“Autacoids” (Greek “self-remedy”) is a collective term for various endogenous peptides, prostaglandins, leukotrienes, and cytokines. These are sometimes also called local hormones.

They play important roles in physiologic processes and also have several pharmacological significances.
1. Histamine

- It is a potent tissue amine widely distributed in plant and animal tissues and in the venoms of bees. In man, it is formed by decarboxylation of histidine and major portion is stored in mast cells and basophils.

- Mechanisms of Action: It acts on 2 major types of receptors
  a. Stimulation of H1 receptors results in smooth muscle contraction, increased vascular permeability, and mucus production. These effects are blocked competitively by H1 antagonists.
  b. Activation of H2 receptors increases gastric acid production, and this effect is blocked by H2 blockers such as cimetidine. Both types of receptors are involved in vascular dilatation and edema formation.
Histamine
Histidine $\overset{\text{CO}_2}{\longrightarrow}$ Histamine
Mechanism of Action of Histamine

- **Histamine**
  - **H₁ Receptors**
    - ↑ Ca²⁺
    - Smooth muscle contraction
    - Increased capillary permeability
    - Vasodilation
    - Sensory nerve endings pain & itching
  - **H₂ Receptors**
    - ↑ cAMP
    - ↑ Gastric acid secretion
    - Blood vessels: vasodilation
    - Increased capillary permeability
  - **H₃ Receptors (presynaptic auto receptors)**
    - ↓ cAMP
    - ↓ histamine release
    - ↓ secretion
    - Vasodilation
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<td>Powerful stimulation of sensory endings, especially nerve mediating pain and itching</td>
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1. Cardiovascular system
   - Histamine produces dilatation of capillaries and venules accompanied by a fall in blood pressure. The mechanism is direct relaxation of the smooth muscles of blood vessels. This effect cannot be adequately reversed by antihistaminic agents but by adrenaline.
   - It also has positive inotropic and chronotropic actions on the heart, impairs AV conduction, and increases coronary blood flow.
2. Smooth Muscles:
Histamine directly stimulates the smooth muscles of various tissues including the bronchi and uterus. Histamine–induced bronchospasm is effectively antagonized by adrenaline.

3. Exocrine Glands:
It is a powerful stimulant of HCl secretion by the gastric mucosa.

4. CNS: Histamine is formed locally in the brain and is believed to be a “waking amine”, acting by “increasing the sensitivity of large cerebral areas to excitation inputs”

5. Miscellaneous actions include induction of itching and pain.
1. Exposure to the offending agent should be terminated.
2. Adrenaline has actions opposite to those of histamine and thus acts as a physiological antagonist. It may be given by SC or IM route.
3. Hypotension should be corrected with the infusion of intravenous fluids.
4. Corticosteroids are occasionally used.
5. Other supportive measures include administration of oxygen and artificial respiration if necessary.
N.B. Antihistaminic drugs are not able to counteract the hypotension and brochospasm characteristic of anaphylactic shock.
These drugs competitively block histamine receptors and are of two types:
1. H1 receptor antagonists

H1 Receptor Antagonists
- Classification of H1 receptor antagonists:
  1. Potent and sedative: such as diphenhydramine and promethazine.
  2. Potent but less sedative: such as cyclizine and chlorpheniramine.
  3. Less potent and less sedative: such as pheniramine.
  4. Non-sedative: such as terfenadine, loratadine, and cetirizine.

The newer generation agents are relatively free of central depressant effects. These agents may also possess anti-emetic effects.
Pharmacological Actions:
1. Antihistaminic Actions:—they block histamine effects at various sites.
2. Other Effects: are independent of the antihistaminic effects and vary widely according to the drug used. Most of them produce CNS depression resulting in sedation, drowsiness, inability to concentrate, and disturbances of coordination.
   - But very few agents such as phenindamine may produce stimulation.
   - Anti-motion sickness effects are exhibited by promethazine, diphenhydramine, and dimenhydrinate.
   - Promethazine and mepyramine have significant local anesthetic effect.
   - Majority possess atropine-like effects.
   - Some have central antimuscarinic actions which is useful in the treatment of Parkinsonism.
Pharmacokinetics:
They are well-absorbed following oral and parenteral administration. And are mainly metabolized by the liver; degradation products are removed in the urine.

