reaction (like allergies), IgE-mediated (and then Mast Cells)
  2. Antibody-mediated (IgG and IgM).
  3. Immune-complex mediated (antibody and antigen meet in the fluid and THEN deposit)
  4. "Delayed-Type" or "Cell-mediated". T-Cells hitting antigens and then causing a cascade.

**Type II Hypersensitivity**

- Antibody-Dependent Cell-mediated Cytotoxicity

**Soluble antigens**

- Particularly lodge in blood vessels (kidney is a great place)

**Non-Soluble Antigens**

- 2 different routes of pathogenesis
Systemic lupus erythematosus: pathogenesis

Possible causes of autoantibody production

Intrinsic B cell defect

Excessive helper T cell activity

Deficient suppressor T cell activity

We just don’t know.

Some people’s B-cells might be inherently hypersensitive to being activated.

Another possibility: you get infected with a microbe whose antigens look like your own tissue. E.g. bacterial dsDNA might be antigenic and cause autoimmunity against your own dsDNA. This theory is speculative at this point.
This slide demonstrates that the diagnosis of lupus hasn’t changed much over time.

Back in 1982 this was the criterion for diagnosis. It’s not that much different now adays, we still use all of these now.

For the diagnosis of lupus, you have to have 4 of 11 (disease symptoms are very disparate and thus hard to diagnosis some times).

He read all of the major bullet points (but didn't do the subdetails within the headings).

<table>
<thead>
<tr>
<th>TABLE 6-5. THE 1982 REVISED CRITERIA FOR THE CLASSIFICATION OF SLE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Butterfly rash</td>
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<tr>
<td>2. Discoid lupus</td>
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<tr>
<td>3. Photosensitivity</td>
</tr>
<tr>
<td>4. Oral ulcers</td>
</tr>
<tr>
<td>5. Arthritis</td>
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<tr>
<td>6. Serositis</td>
</tr>
<tr>
<td>a. Pleuritis: rub heard by a physician or pleural effusion,</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>b. Pericarditis: documented by EKG or rub, or evidence of</td>
</tr>
<tr>
<td>pericardial effusion</td>
</tr>
<tr>
<td>7. Renal disorder</td>
</tr>
<tr>
<td>a. Persistent proteinuria $&gt; 0.5$ gm/dl/day</td>
</tr>
<tr>
<td>b. Cellular casts: may be red cell, hemoglobin, granular,</td>
</tr>
<tr>
<td>tubular, or mixed</td>
</tr>
<tr>
<td>8. Neurologic disorder</td>
</tr>
<tr>
<td>a. Seizures: in the absence of offending drugs or known</td>
</tr>
<tr>
<td>metabolic derangements</td>
</tr>
<tr>
<td>b. Psychosis in the absence of offending drugs</td>
</tr>
<tr>
<td>9. Hematopoietic disorder</td>
</tr>
<tr>
<td>a. Hemolytic anemia: with reticulocytosis or</td>
</tr>
<tr>
<td>b. Leukopenia: 4000 cells/$\mu$l on two or more occasions or</td>
</tr>
<tr>
<td>c. Lymphopenia: 1500 cells/$\mu$l on two or more occasions or</td>
</tr>
<tr>
<td>d. Thrombocytopenia: 100,000/$\mu$l in the absence of</td>
</tr>
<tr>
<td>offending drugs</td>
</tr>
<tr>
<td>10. Immunologic disorder</td>
</tr>
<tr>
<td>a. Positive LE cell preparation or</td>
</tr>
<tr>
<td>b. Anti-DNA: presence of antibody to untreated DNA in</td>
</tr>
<tr>
<td>abnormal titer or</td>
</tr>
<tr>
<td>c. Anti-Sm: presence of antibody to Sm nuclear antigen or</td>
</tr>
<tr>
<td>d. False-positive STS known to be positive for at least six</td>
</tr>
<tr>
<td>months and confirmed by TPI or FTA tests</td>
</tr>
<tr>
<td>11. Antinuclear antibody. An abnormal titer of antinuclear</td>
</tr>
<tr>
<td>antibody by immunofluorescence or an equivalent assay at</td>
</tr>
<tr>
<td>any point in time and in the absence of drugs known to</td>
</tr>
<tr>
<td>be associated with “drug-induced lupus” syndrome</td>
</tr>
</tbody>
</table>
Antibodies in euchromatin (borders of nucleus) and antibodies diffuse throughout the nucleus.

