

TYPE II IMMUNOPATHOLOGY

TYPE II. This form of immunopathology is due to the actions of antibodies directed against a specific target tissue or cell; so it is one of the forms of **autoimmunity**. Type III immunopathology, as we've seen, may also be due to self-reactive antibodies, but the manifestation there is immune complex-based rather than specific tissue damage by antibody. T cell-mediated autoimmunity is referred to as Type IV immunopathology. As we've said before, these conditions are often mixed.

We'll first discuss how antibodies damage or otherwise affect cells, and give some examples. Later, we'll look at the ways in which tolerance to self antigens might be lost.

TYPE II PATHOGENIC MECHANISMS

1. Neutralization. Just as a toxin is neutralized when an antitoxic antibody binds it, a human protein may be inactivated by an autoantibody. Neutralizing anti-interferon (IFN)- γ autoantibodies have been described, most often in adults in Southeast Asia; they are typically associated with disseminated nontuberculous mycobacteria. The most severely affected patients have had multiple infections. Because Th1 cells work largely by releasing IFN- γ , they are ineffective, and the patients appear to be immunodeficient, although the real cause is the autoimmunity.

2. Complement-mediated cell and tissue damage. If for some reason a person starts making antibody against their own cells, it's possible that the destructive power of the immune system could be unleashed. Individual cells might be lysed by complement; tissues might be damaged by complement-induced inflammation.

These mechanisms are exactly the ones we are already familiar with from, say, bacterial immunity. Tissues can be damaged by ► lysis (red cells in autoimmune hemolytic anemia), by ► phagocytosis (platelets in autoimmune thrombocytopenic purpura, ATP) or by ► release of the phagocytes' lysosomal enzymes and reactive oxygen species (demonstrated in myasthenia gravis, and in Goodpasture disease, for example; see below).

2. "Stimulatory hypersensitivity." If the autoantibody happens to be directed against a cell-surface receptor, it may behave as an agonist, mimicking whatever hormone or factor normally works at that receptor. ► The best example of this is an autoantibody found in the blood of most patients with hyperthyroidism. It is IgG against the TSH (thyroid-stimulating hormone) receptor on thyroid cells; when it binds to these receptors, it mimics TSH and causes the cell to secrete thyroid hormones. Of course, the normal feedback controls won't work in this case, so the result is ► hyperthyroidism, known as **Graves disease**.

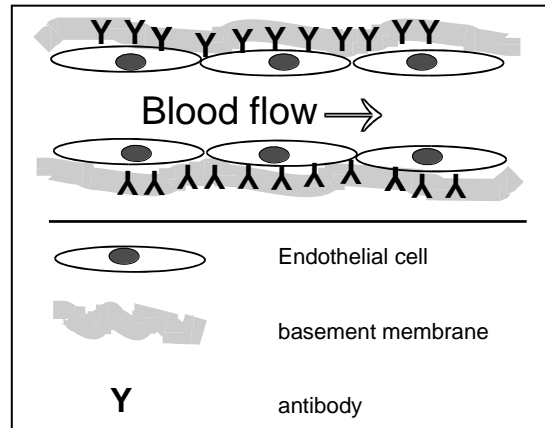
SOME ILLUSTRATIVE CONDITIONS

MYASTHENIA GRAVIS. A disease of progressive muscle weakness. ► Patients make pathogenic antibodies to the nicotinic acetylcholine receptors (AChR) of the neuromuscular junction. Damage is mediated by complement and neutrophils. A recent study¹ shows that the thymic transcription factor Aire (*see* T cells) drives the *thymic* expression of *CHRNA1*, the gene for the AChR alpha subunit. Two families were described in which there is an allele of the

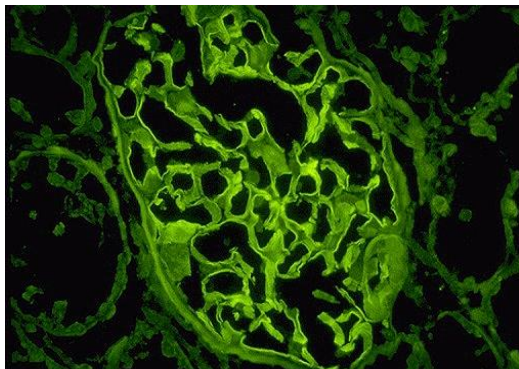
¹ Giraud, M. et al. 2007. An IRF8-binding promoter variant and AIRE control CHRNA1 promiscuous expression in thymus. *Nature* 448: 934-937.

