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Return to Type I Diabetes and Overview of Immune Response

M1 – Immunology Sequence

Winter 2009

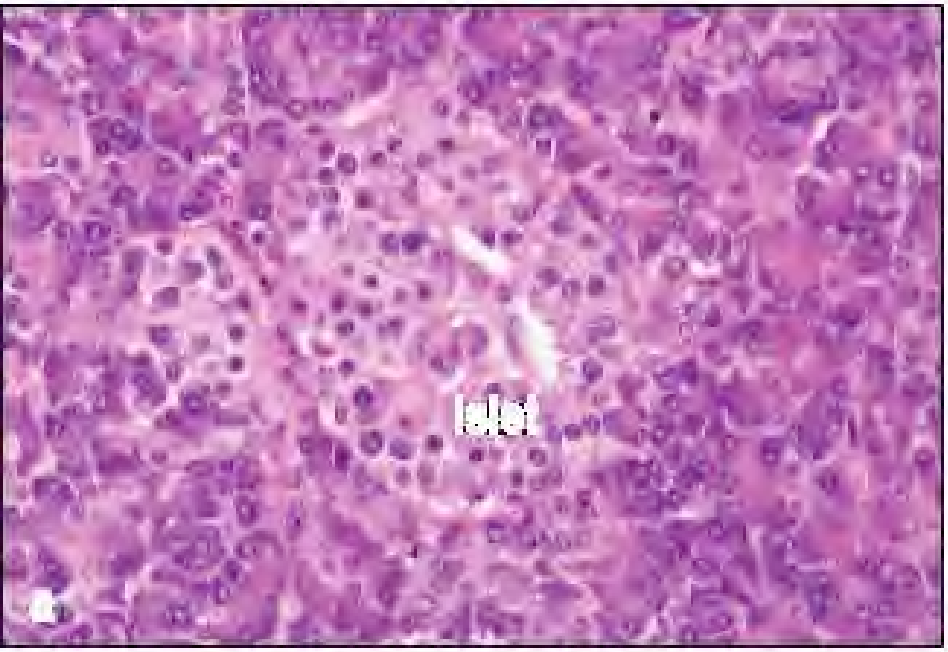
University of Michigan
Medical School

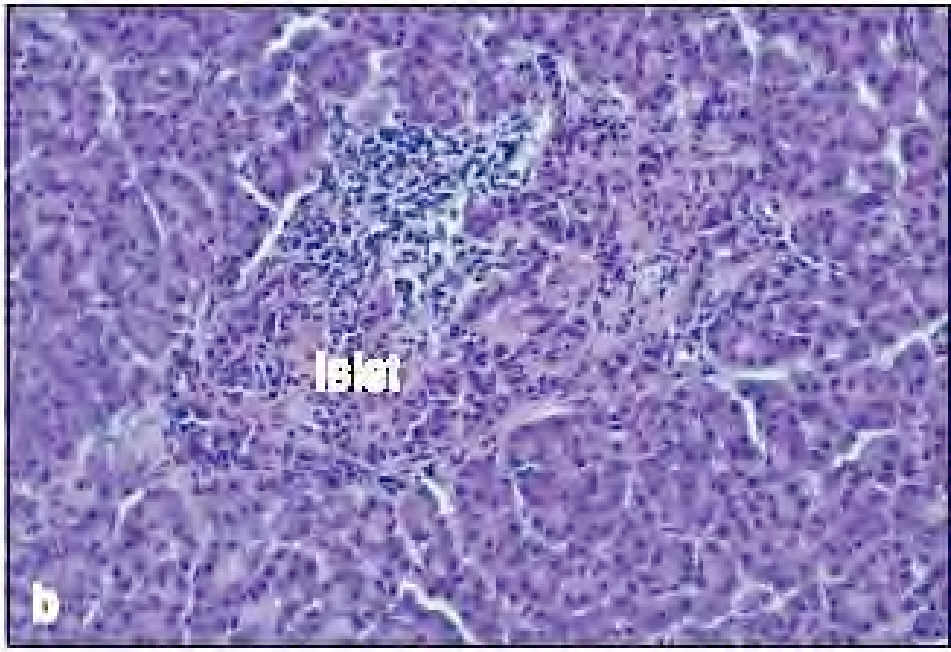
One of the first pathologies observed is infiltration of the pancreatic islets with leukocytes (inflammation—insulitis) and subsequent destruction of the beta cells in the islets. Since the beta cells produce insulin, loss of the beta cells results in loss of insulin production.

By the time a patient presents with the symptoms of diabetes, more than 90% of the beta cells have been destroyed.

Normal pancreas

Insulin-dependent diabetic pancreas





Is the pattern of lymphocyte infiltration consistent with an ongoing infection?

Is the pattern of lymphocyte infiltration consistent with an ongoing infection?

No, no neutrophils. (But could be a viral infection.)

Neutrophils go to the site of an infection, because inflammatory mediators upregulate receptors on endothelial cells.

On Tuesday, Dr. Pietropaolo discussed that the beta cells of the pancreas are destroyed by an immunological mechanism in Type I diabetes. Dr. Fantone, discussed four types of immunopathology.

Which of the four types of immunopathology might be active in Type I diabetes?

What is the effector function (pathology) associated with pancreatic beta cell destruction?

Summary: Type I Reaction

- Antibody: IgE
- Effector Cells: Mast Cell & Eosinophil
- Complement: No
- Reaction: Minutes

Summary: Type II/III Reaction

- Antibody: IgM & IgG
- Effector Cells: Phagocytic
- Complement: Yes
- Reaction: 6-24 hours