We mix patient serum with a substrate cell. Wash it and then add Immunoglobulin against antibodies that also has fluorescence.

Long story short: anything that has been attacked by antibodies glows.

"speckled pattern"
This is a kidney biopsy. It is NOT from a lupus patient. He wants to show you a normal patient.

Note the THINness of the basement membrane of the capillary here on PAS stain.
This is from a lupus patient. Clearly the basement membrane is much thicker and irregular here.
We stain it with a fluorescent antibody against IgG and thus all of this glowy-stuff is IgG antibody stuck to the human material (direct immunofluorescence test). Thus the granular glowy-ness demonstrates that there are immune complexes deposited in these membranes.
Normal kidney on TEM

Capillary Loop

Visceral Epithelial Cell on outside of capillary.

Basement Membrane

Endothelial Cell
Lupus patient.

immune complexes

Thickened basement membrane (grey stuff)
Rheumatoid Arthritis
Rheumatoid arthritis: clinical features

Systemic, chronic inflammatory disease

Principally affects joints: severe, deforming, symmetric polyarthritis

May involve other organs and tissues (e.g., skin, heart, blood vessels, muscles, lungs)

Onset generally in 3rd or 4th decade

Especially prevalent in women

Prevalence: approximately 1% of population
Rheumatoid arthritis: pathogenesis

Activation of CD4+ T cells, possibly by arthritogenic infectious agent

which leads to

Lymphokine production

which lead to
Rheumatoid arthritis: pathogenesis

Activation of **macrophages** and other inflammatory cells, with subsequent tissue destruction

Activation of B cells, including some producing autoantibodies (e.g., IgG anti-IgG, or rheumatoid factor); immune complex formation

Type IV hypersensitivity

Type III hypersensitivity

Why do we need anti-antibodies? It's a way for the body to downregulate an immune response if the infectious agent has already been dealt with.

rheumatoid factor is an Ig that reacts with OTHER Igs (the constant portions). These IgG-Anti-IgG-complexes and form these immune complexes that deposit.

This one is more important for pathogenesis.

This one is important because we can detect it in the lab for diagnosis.
Fingers of someone with rheumatoid arthritis.

Look, it's inflamed. (it has rumor, tumor, pain, etc.)
You know how a few slides ago he described it as "severe" and "deforming"?
....Yea.
Note the ulnar deviation.
From an arthritic patient joint.

Note the absence of synovium and cartilage. It's been replaced by this granular, fibro-vascular inflammatory tissue sitting right on top of the bone.
Rheumatoid nodules (on the extensor surface of the forearm most commonly, as depicted here). They are "necrobiotic."
Histological slide of a rheumatoid nodule. It looks like, and can be confused with, a necrotizing granuloma.

Inflammatory tissue on the border here.

Note the necrotic tissue.

Center of the nodule is THAT a way.
Vasculitis
Lots of things can cause inflammation of the blood vessels (e.g. infectious agents), today we're only going to talk about immune-mediated ones.

"Pull out, Betty! Pull out! ... You've hit an artery!"
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Vessels Involved</th>
<th>Distribution of Vascular Involvement</th>
<th>Principal Morphologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity (leukocytoclastic) vasculitis</td>
<td>Venules, capillaries, arterioles</td>
<td>Widespread, but particularly skin</td>
<td>Necrosis and neutrophil infiltration of venules with leukocytosis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Medium-sized and small arteries</td>
<td>GI tract, liver, kidney, pancreas, muscles, other sites</td>
<td>Panmural acute necrotizing arteritis with fibrinoid necrosis, neutrophil and eosinophil infiltration, and extension into adventitia</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>Small to medium-sized arteries</td>
<td>Upper and lower respiratory tracts; occasionally eye, skin, heart</td>
<td>Acute and chronic (sometimes granulomatous) angiitis with prominent eosinophils and occasional giant cells in association with extravascular granulomas</td>
</tr>
<tr>
<td>Churg-Strauss allergic angiitis and granulomatosis</td>
<td>Medium-sized and small arteries and veins</td>
<td>Systemic, with pulmonary involvement in many cases</td>
<td>Same as for Wegener’s with more eosinophils</td>
</tr>
<tr>
<td>Temporal (cranial) arteritis</td>
<td>Elastic tissue-rich major arteries</td>
<td>Head, including ocular and intracranial vessels; uncommonly systemic</td>
<td>Chronic mononuclear inflammatory infiltration, mostly in inner half of the media, with giant cells and granuloma formation</td>
</tr>
<tr>
<td>Kawasaki’s arteritis</td>
<td>Small and medium-sized arteries</td>
<td>Skin, ocular and oral mucosa, coronary arteries, but may</td>
<td>Acute and chronic infiltration, mainly with lymphocytes and macrophages, and with endothelial cell necrosis and immunoglobulin deposition</td>
</tr>
<tr>
<td>Thromboangiitis obliterans (Buerger’s disease)</td>
<td></td>
<td></td>
<td>Acute and chronic inflammatory infiltration of arteries and veins, often with giant cells, granulomas, intravascular thrombi containing microabscesses, and later perivascular fibrosis trapping nerve trunks</td>
</tr>
</tbody>
</table>