CHRNA1 promoter that cannot interact with Aire, so the protein is not expressed in patient's thymuses, and Th clones reactive with the AChR are not deleted by negative selection; nor do they instead differentiate into Treg. Thus help is available to B cells to make antibody to the receptor. In the majority of patients the thymus becomes abnormal, with hyperplasia and even, sometimes, the appearance of germinal centers. It could be in those cases that Th against the AChR attack that antigen on the surface of intrathymic muscle cells, leading to chronic thymic inflammation and abnormal development of lymphoid tissue in which AChR antibody is made. In such patients, thymectomy often yields dramatic improvement.

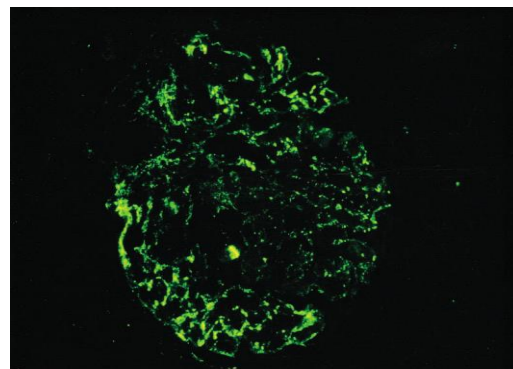
GOODPASTURE SYNDROME. This uncommon condition involves formation of autoantibodies to **lung** and **kidney** basement membranes (BM) (which are the collagenous non-living connective tissue framework upon which the endothelial cells of capillaries sit). ► There is an epitope on the antigen (Type IV collagen) shared between the BM's of these two organs; other organs are not involved. The patients have persistent glomerulonephritis, and former or current smokers risk pneumonitis with pulmonary hemorrhages. This was the first human autoimmune disease in which the antibody was *proved* to cause the condition: kidneys were removed from a patient who had died of



Goodpasture, the antibody eluted from them (low pH breaks antigen-antibody bonds), purified, and injected into a chimpanzee, who came down rapidly with typical Goodpasture syndrome. In Goodpasture the antibody is directed against the basement membrane, not trapped as clumps, so the staining by immunofluorescence is sharp and 'linear,' not 'lumpy-bumpy' as it is in Type III, immune complex conditions.



Type II, linear: Goodpasture



Type III, lumpy-bumpy: Lupus

DRESSLER SYNDROME. Most people who have a heart attack will make some autoantibody which reacts with heart. This seems to do them no harm. Dressler is a syndrome of persistent cardiac pain, fever, malaise, and pericardial effusion seen after heart attack (and commonly after heart surgery) which seems directly related to an immune response to pericardial or myocardial antigens. A better name might be post-cardiac injury syndrome. Treated with anti-inflammatory agents, it usually gets better as the heart heals.

RHEUMATIC HEART DISEASE. Defined as heart disease occurring shortly after a streptococcal infection, for example a 'strep throat.' There is very good evidence that it is due to ► cross-reaction between a Group A *Streptococcus* M-protein antigen and a structure on the heart's endothelial lining, probably laminin on heart valves, followed by neutrophil-mediated tissue destruction. **Rheumatic fever** is the same disease with more widespread manifestations, including in the skin and CNS. These are classic Type II conditions. Poststreptococcal *glomerulonephritis*, on the other hand, is the Type III immunopathology, due to complexes between antibody and strep antigens trapped in the kidney.

AUTOIMMUNE THROMBOCYTOPENIC PURPURA (ATP). These patients have bleeding abnormalities due to destruction of platelets (thrombocytes) by autoantibody; ► the platelets are opsonized and their destruction, mainly in the spleen, is rapid. Platelets are needed for blood clotting. (Treatment: suppress the immune system and/or remove the spleen.) ATP is often seen in young healthy people some weeks after a viral infection; in older people, in association with many other autoantibodies; and in people treated with certain drugs; all of which might suggest to you, when you've read through these notes, the sorts of processes that could be going on.

AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA). Like ATP, this may follow a viral infection, or be associated with an autoimmune syndrome, or cancer. ► Many drugs, such as penicillin, methyldopa, chlorpromazine and quinidine, can induce AIHA, usually temporarily. In the rare condition paroxysmal cold hemoglobinuria (PCH), the patient experiences hemolysis after exposure to cold. It is due to an autoantibody which only binds to red cells at about 15° C.

ASK YOURSELF: Your fingers get to 15° C, so in PCH red cells could agglutinate in skin capillaries and be lysed when they move to warmer regions where complement is activated. But your lymph nodes don't get that cold; so how could B cells ever be stimulated in the first place?

In the following group of diseases, both autoantibodies and autoreactive T cells are implicated in the pathogenesis, so they are mixed Type II and Type IV mechanisms. Sometimes, as we've already seen, Type III is also involved.