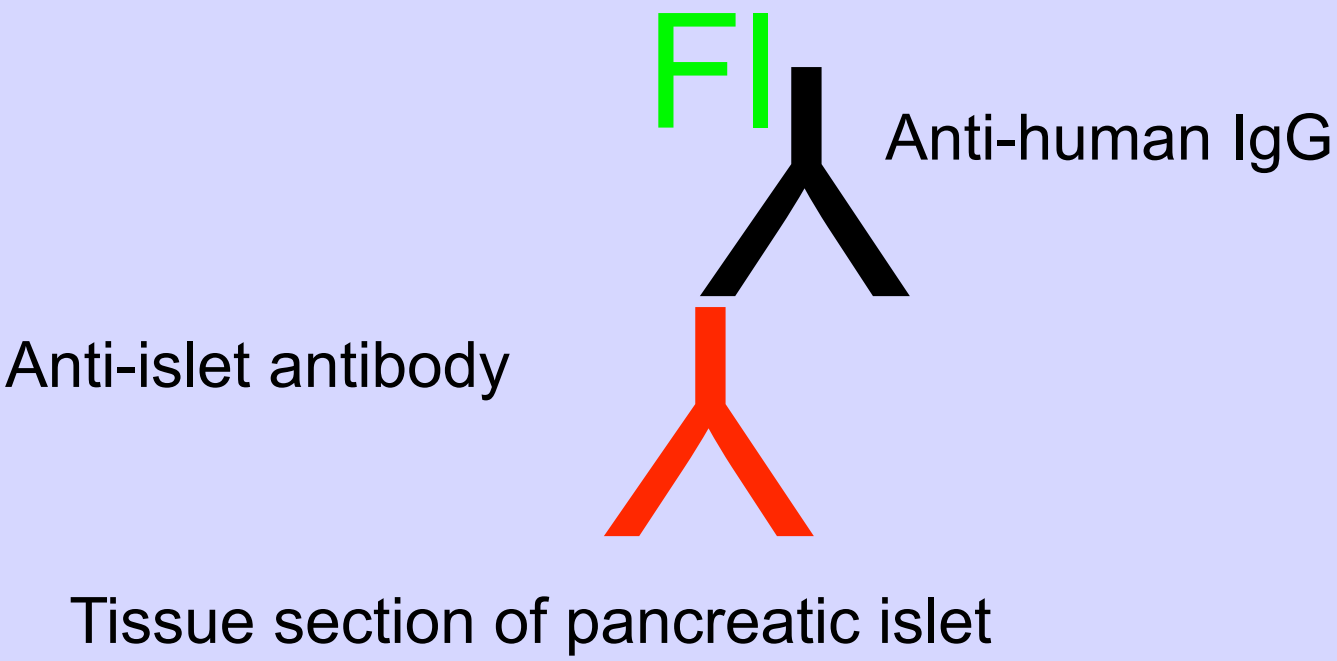
Summary: Type IV Reaction

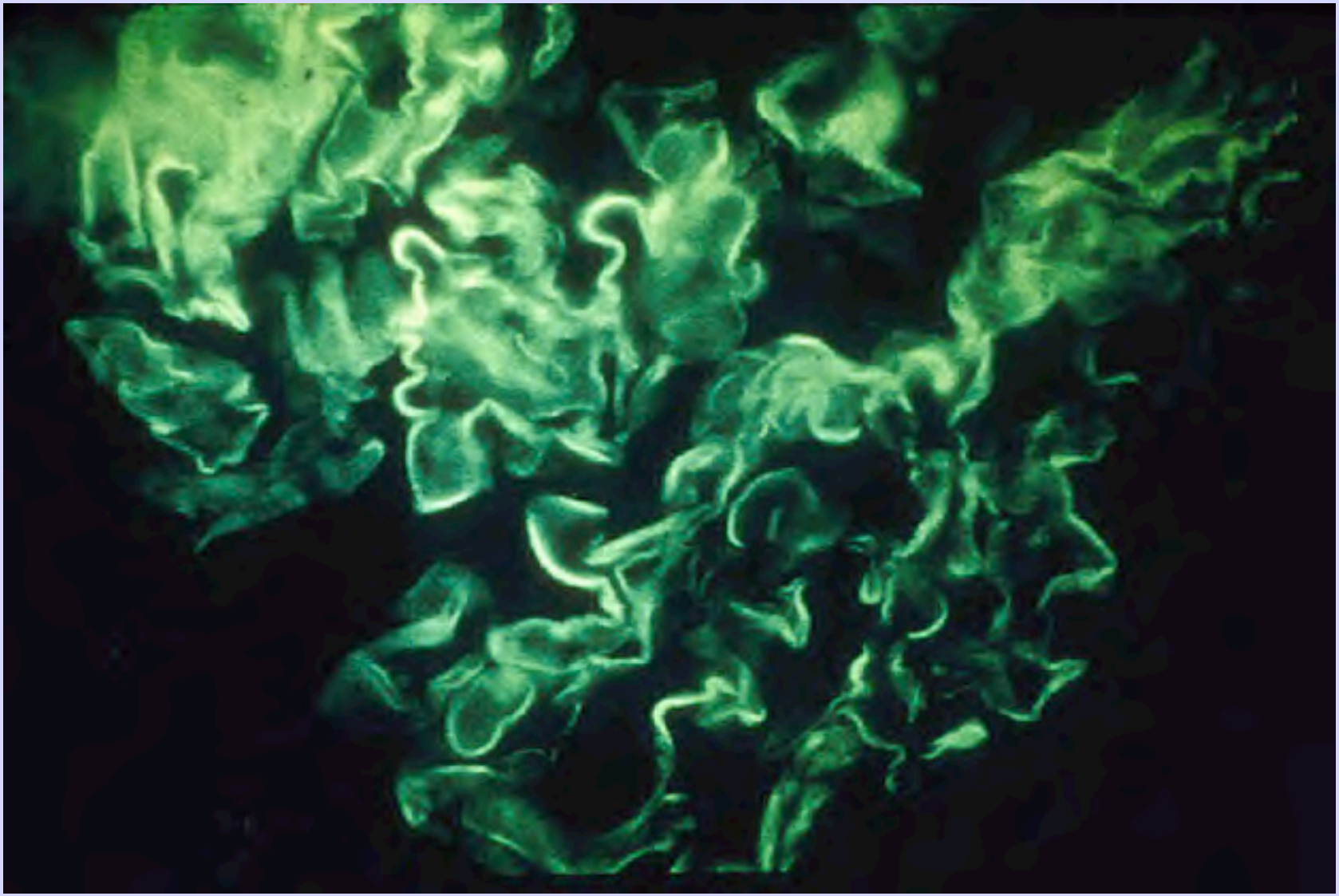
- Antibody: No
- Effector Cells: CD4+ T-lymphocytes, Monocyte/ Macrophage;

  CD8+ T-lymphocytes
- Complement: No
- Reaction: 48-72 hours (skin test)

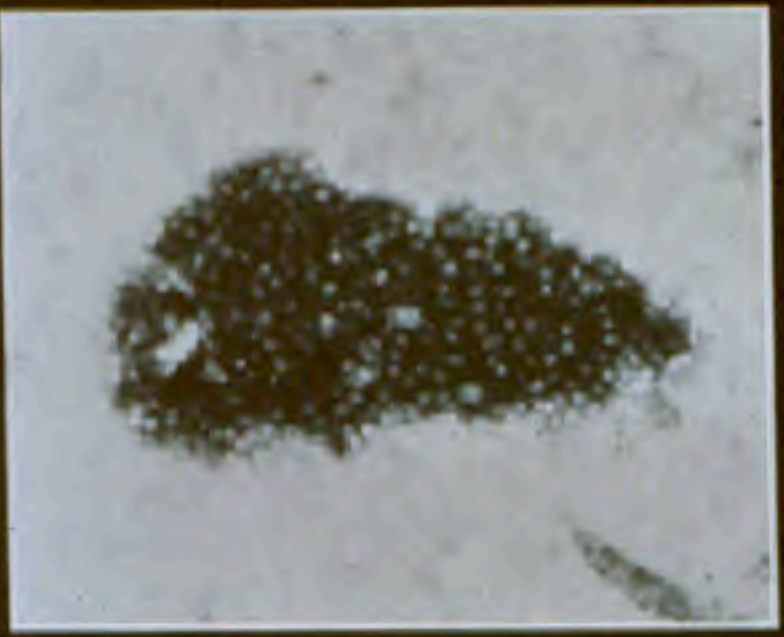
Are anti-self antibodies the primary cause of islet cell destruction (Type II/III immunopathology)?

Test for anti-self antibodies on islet cells

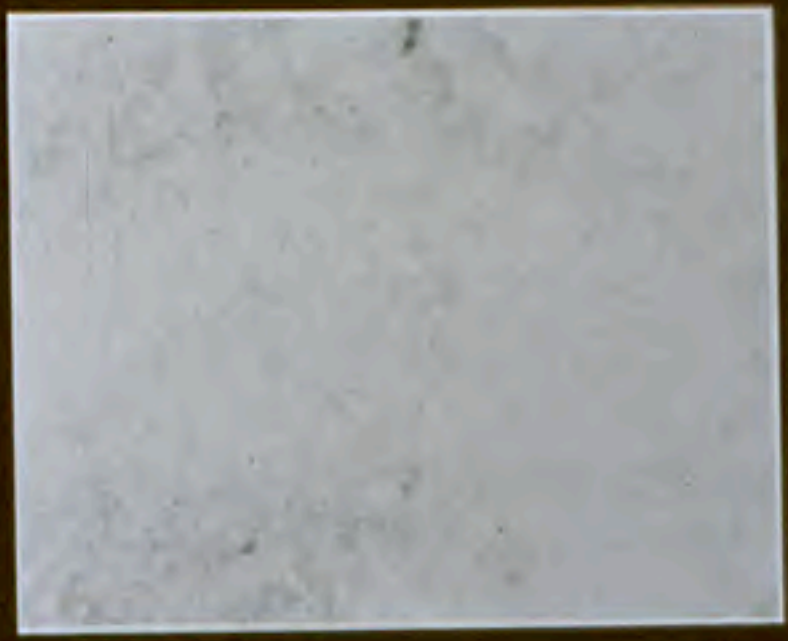




Cytoplasmic Islet-cell-antibody staining



Positive reaction



Negative reaction

Reproduced with permission of the American Diabetes Association, Inc., from Coman PG, Tautius M, Rabizadeh A, Cahill C, Eisenbarth G: Assay for islet cell antibodies with rat pancreas and peroxidase protein A. *Diabetes Care* 1988;367–368, and from Vardi P, Ziegler AG,

Matthews JH, Dib S, Keller RJ, Ricker AT, Wolsdorf JI, Hershowitz RD, Rabizadeh A, Eisenbarth GS, Soeldner JS: Concentration of insulin autoantibodies at onset of type I diabetes: inverse log–linear correlation with age. *Diabetes Care* 1988;736–739.

If antibody mediated the destruction of the beta cells, would B lymphocytes necessarily infiltrate the pancreas? What type of leukocytes would more likely to be found?

If antibody mediated the destruction of the beta cells, would B lymphocytes necessarily infiltrate the pancreas? No, B cells act at a distance, by secreting antibodies.

What type of leukocytes would more likely to be found?

Neutrophils. A lack of neutrophils, antibody, or complement deposition in the pancreas argues that antibodies (including those binding to insulin) are not very important in the disease.

Are these anti-self antibodies the primary cause of islet cell destruction?

Probably not.

If antibodies were the cause, the histopathology would be characterized by the presence of immunoglobulin, complement, and neutrophils.

What are other candidates for the destruction?

CD4+ T cells + macrophages

CD8+ T cell cytotoxicity

What does the lymphocyte infiltration of the pancreatic islets indicate about the pathology of Type I diabetes?

Since the infiltration is mostly lymphocytes, the pathology is not Types I, II, or III (mast cells, eosinophils, neutrophils would be expected).