Therapeutic Uses:
1. Allergic Disorders:—Including urticaria, seasonal hay fever, atopic and contact dermatitis, mild blood transfusion reactions.
N.B. Their topical use is not recommended because of the risk of sensitization and a high tendency to cause eczematous reactions.
2. They are not effective in bronchial asthma and common cold.
2. Other uses:
- Diphehydramine and promethazine are used as hypnotics. Diphenhydramine and orphenadrine are effective in the treatment of Parkinsonism.
- Dimehydrinate and promethazine are employed in the prevention and treatment of motion sickness, other vomiting disorders associated with labyrinthine dysfunction as well as nausea and vomiting associated with pregnancy.
- Diphenhydramine is frequently used in the treatment of cough as combination preparation with other agents.

Adverse Effects:
- Are usually mild. Most common is sedation.
- The most common anticholinergic adverse effect is dryness of the mouth.
- They may themselves occasionally cause allergic reactions.
2. 5-Hydroxytreptamine (Serotonin)

- It is widely distributed in plants and animals. Highest concentration in mammals is found in the pineal gland, acting as a precursor for melatonin.
- It is synthesized from the amino acid tryptophan and acts on several types of receptors.
Tryptophan hydroxylase

L-aromatique amino-acid decarboxylase

5-HTN-acetylase

Hydroxyindole O-methyltransferase

L-tryptophan

CH₂–CH–NH₂

COOH

L-5-Hydroxytryptophan

CH₂–CH–NH₂

COOH

5-Hydroxytryptamine, 5-HT

Serotonin

CH₂–CH₂–NH₂

5-HTN-acetylase

N-acetyl-5-HT

CH₂–CH₂–NH–C—CH₃

Melatonin

H₃CO
Pharmacological Actions:

- 5-HT causes constriction of renal, splanchnic, meningeal, and pulmonary arteries and veins and venules, but dilatation of the blood vessels of skeletal muscles, coronaries, and skin capillaries.

- It has weak direct ino-chronotropic effect on the myocardium.

- It also stimulates smooth muscles, especially of the intestines. Serotonin is widely distributed in the CNS, serving as a neurotransmitter.

- Altered functions may be responsible for disturbances in sleep, mood, sexual behavior, motor activity, pain perception, migraine, temperature regulation, endocrine control, psychiatric disorders and extra-pyramidal activity.
Serotonin Agonists:

- **Sumatriptan** is a selective agonist of 5-HT1 receptors and is highly effective in treating acute attacks of migraine, but is not useful in the prevention. It relieves the nausea and vomiting, but the headache may recur, necessitating repeated administrations.

- It is administered orally or by the subcutaneous route. The bioavailability of oral dose is only 14%; thus, the oral dose is several times larger than the subcutaneous dose.

- **Adverse effects** include flushing and heat at the injection site, neck pain, dizziness, and tingling of the hands.

- The drug is contraindicated with symptomatic ischemic heart diseases, angina, and hypertension as it may cause coronary vasoconstriction.

- **Buspirone**, another serotonin agonist, is a useful effective anxiolytic agent.
Serotonin Antagonists:

a. Methysergide: blocks the actions of 5–HT on a variety of smooth muscles. It also has a weak direct vasoconstrictor effect. It is an effective prophylactic agent for migrainous headaches. But has no effect in treating acute attacks, even may worsen the condition.

**Adverse reactions** include gastrointestinal irritation, drowsiness, vertigo, and psychic disturbances.

b. Cyproheptadine: is a potent antagonist of 5–HT and to a smaller extent of histamine and acetylcholine. It stimulates appetite probably by acting directly on the hypothalamus. It can block the release of hydrocortisone, and the production of aldosterone. It is mainly used to relieve the itching associated with skin disorders such as allergic dermatitis. The common **adverse reaction** is drowsiness.

c. Ondansetron: is specific 5–HT3 receptor antagonist. Given orally or intravenously, it is useful in the management of nausea and vomiting associated with cytotoxic therapy. **Adverse reactions** include headache, constipation, and allergic reactions.

d. Prochlorperazine and haloperidol have anti–5–HT activity and are sometimes used for resistant acute attacks.
Prostaglandins