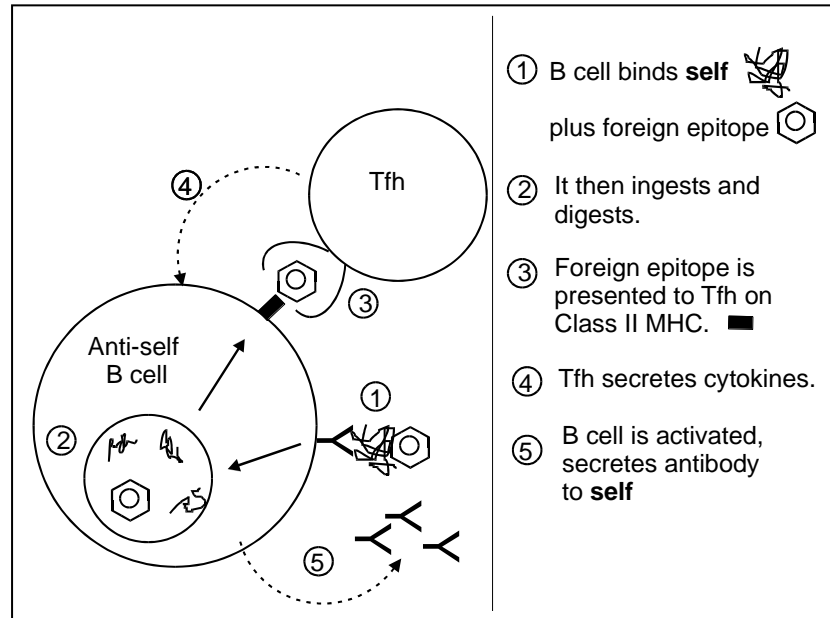
HASHIMOTO THYROIDITIS. An inflammatory disease of the thyroid in which there is very good evidence for both T and B cell immunity to various thyroid antigens, including thyroglobulin. The antibodies to thyroid antigens are destructive, not stimulatory. Histologically the thyroid is infiltrated by T cells. It may be that T cell damage releases normally sequestered antigens, to which antibodies are made, worsening the condition. The result is hypothyroidism.

OTHER DISEASES. In celiac disease, there is an autoantibody made to tissue transglutaminase that is very useful for diagnosis; in Type 1 (childhood) diabetes several antibodies to islet-associated antigens are seen which provide prognostic information; and diverse autoantibodies are seen in rheumatoid arthritis and lupus. But in none of these conditions are they thought to be pathogenic, so diabetes and RA are considered here under Type IV immunopathology, celiac disease under Chronic Frustrated Immune Responses, and SLE as a Type III condition.

ETIOLOGY: MECHANISMS OF LOSS OF TOLERANCE. We don't know in most cases what causes a breakdown of tolerance, the body's '*horror autotoxicus*' rule²; possible and known mechanisms follow. You could probably think up others.

1. Emergence of a **forbidden clone**. A clone of autoreactive T cells might somehow escape the normal thymic clonal deletion mechanisms, and mature so that encounters with antigen immunize it. This has been described in some cases of myasthenia gravis, and other syndromes.

2. **Hybrid (foreign + self) antigen formation.** Suppose you had anti-self B cells that hadn't been deleted. They would not get you into trouble if the self antigens were T-dependent, and you did not have antiself follicular helper T cells. This actually seems to be the case for many self proteins. But: suppose that a foreign antigen were to couple to the self antigen. ► The anti-self B cell could bind to the self part and ingest it, carrying along the coupled foreign antigen. Then foreign epitopes might be presented



to a Tfh cell on the B cell's Class II MHC. The B cell would have received all necessary signals and become activated. Then it would make its antibody, ► *against self*. Celiac disease is the best example of this. This process has also been called "illicit help." It is also illustrated in the [movie](#).

ASK YOURSELF: Can you see how this mechanism is very similar to what goes on when you use a conjugate carbohydrate-protein vaccine?

3. **Cross-reaction** between a foreign antigen and a self-antigen. We've been talking about this one since the beginning. Undoubtedly important, and it would become more so if only we could identify more antigens that get things started. By the time the patient develops clinical symptoms, the triggering antigen may be going or gone, so the process wanes. But sometimes it is maintained by autoimmune responses to normally-sequestered antigens released from damaged cells.

4. Release of a **sequestered antigen**. Note that in the special case of sequestered antigens, the antigen cannot get out into the general system, and therefore is not normally immunogenic, ► but if an immune response *does* get initiated, then the response can usually get into the place where the antigen was sequestered. Example: some adult men who get mumps end up sterile. This is because the virus breaks down the blood/testis barrier, allowing immunization to sperm antigens. Because these are not yet expressed in childhood, some sperm-reactive B and T cells never got deleted.

² Paul Ehrlich (1854-1915) believed that a well-behaved and properly educated immune system would have a horror of harming the body. Maybe it has, but it does so anyway.

► There is a phenomenon in autoimmunity called ‘epitope spreading.’ Early in the disease antibodies are made to just one or two epitopes of some ‘self’ protein. With time, more epitopes, and more proteins are involved. Does tissue damage gradually reveal more sequestered antigens?