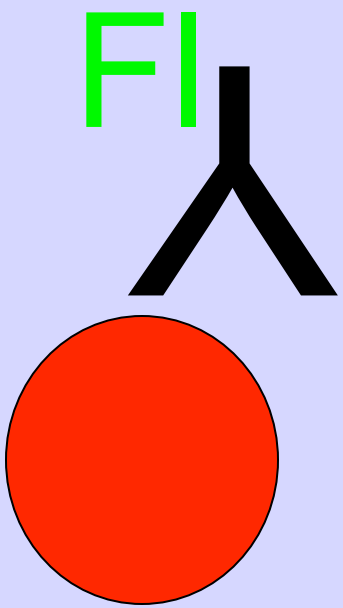
However, the lymphocyte infiltration is consistent with a Type IV reaction.

To understand the lymphocyte infiltration better, what more detailed histological test would you like to perform?

To understand the lymphocyte infiltration better, what more detailed histological test would you like to perform?

To distinguish between DTH and cytotoxicity by CD8+ cells, look for macrophages, and also do immunofluorescence with anti-CD4 and anti-CD8 antibodies conjugated with fluorescein.

Test for anti-self antibodies on islet cells



Anti-CD4

Anti-CD8

Anti-CD19

Anti-NK1.1

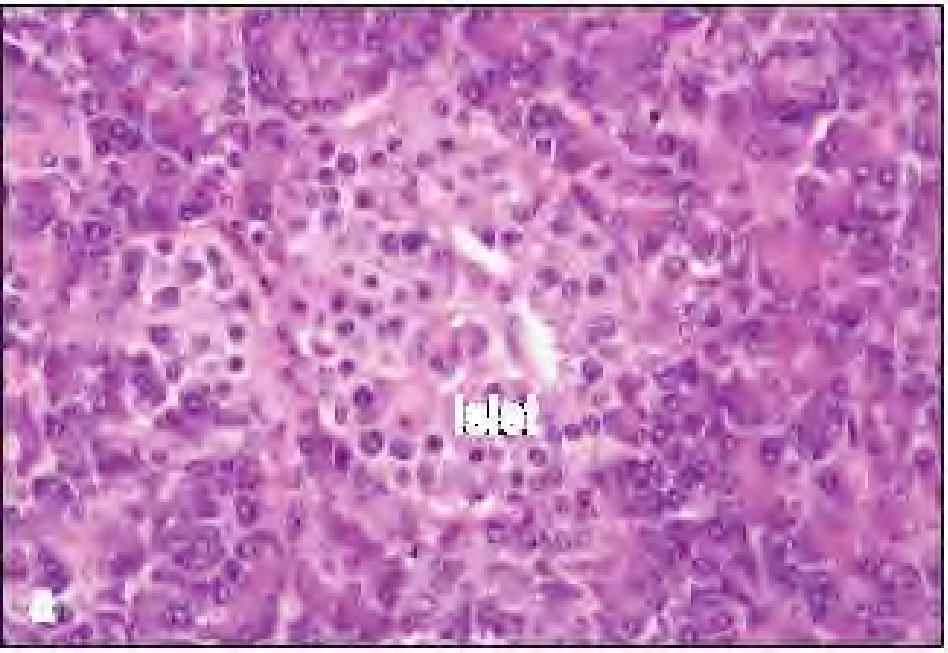
Tissue section of pancreatic islet

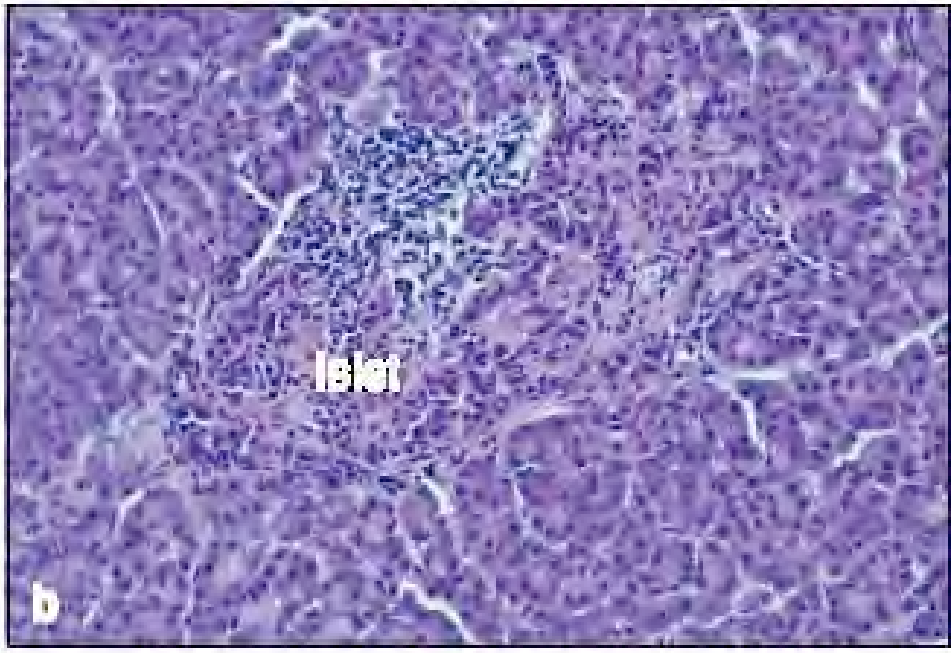
(Morphology would define the presence of macrophages or neutrophils.)

Normal pancreas

Insulin-dependent diabetic pancreas

Figure 11.8





HLA Type and Insulin Dependent Diabetes

	Population	Type I Diabetics
DR3/DR4	2.5%	39%

One can imagine that Type I diabetes is initiated as follows:

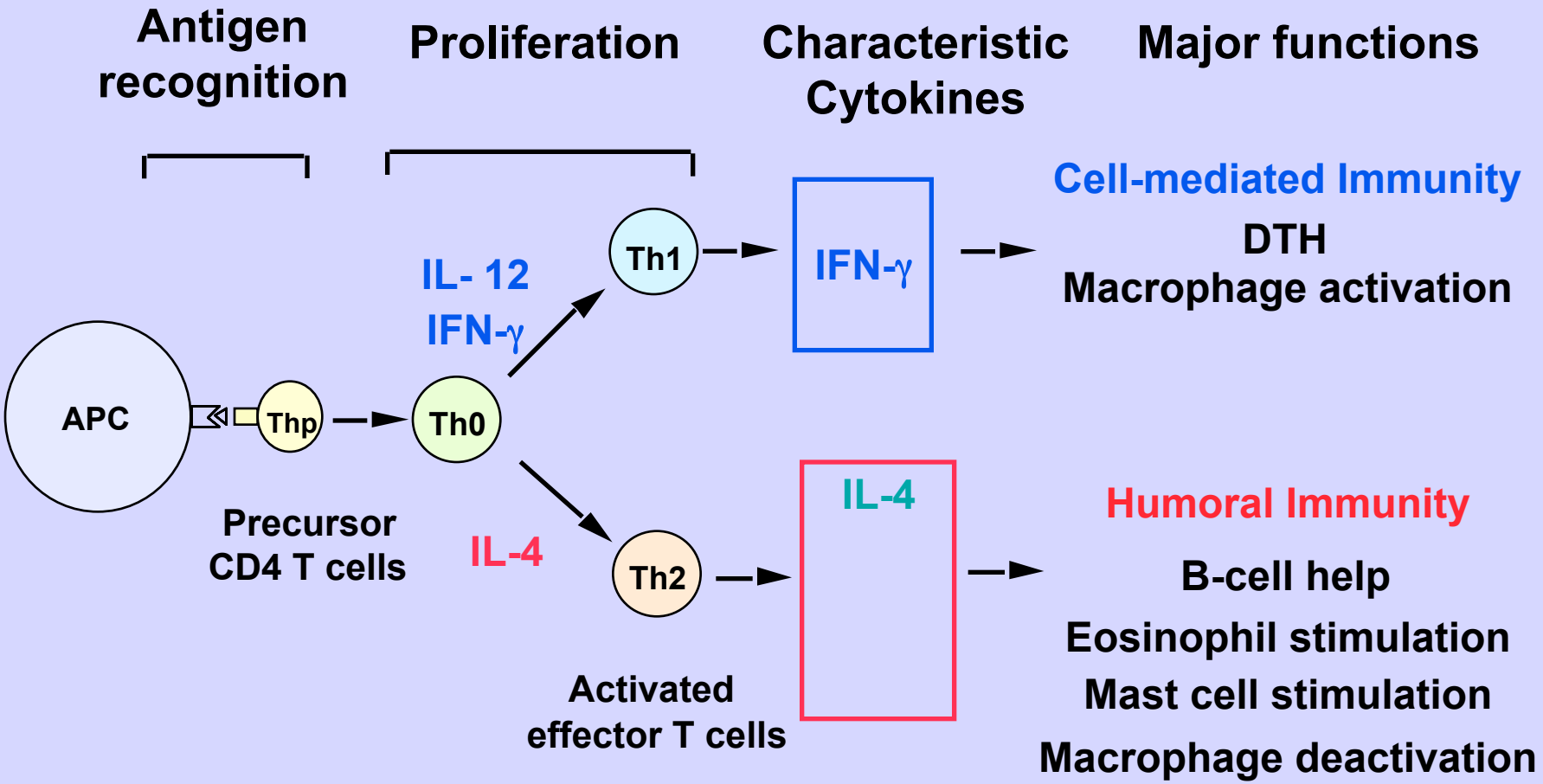
1. Some physical trauma or infection causes damage to the islets.
2. Inflammatory cells (macrophages, neutrophils) enter the islets, cause further damage (on a micro scale).
3. Epitopes on self proteins like insulin or GAD that are not exposed in a healthy islet, are now exposed, and these epitopes are taken up by dendritic cells and macrophages. Those individuals who are DR3/DR4 heterozygotes are more likely to present the critical self peptide on their MHC class II molecules.
4. A CD4+ T cell clone specific for the self peptide:MHC class II complex is activated, begins to divide and differentiate.