Not going to talk about all of them today, just the circled ones. Note that there are 3 different ways we can classify these vasculitises (the headings up top):
1) Which type of vessels are hit (big / small / arteries / veins?)
2) Distribution of the vessels hit: (which organs affected?)
3) Histological / morphological features: (necrosis? giant cells? chronic vs acute inflammation?)
Shows how different vasculitides are distributed, note that there is an overlap in which types of vessels the different diseases hit (e.g. multiple different diseases affect arterioles).
Hypersensitivity (leukocytoclastic) vasculitis

Henoch-Schönlein purpura

Serum sickness

Connective tissue diseases (e.g., systemic lupus erythematosus)

Mixed cryoglobulinemia

Chronic active hepatitis B

Lymphoproliferative disorders

Reactions to drugs, pathogens

These all look very similar under the microscope but have different clinical presentations.

Involves kidneys, will hear more about later.

Used to happen when we treated people with animal serum.

Important: "By far the most common type of hypersensitivity vasculitis"
Hypersensitivity vasculitis

Vessels involved

Venules
Capillaries
Arterioles

Small vessels involved. Will often involve the skin (because there are so many capillaries there).
Hypersensitivity vasculitis: clinical features

Skin lesions (palpable purpura, macules, vesicles, necrosis, ulceration)

Vascular lesions in other organs (lungs, brain, kidneys, gastrointestinal tract) with variable manifestations (e.g., glomerulonephritis, infarcts)
Hypersensitivity vasculitis: pathogenesis

1. Antibody response to exogenous antigen or autoantigen

Which leads to:

2. Immune complex formation

Which leads to:

3. Deposition of immune complexes in vessels (especially venules)

"exogenous antigen" e.g. a drug. "autoantigen" like in lupus.
Hypersensitivity vasculitis: pathogenesis

4. Complement fixation; generation of chemotactic fragments (e.g., C5a)

5. Attraction of inflammatory cells (especially neutrophils); tissue destruction
Hypersensitivity vasculitis: pathogenesis

4. Complement fixation; generation of chemotactic fragments (e.g., C5a)

5. Attraction of inflammatory cells (especially neutrophils); tissue destruction

Type III hypersensitivity
Hypersensitivity vasculitis: histology

Infiltration of vessel walls by neutrophils, neutrophil degeneration (leukocytoclasia), vessel wall necrosis

Immune complex deposition

Immunoglobulin components may vary:

  Henoch-Schönlein purpura: IgA
  Systemic lupus erythematosus: mixed

Thus, you can use different fluorescent anti-bodies to differentiate between the different types of hypersensitivity vasculitises (vasculitii?)

Which leads to the term "leukocytoclastic vasculitis" as a synonym for hypersensitivity vasculitis.
Cartoon demonstrated what's on the previous slides. Just to recap: We have immune-complexation in the blood, it deposits in the small vessels, induces inflammation and cell destruction, and possibly eventually rupture (in the venule).

Figure 10–7. A schematic representation of the pathogenesis of hypersensitivity venulitis.
This is a venule from a leukocytoclastic vasculitis pt. (aka hypersensitivity vasculitis). Note that the neutrophils are all kind of collected into the vessel wall and the lumen is pretty much completely occluded.

Also note that there are pieces of leukocytes here (hence the leukocytoCLASTic portion of the name).
These are purpura. They are somewhat raised (hard to see here), so they would be palpable purpura.

This guy might be palpable? I dunno, try touching your screen now, see what happens.
Did it work?

Slide of those purpura. Note the RBCs leaked out into the extravascular space.