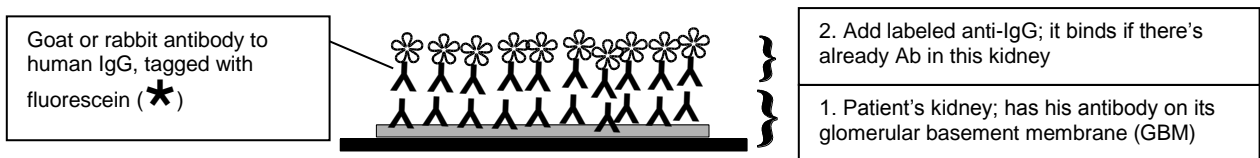
5. **Passive antibody.** In a child with hemolytic disease of the newborn (*see* Immunohematology); in a patient getting a mismatched transfusion; in a newborn child of a mother with myasthenia gravis or SLE. A rare child of a lupus mother may be born with heart block due to cross-reactive antibodies received transplacentally from its mother.

6. **Innocent bystander.** A common mechanism, in which there is damage to normal tissue which happens to be associated with or infected by the antigen, which is truly foreign. Imagine a drug adhered to your red blood cells, and you made antibody against the drug. What would get lysed by complement—the drug? No, the poor innocent red cell.

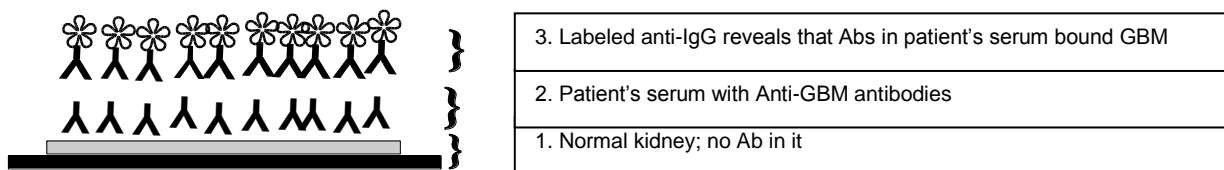
7. **Failure of regulatory mechanisms.** ► A proper balance between Th1, Th17, Tfh, Th2, and Treg activity assures that immune responses are appropriate. Does this balance get perturbed in some way, so that some responses are exaggerated, and eventually self/non-self discrimination breaks down? This is an area of intense speculation lately. Some recent experiments that cause major shifts in T cell balance look very promising as therapy, if they can make the **translational jump** from the lab or the Phase I trial into safe general use. We’ll talk more about this in the last of our immunopathology discussions.

DIAGNOSIS. For diagnosing a Type II condition we look for antibody directed against the antigen or tissue in question. Antibody can be detected in the patient’s serum by any of the tests you’ve already heard about, including ELISA.

In general the hallmark test is immunofluorescence. You can do a *direct* test, looking for antibody that is already in the patient’s tissues, if you happen to have a sample of the patient’s *tissues*:



Or, if you only have the patient’s *serum*, you can look for antibody in it by an *indirect* immunofluorescence test, using normal human tissue (autoantibodies are almost always tissue specific but not individual-specific):



ASK YOURSELF: How would you decide whether a patient had Type III or Type II glomerulonephritis, if you had patient’s serum and any antibody you needed, and either a biopsy of the patient’s kidney, or of only a normal kidney?

Learning objectives for Type II Immunopathology

1. Describe the molecular and cellular details of the immunologic mechanisms by which tissue damage occurs in a Type II ('cytotoxic antibody') reaction.
2. Give an example of a Type II mechanism disease of muscle, kidney, heart, red cells, platelets, thyroid, and pancreatic islets.
3. Distinguish between the 'lumpy-bumpy' and 'linear' immunofluorescent patterns in terms of the most probable immunopathologies they represent.
4. Describe how you could tell, using fluorescent antibodies and biopsies of **patient's** kidney, if Type II or Type III immunopathology was involved. Name the antibodies you would use and the fluorescent patterns you would see.
5. Given patient's serum, fluorescent antibody to human immunoglobulins, and slices of **normal** kidney, describe how you could tell if the patient's glomerulonephritis was due to Goodpasture disease or SLE.
6. Describe how antibody-mediated tissue damage could result from:
 - The innocent bystander phenomenon.
 - Cross-reaction of a foreign antigen with self.
 - Coupling self antigen with a foreign antigenic 'carrier'.
 - Exposure of a sequestered antigen.
7. Identify 'Rheumatoid Factor' and describe its molecular nature.
8. Describe the Type II mechanism of Graves Disease.
9. Discuss how the *Aire* gene is involved in preventing autoimmune disease.
10. Describe a condition in which autoantibody **stimulates** rather than damages its target tissue.