5. This CD4+ T cell clones provides help to both B cell clones and CD8+ T cell clones that recognize other self epitopes expressed by islet cells. These self epitopes recognized by B cells cannot have been expressed in bone marrow, and the self epitopes expressed by CD8+ T cells cannot have been expressed in the thymus.

6. Cytotoxic CD8+ T cells or antibodies secreted by plasma cells begin to destroy islet cells, leading to Type I diabetes.

7. Alternatively, CD4+ T cells might activate macrophages, which in turn destroy the islet cells.

Differentiation of T helper cells



CTL induces programmed cell death (apoptosis) in target cells.

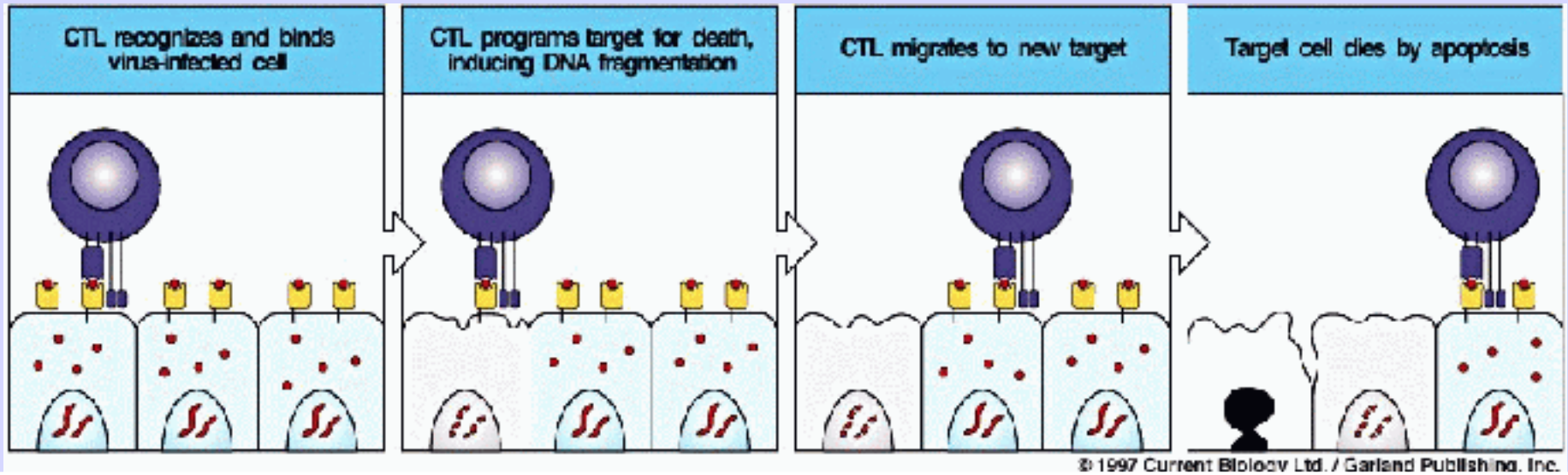


Fig 6.24

Janeway. Immunobiology: The Immune System in Health and Disease. Current Biology Ltd./Garland Publishing, Inc. 1997

Cytokines: AT&T of the immune response

- The major means for inflammatory cell activation
- Two-way communication between innate and acquired immune response
- Two-way communication between cells of the acquired immune response

Have immunologists defined the autoantigen that is recognized by the CD4+ T cell, leads to an immune response, and ultimately to Type I diabetes?

Have immunologists defined the autoantigen that is recognized by the CD4+ T cell, leads to an immune response, and ultimately to Type I diabetes?

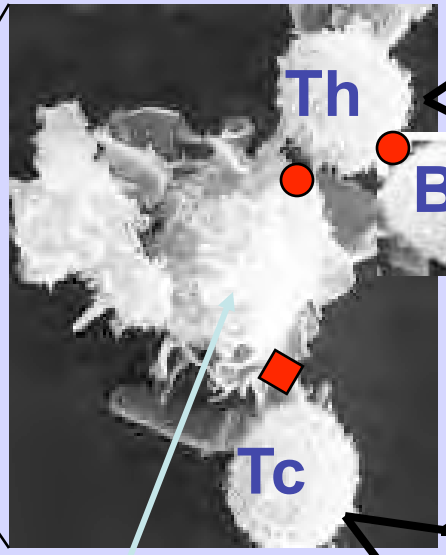
No, it is not defined. However, it is almost surely an antigen expressed by a pancreatic beta cell.

There remains a small chance that the anti-insulin and anti-GAD antibodies are the cause of the Type I diabetes. Alternatively, pancreatic beta cells might be damaged via some other type of pathology, releasing insulin and GAD antigens so that APCs can take them up and present them to Th and B cells. In this scenario, anti-self antibodies would be a result of Type 1 diabetes. Current thinking favors the latter scenario.

An immune response to a pathogen is fundamentally the same as an immune response to a self antigen of the islet cell.

Review of immune responses to two types of pathogens—extracellular (usually bacteria) and intracellular (viruses and some bacteria).
Return to the BIG PICTURE, without concerning ourselves with all of the details.

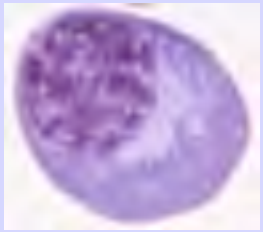
Simplified overview of an immune response