- Prostaglandins and related compounds are produced in minute quantities by virtually all tissues.
- They generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action.
- Therefore, the prostaglandins do not circulate in the blood in significant concentrations.
- Thromboxanes and leukotrienes are related lipids that are synthesized from the same precursors as the prostaglandins.
- Prostaglandins—unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure.
- Compounds are sometimes referred to as eicosanoids; “eicosa” refers to the 20 carbon atoms.
- All eicosanoids with ring structures: the prostaglandins, thromboxanes, and prostacyclins.
Synthesis of prostaglandins

- Arachidonic acid is the primary precursor of the prostaglandins and related compounds.
- Arachidonic acid is present as a component of the phospholipids of cell membranes.
- Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A2 via a process controlled by hormones and other stimuli.
- There are two major pathways in the synthesis of the eicosanoids from arachidonic acid, the cyclooxygenase and the lipoxygenase pathways.
PGE₂, PGF₂, TXA₂, PGI₂
COX-2 has a larger and more flexible substrate channel than COX-1, and COX-2 has a larger space at the site where inhibitors bind.
**Cyclooxygenase pathway**

- COX-1 gene transcription
- COX-2 gene transcription

**Induced by:**
- Oxidative stress
- Injury
- Ischemia
- Seizures
- Neuro-degenerative diseases

- Glucocorticoids

- mRNA
  - Membrane phospholipids
    - Arachidonic acid
      - COX-1
      - COX-2
    - Nonsteroidal anti-inflammatory drugs (NSAIDs)
    - Selective COX-2 inhibitors
  - Prostaglandins

**Lipoxygenase pathway**

- Membrane phospholipids
  - Arachidonic acid
    - 5-Lipoxygenase
    - Leukotrienes
  - Prostaglandins
Pharmacological Actions:

a. Smooth muscle: most stimulate myometrium and are known to be important in the initiation and maintenance of labor. **Prostaglandin E** has bronchodilator action.

b. GIT: they increase intestinal motility. PG E inhibits gastric acid secretion and has cytoprotective action on the gastroduodenal mucosa.

Both PG E and F produce contraction of the longitudinal muscle of the gut. They also stimulate intestinal fluid secretion, resulting in diarrhea.

c. CVS: PGE is peripheral vasodilator and powerful natriuretic. **PGF** constricts arterioles and veins.
d. Platelets: Thromobxane causes platelet aggregation and vasoconstriction.
  - PG I (prostacycline) is found in the vascular endothelium and is a potent inhibitor of platelet aggregation and is a vasodilator.
e. Miscellaneous: Prostaglandins are important in pain generation and perception.
  - PGE and PGI produce hyperalgesia associated with inflammation. In addition, PG E is a potent pyrogenic substance.
  - Natural prostaglandins have no therapeutic application because of short duration of action, but their derivatives such as carboprost, dinoprostone and misoprostol find clinical application.
Prostaglandins have a major role in modulating pain, inflammation, and fever. They also control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow. Prostaglandins are also among the chemical mediators that are released in allergic and inflammatory processes.
Alprostadil

- Alprostadil is a PGE1 that is naturally produced in tissues such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus.
- Therapeutically, alprostadil can be used to treat **erectile dysfunction**
- In fetal life there is an opening between the pulmonary artery and the aorta. After delivery, this duct or opening will be closed normally. However in some congenital conditions, we need to maintain this opening so the blood can still transfer until we fix the congenital problem.
- keep the **ductus arteriosus open in neonates** with congenital heart conditions until surgery is possible.
- PGE1 maintains the patency of the ductus arteriosus during pregnancy. The ductus closes soon after delivery to allow normal blood circulation between the lungs and the heart.
- Infusion of the drug maintains the ductus open as it naturally occurs during pregnancy, allowing time until surgical correction is possible.
Lubiprostone PGE1 derivative indicated for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation.

