CHAPTER 7: AUTACOIDS AND THE THERAPY OF INFLAMMATION

I. AUTACOIDS

A. HISTAMINE AND ANTIHISTAMINES

1. HISTAMINE
   a. General Considerations
      1) **Tissue Localization:** stored in the blood in basophils; stored in tissues in
         mast cells; high concentrations in the skin, mucosa of the bronchi, and
         intestinal mucosa; also found in CNS neurons
      2) **Synthesis:** synthesized from histidine by L-histidine decarboxylase
      3) **Metabolism:** two main pathways; metabolites excreted in the urine
         a) Ring methylation -- catalyzed by histamine-N-methyltransferase;
            further metabolized by monoamine oxidase
         b) Oxidative deamination -- catalyzed by diamine oxidase
      4) **Tissue Release:** release and production stimulated by damage to cells
         and tissue; antigen-antibody reactions, snake venoms and drugs (e.g.,
         curare and morphine) also can liberate histamine from tissue stores
      5) **Functions:** involved in hypersensitivity reactions, regulation of gastric
         secretions, and CNS neurotransmission
   b. Receptor Types:
      1) **H₁** -- mediate bronchoconstriction, contraction of the gut and vascular
         dilation
      2) **H₂** -- mediate gastric secretion and vascular dilation
      3) **H₃** -- localized in both the peripheral and central nervous system;
         mediate synthesis and release of histamine from non-mast cell sites
   c. Pharmacologic Effects
      1) **Cardiovascular System:** dilation of small blood vessels results in flushing
         and decreased systemic pressure; increased capillary permeability
         results in edema; effects are mediated by both H₁ and H₂ receptors
         a) **Triple Response:** intradermally injected histamine elicits: 1) a
            localized red spot, 2) a brighter red flush or flare extending about 1
            cm beyond the original red spot, and 3) a wheal that develops in 1-2
            minutes
      2) **Smooth Muscle:** with the exception of vascular smooth muscle (which is
         relaxed), most other smooth muscle is stimulated by histamine.
         Constrictor effects (H₁) are most prominent in the bronchi and uterus;
         responses of intestinal muscle vary, and there are few effects on the
         bladder, gallbladder, ureter and iris
      3) **Glands:** stimulates secretions from the salivary, bronchial and gastric
         glands; effects mediated by H₂ receptors
      4) **Nerve Endings:** stimulates nerve endings causing pain and itching;
         mediated by H₁ receptors
d. Toxicity
   1) Life-threatening symptoms include shock (general vasodilation and a
      marked fall in blood pressure) and severe bronchoconstriction.
      Mediators other than histamine also are involved in the anaphylactic
      response.
   2) Most effective treatment for anaphylactoid reactions is epinephrine;
      antihistamines and glucocorticoids decrease the magnitude of the late
      occurring response (e.g., hives and itching).

e. Clinical Uses
   1) Used diagnostically for: achlorhydria (inability of histamine to induce
      gastric secretions) and pheochromocytoma (histamine-induced release of
      adrenal catecholamines)
   2) Betazole: H₂ agonist used to test for gastric acid-secreting ability

2. H₁ ANTIHISTAMINES
   a. Possess sedative, local anesthetic and anticholinergic properties.
   b. Modify some of the signs and symptoms of histamine release, but do NOT
      prevent the release of histamine from mast cells.
   c. Pharmacologic Effects
      1) Smooth Muscle: antagonize the constrictor action of histamine on
         respiratory and vascular smooth muscle; antagonize the changes in
         capillary permeability produced by histamine that result in edema
      2) CNS: bind to H₁ receptors in the CNS; can cause both depression and
         stimulation; depression commonly occurs with older agents causing
         sedation; stimulation of receptors may cause restlessness, nervousness
         and insomnia; may possess antiemetic effects and be effective against
         motion sickness
      3) Autonomic Nervous System: many antihistamines possess
         anticholinergic properties
      4) Local Anesthetic Effect: some antihistamines have local anesthetic and
         quinidine-like properties
   d. Absorption, Metabolism and Excretion
      1) Well absorbed following oral administration
      2) Widely distributed and extensively metabolized; induce hepatic
         microsomal enzymes; may facilitate their own metabolism; frequently
         eliminated more rapidly by children
      3) Metabolites eliminated in the urine
   e. Side Effects
      1) Sedation: most common; may limit use
      2) Gastric effects: loss of appetite, constipation or diarrhea, nausea and
         vomiting
      3) Anticholinergic effects: dry mouth, cough, palpitations, headache
      4) Allergic dermatitis with topical application
   f. Toxicity
      1) Initial central excitatory effects: hallucinations, excitement, ataxia,
         convulsions, etc.