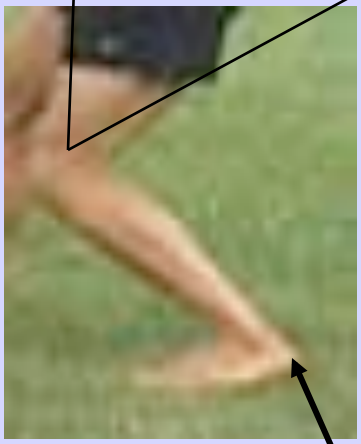


help

killing

IgM,IgG,IgA





Dendritic cell or macrophage

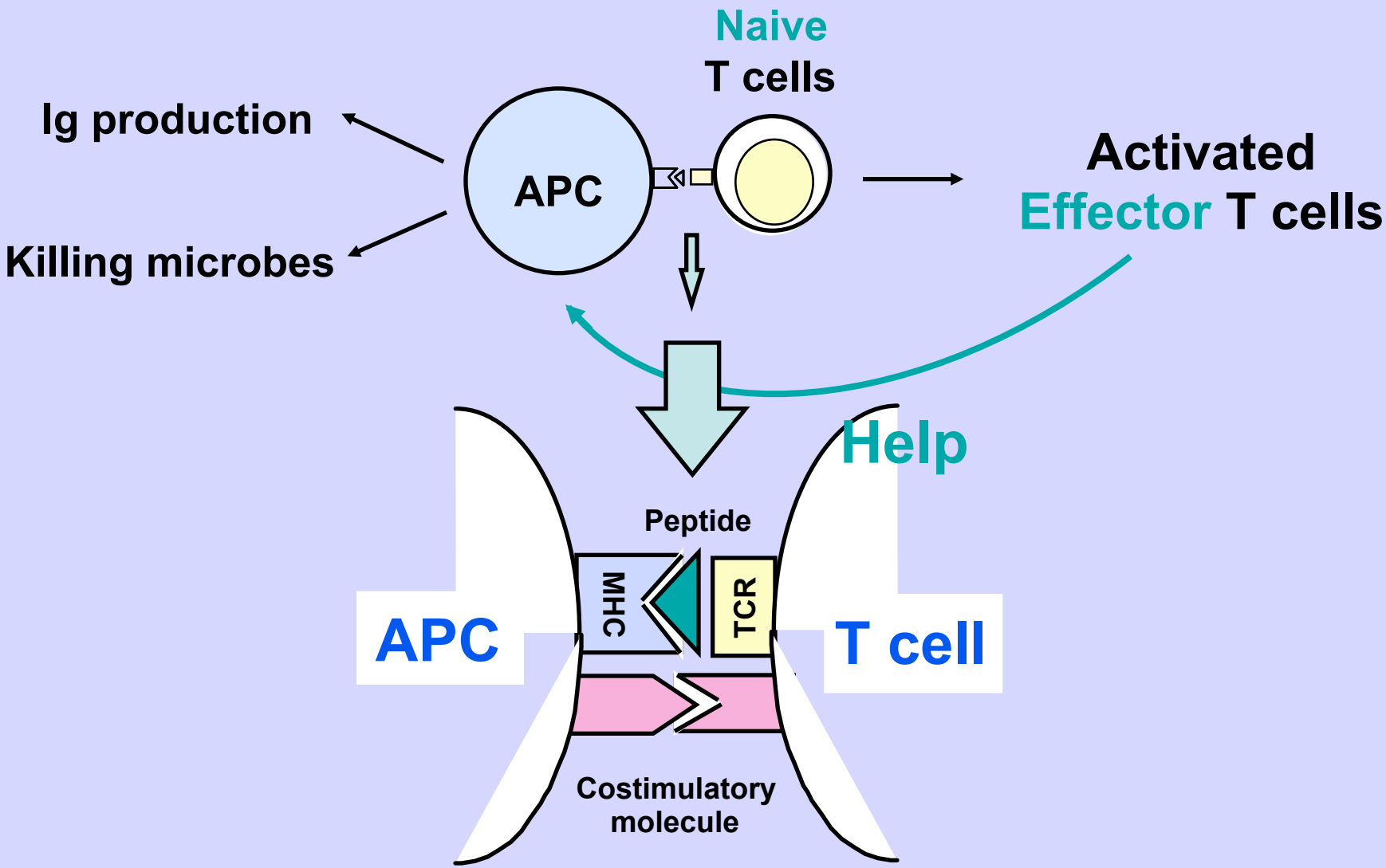
Often eliminated by innate immunity: neutrophils or macrophages

Clostridium tetani

Differences between innate and adaptive immunity

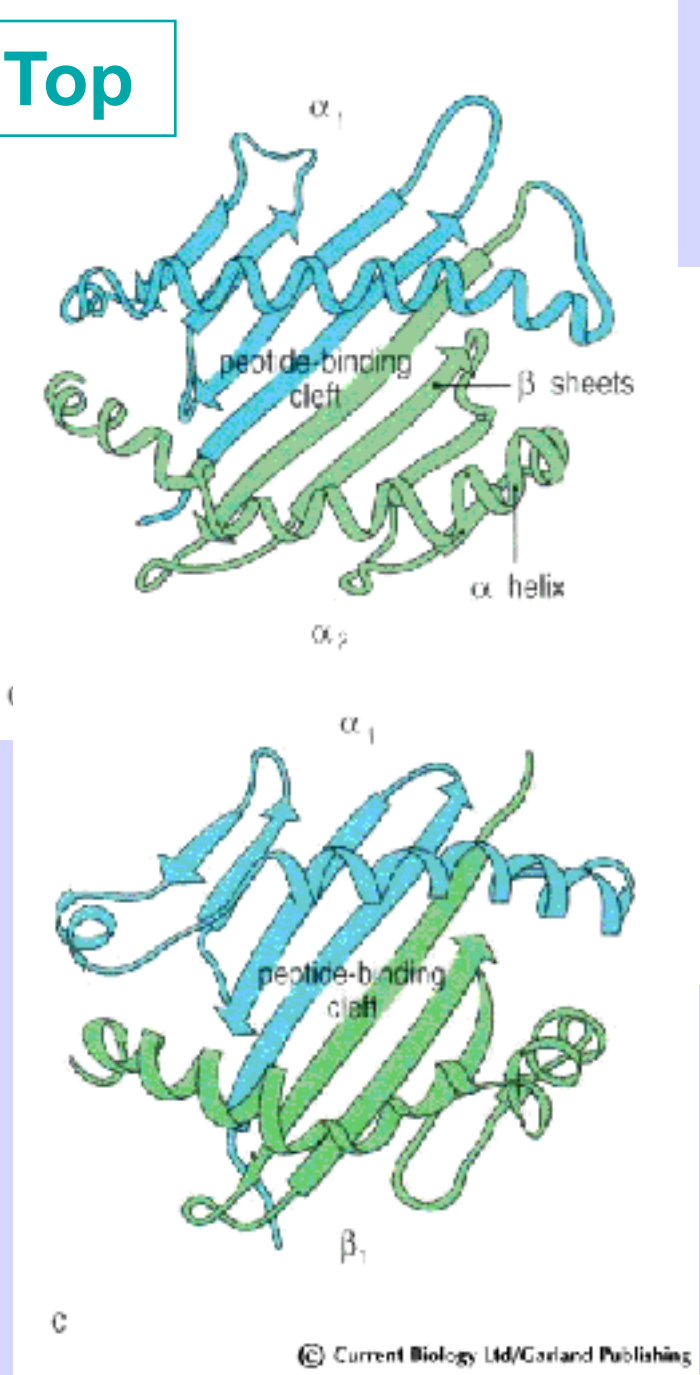
Innate Immunity	Adaptive Immunity
	Response is antigen-dependent
There is immediate maximal response	There is a lag time between Exposure and maximal response
Not antigen-specific	Antigen-specific
Exposure results in no immunological memory	Exposure results in immunological memory
	Recognition by antibody and T cell receptors

Activated APC



Top

Side



Class I

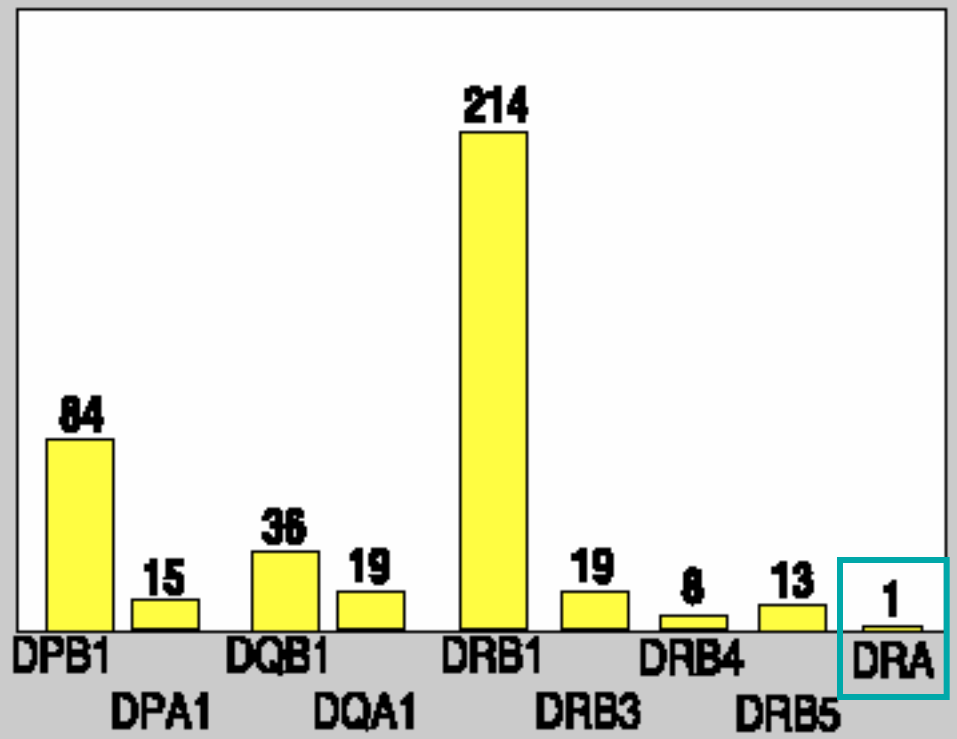
Intracellular

Class II

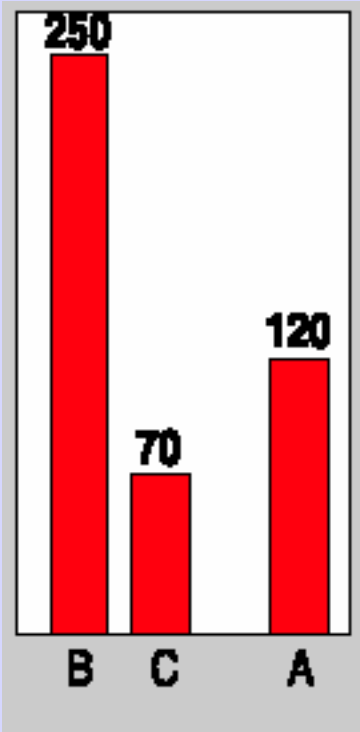
Extracellular (and intracellular)

Figure 3.8

HLA class II



HLA class I



Human MHC genes are highly polymorphic.