Also note the inflammation here.
This is a purpura stained with fluorescent anti-IgA-antibodies (This pt has Henoch-Schönlein).
Temporal arteritis

(giant cell arteritis; cranial arteritis)

Okay, second vasculitis we’re talking about. This is at the other end of the spectrum, targets LARGE vessels.
Temporal arteritis

Vessels involved

Elastic tissue-rich major arteries

(branches of carotid artery, including temporal and ophthalmic arteries; less frequently, aorta and other arteries; heart and lungs generally spared)

involvement here can lead to blindness.

not necessarily true of other vasculitides
Temporal arteritis: clinical features

Severe headache or facial pain, often unilateral and most intense along temporal artery
Visual disturbances (diplopia, blindness)
 Constitutional symptoms (fever, fatigue, weight loss)
Associated in approximately half of cases with polymyalgia rheumatica (syndrome of pain and muscle stiffness)
Most common in older adults
Male:female ratio 1:2 or 1:3
Temporal arteritis: pathogenesis

Unknown; may involve type IV hypersensitivity to antigens associated with elastic tissue or smooth muscle

Familial clustering of cases and predilection for white patients suggests genetic component
Temporal arteritis: histology

Two histologic patterns:

1. **Granulomatous inflammation with multinucleate giants cells**, centered on internal elastic lamina, which is often disrupted

2. **Mononuclear inflammatory infiltrate without giant cells**, occasionally with fibrinoid necrosis

Vascular lumen often obliterated or thrombosed

In healing phase, vessel may be largely replaced with fibrous tissue

Segmental lesions alternating with unaffected areas may produce “nodular” morphology

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He read this slide.

Can either be 1 or 2. #1 is the more traditional / textbook example but you can see #2.

Only select portions ALONG the artery are affected. Thus you need to take a lot of slices along the artery when you're looking at slides (and look at all of them).

Luckily you don't really need your temporal artery.
A temporal artery of a temporal arteritis pt. Note the inflammation of the muscular layer and the near-completely occluded lumen.
A closer view of the same slide.

The much talked-about giant cell in "giant cell arteritis" (aka temporal arteritis)
Wegener’s granulomatosis and Microscopic polyangiitis

Vessels involved

Venules, capillaries, arterioles
Small to medium sized arteries

They are fairly UNcommon diseases.

Note: these are TWO DIFFERENT things, but they are similar in many ways.

The "baby bear" vasculitis is (it effects medium-sized vessels, those that are juuuuuuuust the right size).
Wegener’s granulomatosis: clinical features

Upper respiratory inflammation (e.g., sinusitis, often severe, with bloody nasal discharge)

Pulmonary symptoms (cough, hemoptysis, shortness of breath)

Renal manifestations (hematuria, rapidly progressive renal failure)

Lesions involving other organs (eyes, skin, occasionally heart)

Most common in middle aged adults

Males more commonly affected
Microscopic polyangiitis: clinical features

Variable, can involve different organ systems

Isolated renal disease with hematuria, renal insufficiency is a common presentation

Different kidney presentation and doesn't involve the pulmonary system like Wegener's.
Pathogenesis

Generation of **autoantibodies to neutrophils** (anti-neutrophil cytoplasmic antibodies, or ANCA), neutrophil activation, tissue damage

Patients with Wegener’s granulomatosis often have “cytoplasmic” ANCA (c-ANCA) (anti-proteinase 3)

Patients with microscopic polyangiitis often have “perinuclear” ANCA (p-ANCA) (anti-myeloperoxidase)

The two diseases are different clinically but have common pathogenic processes.

Note that ANCA target things INSIDE the cytoplasm of the neutrophils.
Wegener’s granulomatosis: histology

Necrotizing granulomas of upper respiratory tract (ear, nose, sinuses, throat)

Necrotizing granulomatous vasculitis in other organs, especially lungs

Necrotizing glomerulonephritis, often with crescents

"Don't worry about it" for now.
Pt. lung piece from someone with Wegener’s
Note the granulomatous inflammation here (from the Wegener's pt lung biopsy).
This is a lung slide from a Wegener's pt w/ a stain for elastic tissue. The wall of the blood vessel has been destroyed.
This is a glommerulus from a Wegener’s pt.

Note the necrosis (compare to slide 12 if you're really that interested).

Also note this thing down here called a "crescent". We'll talk about it later apparently. Note how crescent-shaped it is.....
Lol, he didn't get to talk about Kawasaki disease (it's a real thing, supposedly) but he meant to talk about it here.