General Immunology

- Innate vs Adaptive Response
  - Innate-
    - non-specific (4 types of barriers)
      - anatomic- mechanical (skin), pH, mucous, normal flora
      - Physiologic- temperature, pH, chemicals (lysozyme, IFN, complement)
      - phagocytic- monocytes, neutrophils, mϕ
      - inflammatory- tissue damage, serum containing proteins with anti-bacterial properties, influx of phagocytic cells

Anatomic barriers

- Epidermis- physical barrier, until broken
- Sebaceous glands- secrete sebum (maintains skin pH 3-5 due to lactic acid and fatty acid production
- cilia- mucus entrapped organisms pushed up by cilia (influenza have adapted to attach to mucous cells and not be brought up, also adherence by bacteria using fimbriae or pili)

Physiologic Barriers

- Temperature, pH, serum factors
  - temperature range specific for bacteria (chickens body temp too high to be infected with anthrax)
  - pH specific zones of survival
  - serum factors:
    - Lysozyme- tears= destroys peptidoglycan
    - IFN- inhibits viral infection
    - Complement- series of serum proteins that result in lysis of cell membranes

Inflammatory barriers

- Tissue damage initiates series of events leading to inflammatory response
  - vasodilation- of blood vessels entering damaged area and constriction of vessels leading away from damaged area
  - increase in permeability- exudate has higher levels of cells, fluid and protein (edema)
  - influx of phagocytes- margination (adherence of cells to endothelial wall of blood vessels), diapedesis (movement out of cells to tissue), and chemotaxis (directed movement)

Inflammation

- Chemical Mediators:
  - some derived from microorganism, some from damaged cells, some from WBC's, some from plasma enzyme systems
    - Acute Phase Proteins- increase with tissue damage: C-reactive protein= produced by liver and it binds to the C-polysaccharide cell wall component found in bacteria and fungi. Binding activates the COMPLEMENT system
    - Histamine- causes vasodilation and increased permeability
    - Kinins- increase permeability and vasodilation and bradykinin stimulates pain in skin
    - Inc permeability and dilation allow blood clotting factors to enter tissue (fibrin)

Inflammation

- Chemical mediators released by a number of cells: neutrophils, macrophages, eosinophils, lymphocytes, basophils
  - these factors control
    - adhesion- traffic in and out of area
    - chemotaxis- directed movement towards injury
    - activation- specific and non-specific cells
  - chemokines action mediated by receptors which activated signal transduction responses and 2nd messengers (cAMP, IP_3, Ca^{2+}, G proteins, kinases)
  - 15 chemokines and 14 different receptors

Kinin System

- Plasma contains 4 connected mediator producing systems:
  - kinin
  - clotting
  - fibrinolytic
  - complement
- Kinin-
  - begins when a clotting factor (Hageman) is activated at injury-- this activates prekallikrein to form Kallikrein which cleaves kininogen to produce bradykinin (potent vasodilator and permeability factor, causes pain)- also cleaves C5 into C5a and C5b. C5a is an anaphylatoxin that induces mast cell degranulation

Clotting System

- Another protein cascade
  - prothrombin-----> thrombin caused by platelet damage and release of Ca2+.
  - Thrombin acts as catalyst to activate fibrinogen----> fibrin which forms a clot
- Removal of the fibrin clot is mediated by the fibrinolytic system
  - plasminogen----> Plasmin (breaks down clot and biproducts act as chemotaxins for neutrophils). Plasmin also activated classical complement pathway

Complement System

- Activation of C' system results in formation of a number of split products that are mediators of inflammation.
  - Anaphylatoxins (C3a, C4a, and C5a) bind to cell receptors and induce mast cell degranulation with release of histamine & other products (these cause smooth muscle contraction, and increase vascular permeability)
  - C3a, C5a, and C5b67 act to induce monocytes and neutrophils to adhere to vascular tissue and to migrate towards the site of complement activation (Ab-Ag binding)