- It stimulates chloride channels in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion.
- Nausea and diarrhea are the most common side effects of lubiprostone.
- Nausea can be decreased if taken with food.
Misoprostol

- Misoprostol, a PGE1 analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment.
- Misoprostol interacts with prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion.
- Misoprostol has a GI cytoprotective effect by stimulating mucus and bicarbonate production.
This combination of effects decreases the incidence of gastric ulcers caused by NSAIDs. Misoprostol is also used off-label in obstetric settings for labor induction, since it increases uterine contractions by interacting with prostaglandin receptors in the uterus. Misoprostol has the potential risk to induce abortion in pregnant women. Therefore, the drug is contraindicated during pregnancy. Its use is limited by common side effects including diarrhea and abdominal pain.
Prostaglandin F2α analogs

- Bimatoprost
- latanoprost
- tafluprost
- travoprost
- are indicated for the treatment of open-angle glaucoma.
- By binding to prostaglandin receptors, they increase uveoscleral outflow, reducing intraocular pressure.
- They are administered as ophthalmic solutions once a day and are as effective as timolol or better in reducing intraocular pressure.
- Bimatoprost increases eyelash prominence, length, and darkness and is approved for the treatment of eyelash hypotrichosis.
- Ocular reactions include blurred vision, iris color change (increased brown pigmentation), increased number and pigment of eyelashes, ocular irritation, and foreign body sensation.
Prostacyclin (PGI2) analogs

- **Epoprostenol**, the pharmaceutical form of naturally occurring prostacyclin, and the synthetic analogs of prostacyclin and **treprostinil** are potent pulmonary vasodilators that are used for the treatment of pulmonary arterial hypertension.
- These drugs mimic the effects of prostacyclin in endothelial cells, producing a significant reduction in pulmonary arterial resistance with a subsequent increase in cardiac index and oxygen delivery.
- These agents all have a short half-life.
- Epoprostenol and **treprostinil** are administered as a continuous intravenous infusion,
- **treprostinil** may also be administered orally or via inhalation or subcutaneous infusion.
- Inhaled **iloprost** requires frequent dosing due to the short half-life.
- Dizziness, headache, flushing, and fainting are the most common adverse effects
- Bronchospasm and cough can also occur after inhalation of iloprost.
Aspirin: (Acetyl salicylic acid)

- Aspirin and other nonsteroidal anti-inflammatory drugs are weak organic acids.
- They all inhibit prostaglandin biosynthesis.
- They decrease the production of free radicals and of superoxide and may interact with adenylyl cyclase to alter the cellular concentration of cAMP.
- Aspirin is the drug of choice for treating the majority of articular and musculoskeletal disorders.
- It is also the standard against which all anti-inflammatory agents are compared.
The salicylates are rapidly absorbed from the stomach and upper small intestine.

The acid medium in the stomach keeps a large fraction of the salicylate in the nonionized form, promoting absorption.

However, the drug may damage the mucosal barrier.

Aspirin is absorbed as such and is rapidly hydrolyzed to acetic acid and salicylate by esterases in tissue and blood.

Salicylate is bound to albumin.

Ingested salicylate and that generated by the hydrolysis of aspirin may be excreted unchanged, but most is converted to water-soluble conjugates that are rapidly cleared by the kidney.

Alkalization of the urine increases the rate of excretion of free salicylate.
Mechanism of Action: Aspirin irreversibly blocks the enzyme cyclooxygenase; the drug decreases the formation of both the prostaglandins and thromboxane A2 but not the leukotrienes.

Anti-inflammatory Effects: In addition to reducing the synthesis of eicosanoid mediators, aspirin also interferes with the chemical mediators of the kallikrein system. Thus, aspirin inhibits granulocyte adherence to damaged vasculature, stabilizes lysosomes, and inhibits the migration of polymorphonuclear leukocytes and macrophages into the site of inflammation.

Analgesic Effects: Aspirin is most effective in reducing pain of mild to moderate intensity. Muscular, vascular, and dental origin, postpartum states, arthritis, and bursitis are alleviated by aspirin.

Aspirin acts peripherally through its effects on inflammation but probably also inhibits pain stimuli at a subcortical site.

Antipyretic Effects: Aspirin reduces elevated temperature. The fall in temperature is related to increased dissipation of heat caused by vasodilation of superficial blood vessels. The antipyresis may be accompanied by profuse sweating.

Aspirin blocks the pyrogen-induced production of prostaglandins and the central nervous system response to interleukin-1.

Platelet Effects: Aspirin inhibits platelet aggregation by inhibition of thromboxane synthesis.

Because its action is irreversible, aspirin inhibits platelet aggregation for up to 8 days (until new platelets are formed).
Clinical Uses

- **Analgesic, antipyretics, and anti-inflammatory effects:** Aspirin is one of the most frequently employed drugs for relieving mild to moderate pain of varied origin.