Each individual express only two of these alleles by co-dominance.

Fig 3. 20

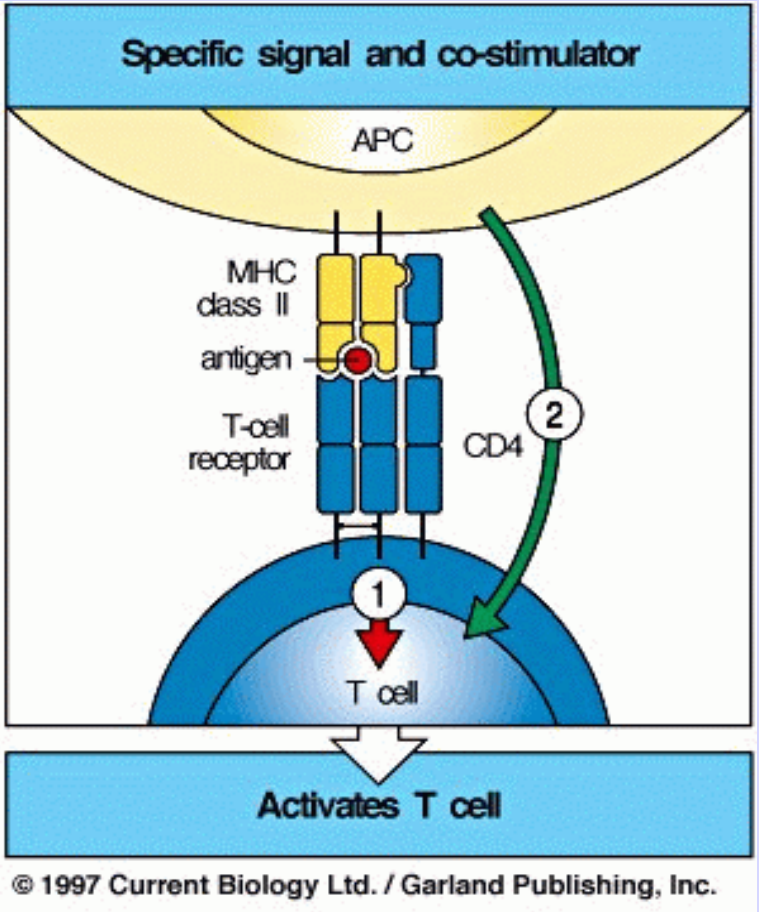
 Parham. The Immune System. Garland Publishing/Elsevier Science Ltd. 1997

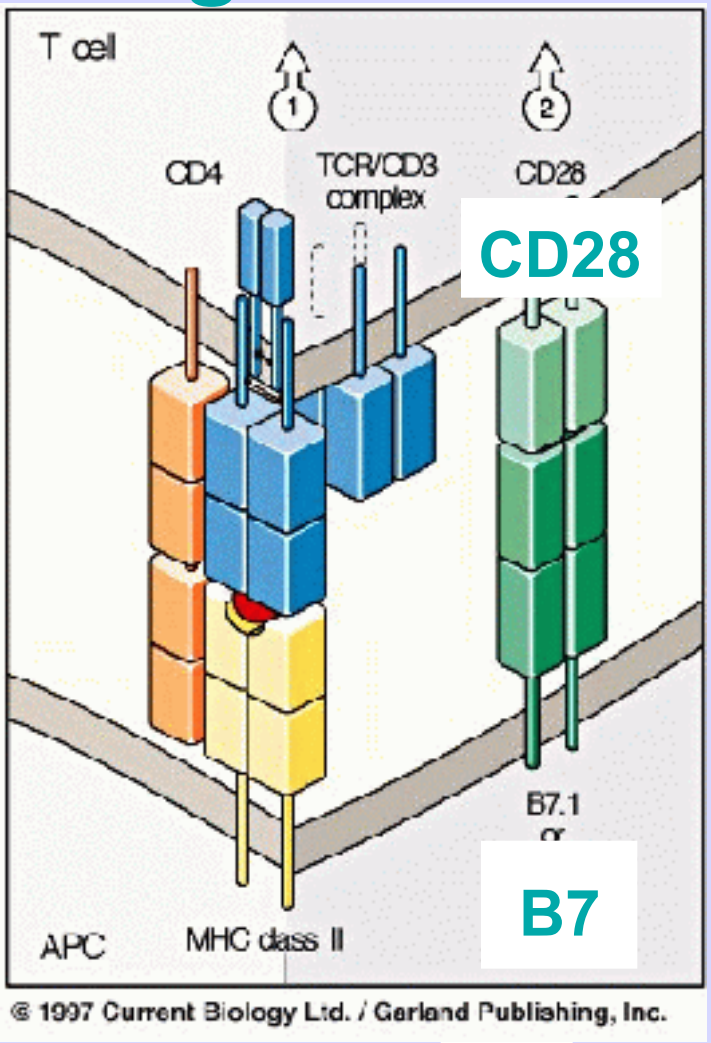
Antigen processing and presentation to T lymphocytes

MHC class I pathway (cytosolic source)
Present antigen to CD8 T cells
Virus and intracellular bacteria
Mutated tumor antigen

MHC class II pathway (endosomal source)
Present antigen to CD4 T cells
Bacteria

Activation of naive T cells requires two independent signals.





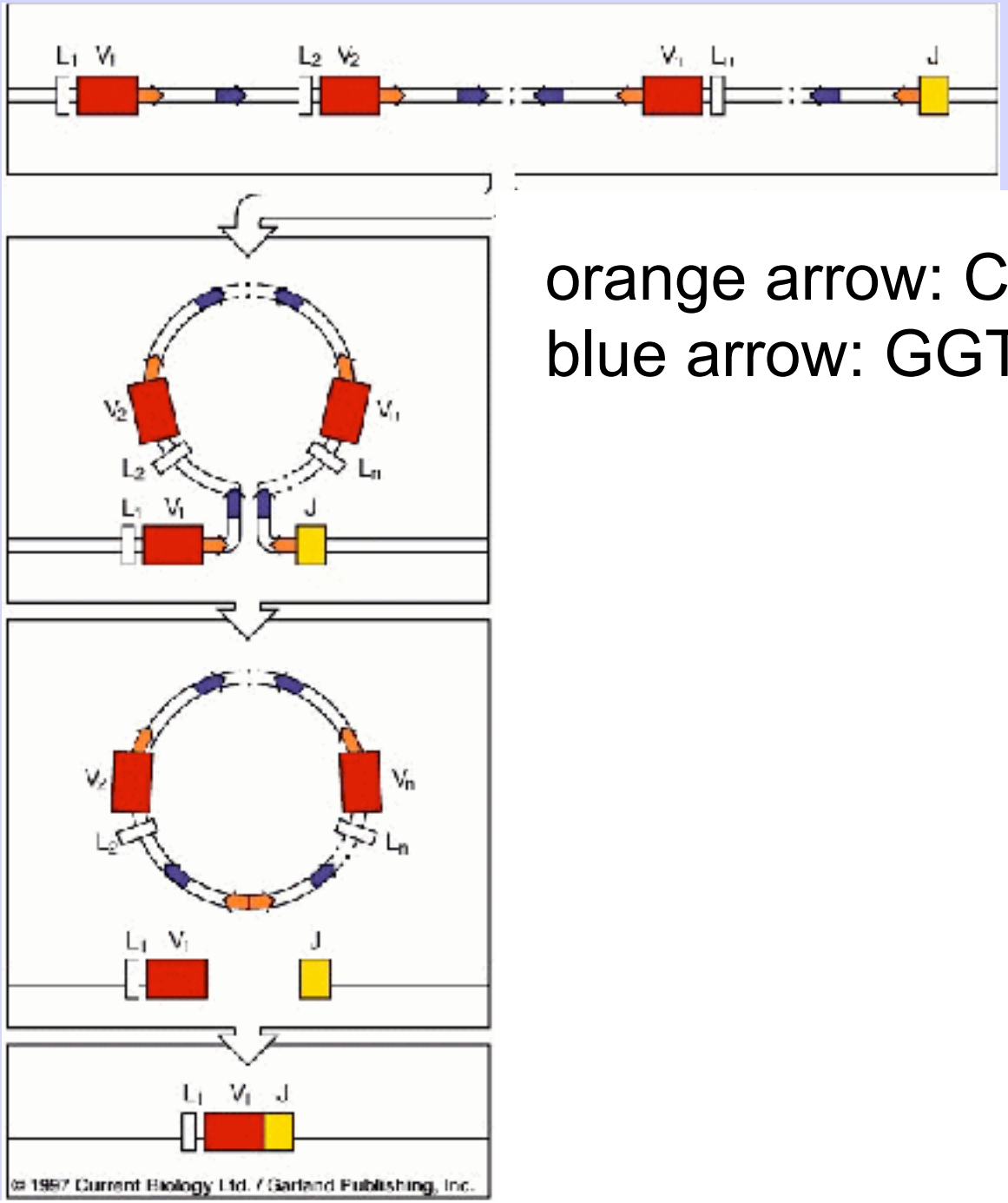
PD-INEL Janeway. Immunobiology: The Immune System in Health and Disease. Current Biology Ltd./Garland Publishing, Inc. 1997

Fig 6.7

Where do the anti-virus or anti-bacteria cell T cells and B cells come from in the first place?