VISUALIZING CONCEPTS

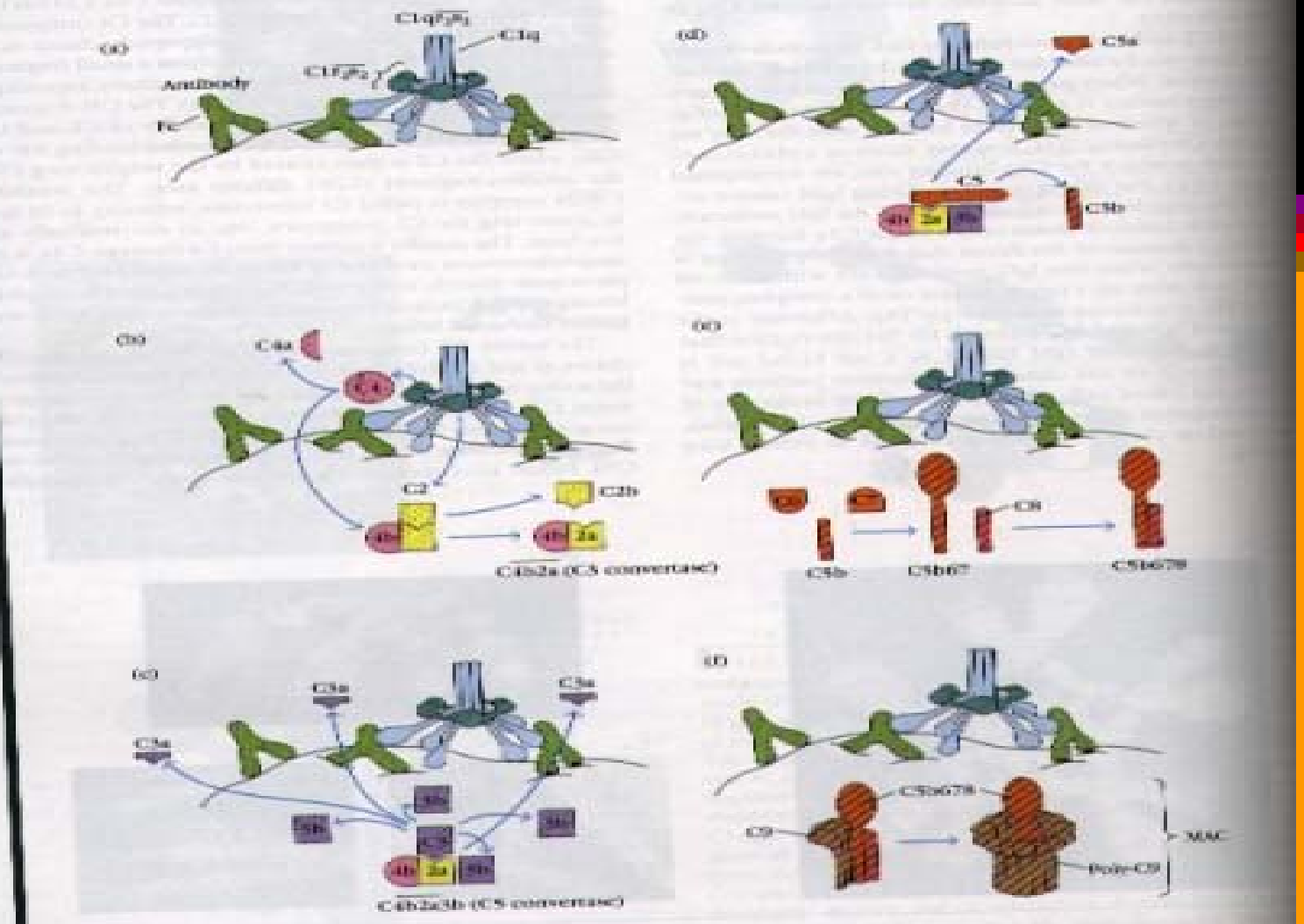

FIGURE 13-5 Schematic diagram of intermediates in the classical pathway of complement activation. Complement components, shown in solid colors, are bound to the antigenic surface but do not penetrate it; components that can insert into the cell membrane are [illegible] with diagonal lines; and the freely diffusible components are stippled. The completed membrane-attack complex (MAC) forms a large pore in the membrane.

TABLE 13-1 CLASSICAL COMPLEMENT PATHWAY: PROTEINS THAT PARTICIPATE IN FORMATION OF C5 CONVERTASE

Component	Active protein/split product	Immunologic function
C1	C1q	Binds to Fc region of IgM and IgG
	C1r	Serine protease: enzymatically activates C1s
	C1s	Serine protease: enzymatically activates C4 and C2
C4	C4a	Peptide mediator of inflammation (anaphylatoxin)
	C4b	Binds C2 forming complex that is cleaved by C1s to yield $\overline{C4b2a}$
C2	C2a	Serine protease: $\overline{C4b2a}$ acts as C3 convertase
	C2b	Unknown function
C3	C3a	Peptide mediator of inflammation (anaphylatoxin)
	C3b	Binds to $\overline{C4b2a}$ to form C5 convertase; major opsonin