They arise from random, antigen-independent differentiation.

T cells and B cells derive from the bone marrow.



orange arrow: CACAGTG
blue arrow: GGTTTTTGT

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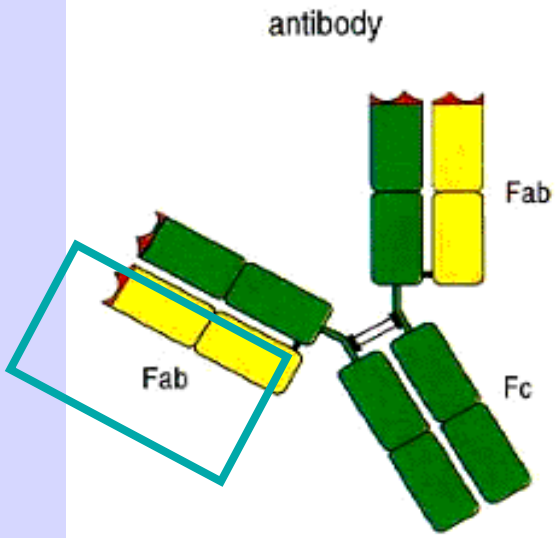
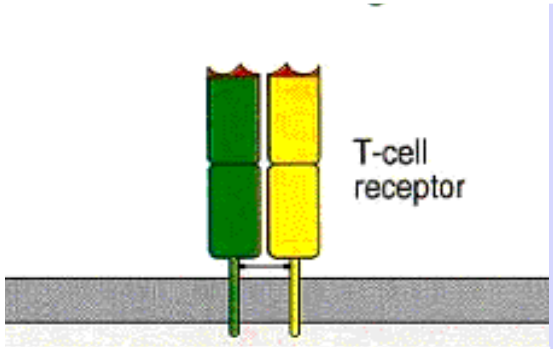
The T cell receptor resembles a membrane-bound Fab fragment of antibody.

BCR



TCR



- Bivalent
- Secreted and membrane-bound forms

- Monovalent
- Membrane-
- bound form

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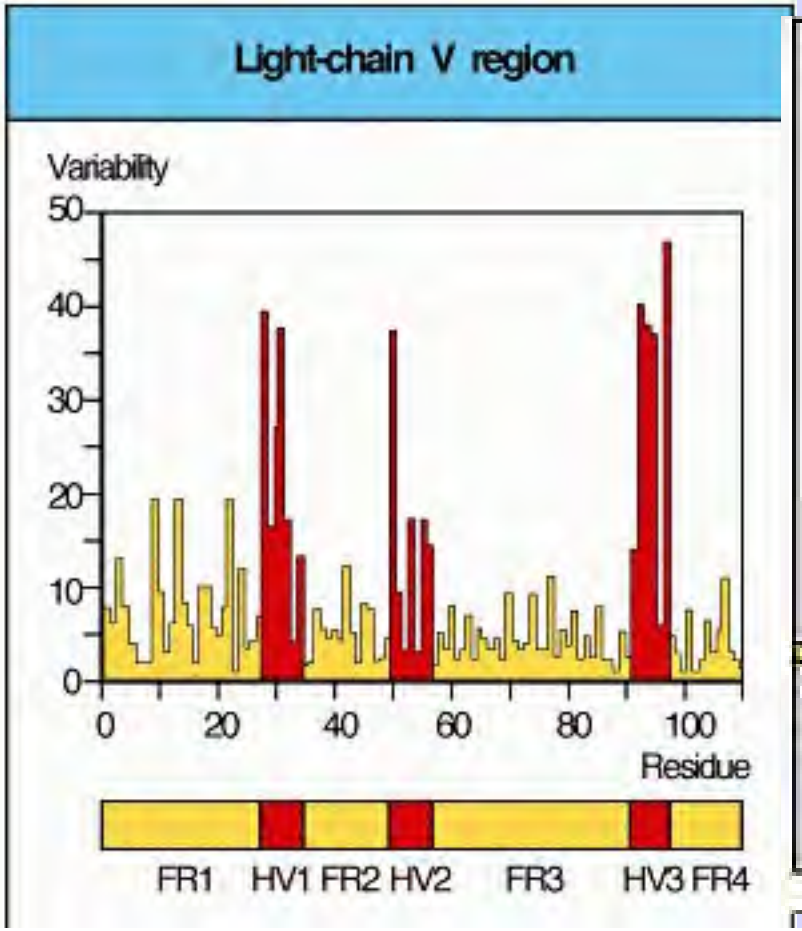

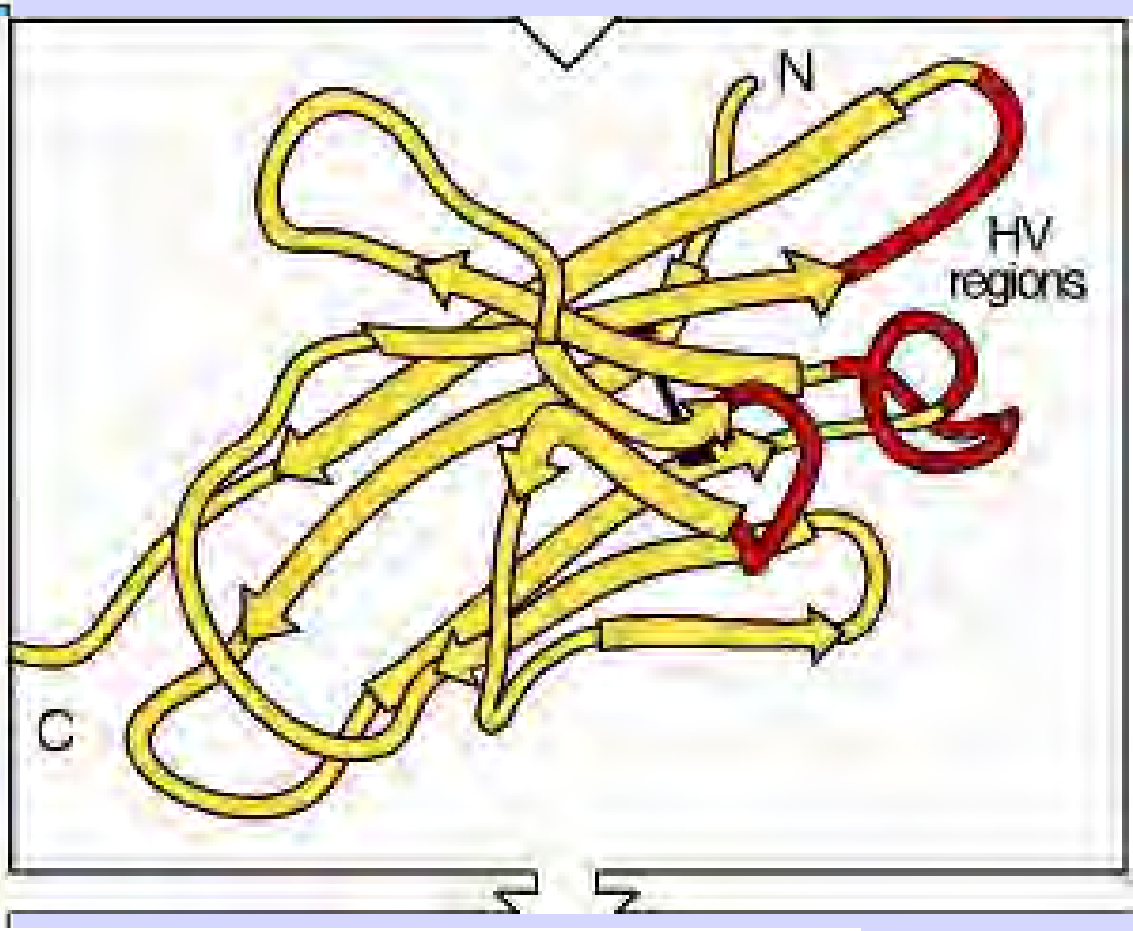

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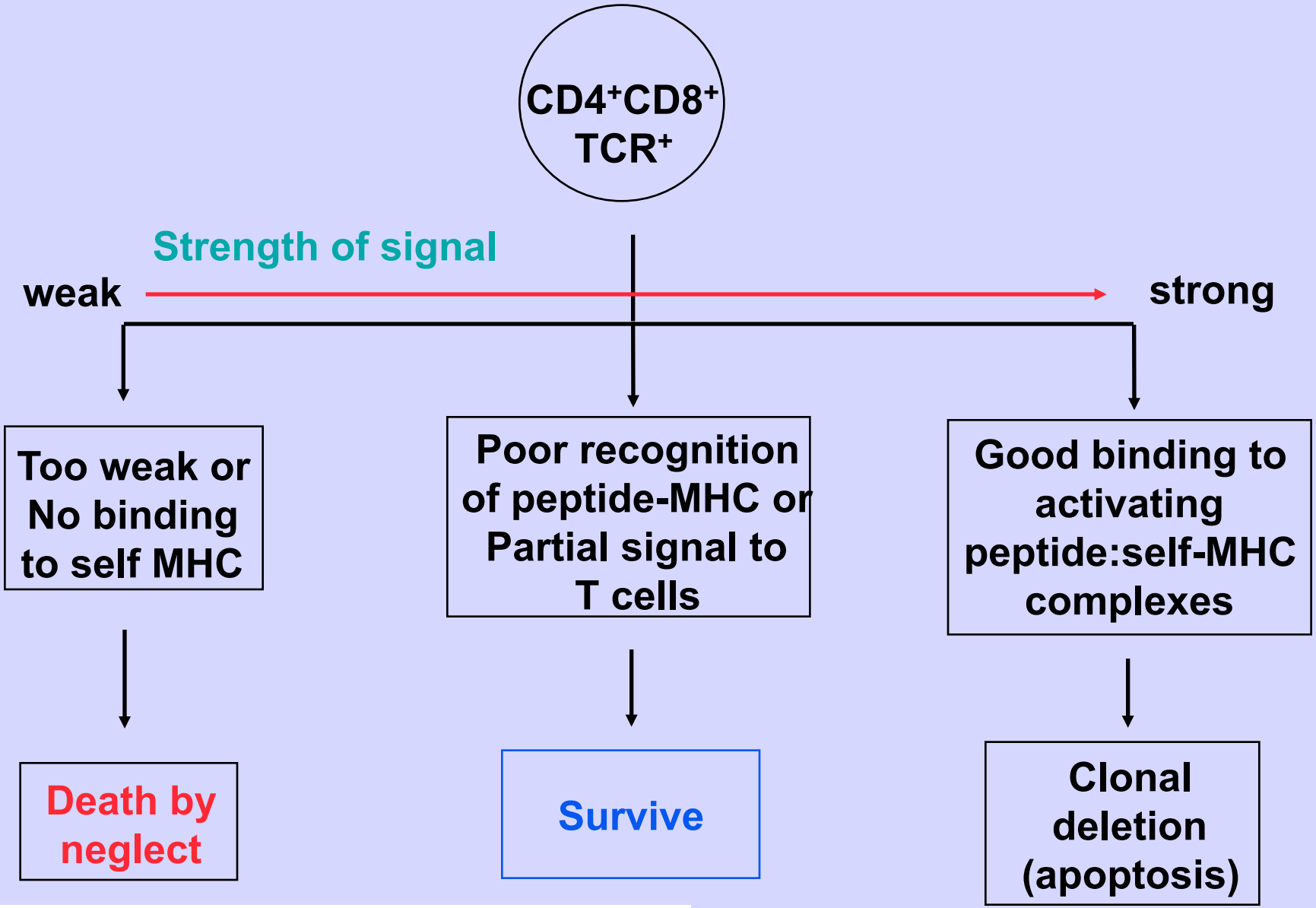
A. Specificity of recognition by cells and molecules—each antigen is distinguished from (almost) all other antigens.

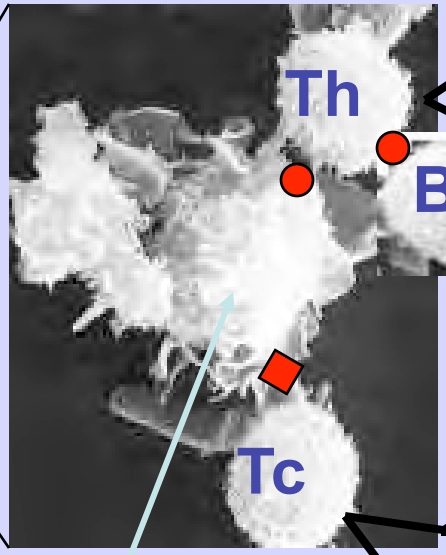
B. Diversity of recognition--The immune response can recognize ten million or more different antigens.

A simple view of the thymic selection



Tolerance--Depending on how an antigen is encountered, the immune system can become non-responsive to that antigen. Individuals are (usually) tolerant to self antigens.

Simplified overview of an immune response



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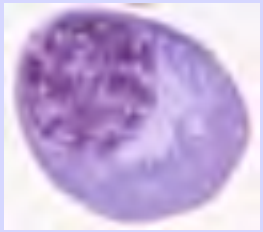
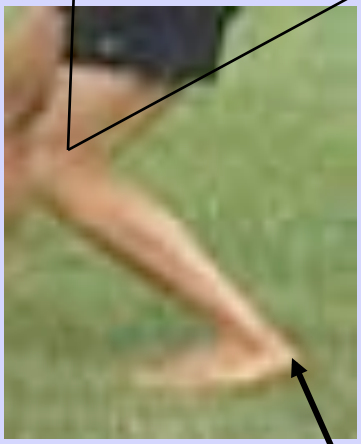
killing

IgM,IgG,IgA





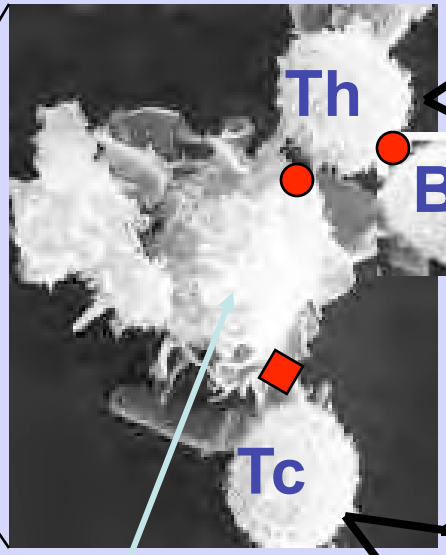
Dendritic cell or macrophage

Often eliminated by innate immunity: neutrophils or macrophages

Clostridium tetani

For extracellular pathogens, once CD4+ T cells are activated, they will help B cells to become activated, differentiate, and produce antibodies. The antibodies eliminate the pathogen by neutralization, by opsinization for macrophages or neutrophils, by complement mediated lysis, and so on.

Simplified overview of an immune response



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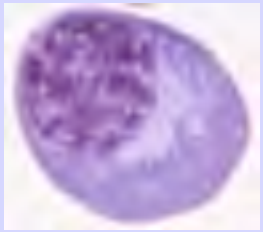

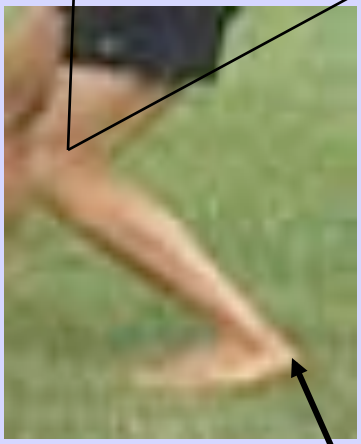

Dendritic cell or macrophage

Often eliminated by innate immunity: neutrophils or macrophages

Clostridium tetani

For intracellular pathogens, once CD4+ T cells are activated, they may help CD8+ T cells to divide, differentiate, and become cytotoxic. Alternatively, the CD4+ T cells may produce large amounts of interferon-γ, and activate macrophages. Both cytotoxic CD8+ T cells and activated macrophages eliminate the intracellular pathogen by killing the cell in which it resides. Many intracellular bacteria grow only in macrophages, and activated macrophages kill bacteria growing in them better than do macrophages not exposed to interferon-γ, etc.

Transplantation reactions are mediated by T cells recognizing allogeneic MHC molecules

Summary

1. The immune response is a FANTASTICALLY interesting inter-relating set of biological effects that result in protection against pathogens.
2. At times the immune response goes awry, leading to autoimmune disease and allergies.
3. Its difficult to learn immunology in eight days.

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