Lipid Inflammatory Mediators

- Phospholipids of cell are degraded into arachidonic acid and lyso-platelet-activating factor and then into PAF
- Cyclooxygenase converts arachidonic acid into prostaglandins (PGE2) and thromboxanes (increased vascular permeability, vascular dilation, and PMN chemotaxis)
- AA also metabolized by lipoxygenase to produce leukotrienes (slow-reacting substance of anaphylaxis [SRS-A] which cause smooth muscle contraction and chemotaxis

Acute Inflammation

- Both local and systemic responses
  - swelling, redness, heat, pain and loss of function. Within minutes there is an increase in vasodilation (inc blood flow to area and decreased flow of blood). Vascular permeability increases and edema ensues.
  - Histamine & prostaglandins involved and anaphylatoxins
  - within a few hours neutrophil migrate into site, and macrophages enter 5-6 hours after inflammation begins

Chronic Inflammation

- Develops because of persistence of Ag
  - some microorganisms have cell wall components that resist phagocytosis (encapsulated bacteria and TB)
  - autoimmune disease causes continuous release of self-Ags (SLE)
  - Accumulation of activated macrophages is hallmark of this disease which cause fibroblast proliferation and collagen release (scar tissue forms by process of fibrosis- normal healing process but interferes with normal tissue). May lead to formation of granuloma. Center of granuloma contains “giant cells” formed by fusion of activated macrophages

Anti-Inflammatory Agents

- Agents that reduce Leukocyte migration
  - block adhesion molecules with antibodies
    - ICAM-1 and LFA-1: antibodies to these useful in treating kidney transplant patients
  - Corticosteroids:
    - cholesterol derivatives (prednisone)- reduce number of activated immune cells, decrease number of circulating lymphocytes (lysis or alteration in movement to specific tissue sites). Immature lymphocytes more sensitive to killing by steroids. Also reduce killing ability of macrophages
  - Non-steroidal anti-inflammatory drugs- NSAIDs, inhibit cyclooxygenase

Adaptive Immunity

- Specific Immune Response- Cellular
  - T lymphoyctes-- T_H CD^{4+} and T_c (CD^{8+})
    - Education- Thymus
    - MHC class I and class II proteins
    - self-MHC and foreign Ag receptor
    - recognize processed Ag with self MHC
    - Ag presented by APCs (macrophage, dendritic cells)
    - Kill
      - virally infected cells
      - transplant cells
      - TB cells

Adaptive Immunity

- B cell (Humoral)
  - serum transfers immunity
  - antibody receptor on surface “sees” native Ag
  - 5 classes of Ab’s--- structure & specificity
    - IgG, IgA, IgM, IgE, IgD
    - antigen binding on variable region (VDJ genes and recombination)
    - function (property) of Abs due to constant region
      - cross placenta
      - activate complement
      - bind to IgGR (macrophages) or IgER (mast cells)
      - cross epithelial cell barrier

Antibody Action

- Antibodies work to clear Ag in 4 ways:
  - opsonization- enhanced phagocytosis
  - Blocking- bind to and block viral receptors so that the virus cannot bind to target cell
  - neutralization- bind to active site or binding site of toxins and prevent action
  - complement activation- only antibodies that have combined with antigen are able to bind to and begin activation of complement cascade.
- One B cell is specific for Ag before it encounters Ag. It is able to switch classes of Abs without changing specificity for Ag

Immune System Action

- T cells-
  - virally infected cells
  - internal parasites
  - TB
  - graft (transplant) rejection
  - contact hypersensitivity
- B cells
  - bacteria (no self MHC)
  - soluble viruses
  - toxins (bacterial or other)
  - IgE- parasites

Vaccines

- Passive immunization- transfer of preformed Abs
- Active immunization- activate your own immune response to obtain memory cells (attenuated, dead, protein fragments, live, toxoids)
  - How would you make a vaccine to AIDS?
  - What are the pluses to a vaccine?
  - What are the negatives to a vaccine?
  - Can you clear infectious virus from your system?
    - Difference between retrovirus and RNA and DNA viruses that you can control with a vaccine

Bacterial & Viral Defense

- How do Bacteria protect themselves from immune system?
  - Capsule-- phagocytosis
  - Strep “Protein A”-- binds to IgG/ LPS release
  - intracellular existence
  - spore formation
  - mutation of receptors
- Viruses?
  - Decrease MHC
  - intracellular & genome integration
  - no surface Ag’s/ envelope with cell Ag’s
  - mutation