- **Aspirin is not effective** in the treatment of severe visceral pain (acute abdomen, renal colic, pericarditis, or myocardial infarction).

- It and other NSAIDs have been combined with opioid analgesics for treatment of **cancer pain**.

- Used in the treatment of **rheumatoid arthritis**, rheumatic fever, and other inflammatory joint conditions.

- **Inhibition of platelet aggregation:** Aspirin has been shown to decrease the incidence of transient ischemic attacks and unstable angina in men.

- It reduces the incidence of **thrombosis in coronary artery** bypass grafts. It may also reduce the incidence of myocardial infarction.
**Adverse Effects**

- **Gastrointestinal Effects:** the main adverse effect is gastric upset (intolerance).
  - The gastritis that occurs with aspirin may be due to irritation of the gastric mucosa by the undissolved tablet, to absorption in the stomach of nonionized salicylate, or to inhibition of protective prostaglandins.
- **Central Nervous System Effects:** With higher doses, patients may experience "salicylism" tinnitus, decreased hearing, and vertigo reversible by reducing the dosage.
  - Still larger doses of salicylates cause hyperpnea through a direct effect on the medulla.
  - At toxic levels, respiratory alkalosis may occur as a result of the increased ventilation.
  - Later, acidosis supervenes from accumulation of salicylic acid derivatives and depression of the respiratory center.
- **Other Adverse Effects:** Aspirin in a low daily dose usually increases serum uric acid levels, whereas doses exceeding 4 g daily decrease urate levels below 2.5 mg/dL.
  - Salicylates may cause reversible decrease of glomerular filtration rate in patients with underlying renal disease.
Asprin is contraindicated in children with upper respiratory tract infections, because it may precipitate Raye syndrome.
Disease states leading to increased vasoconstrictors

Renal disease
Cardiovascular disease

Cirrhosis
Nephrosis
Heart failure
Diuretics

Decreased renal blood flow
Decreased blood volume

Increased vasoconstrictors:
Angiotensin II
Catecholamines
Vasopressin

Response of renal blood flow

Prostaglandin synthesis normally antagonizes intrarenal effects of vasoconstrictors.

NSAIDs inhibit prostaglandin synthesis, leaving actions of vasoconstrictors unopposed.

Patient treated with NSAIDs

Vasoconstriction
Newer Nonsteroidal Anti-Inflammatory Drugs

- The newer NSAIDs inhibit biosynthesis of prostaglandins.
- In addition, they inhibit chemotaxis, down-regulate interleukin-1 production, and interfere with calcium-mediated intracellular events.
- These drugs are reversible inhibitors of cyclooxygenase.
- Most of these drugs are well absorbed.
- Most of the NSAIDs are highly metabolized, some by phase I and phase II mechanisms and others by direct glucuronidation (phase II) alone.
- While renal excretion is the most important route, all undergo varying degrees of biliary excretion and reabsorption (enterohepatic circulation).
- All of the NSAIDs are highly protein-bound, usually to albumin.
- Ibuprofen
- Diclofenace sodium
- Sulindac
- Mefenamic acid
- Piroxicam
- Indomethacin
- Nimesulide
- Rofecoxib
Celecoxib is a selective COX–2 inhibitor, is significantly more selective for inhibition of COX–2 than COX–1. Unlike the inhibition of COX–1 by aspirin (which is rapid and irreversible), the inhibition of COX–2 is reversible.

Therapeutic uses:

- Celecoxib is approved for the treatment of RA, osteoarthritis, and acute mild to moderate pain.
- Celecoxib has similar efficacy to NSAIDs in the treatment of pain.
**Pharmacokinetics:**

- Celecoxib is readily absorbed after oral administration.
- It is extensively metabolized in the liver by cytochrome P450 (CYP2C9) and is excreted in feces and urine.
- The half-life is about 11 hours, and the drug may be dosed once or twice daily.
- The dosage should be reduced in those with moderate hepatic impairment, and celecoxib should be avoided in patients with severe hepatic or renal disease.
Adverse effects:

- Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects.
- Celecoxib, when used without concomitant aspirin therapy, is associated with less GI bleeding and dyspepsia than other NSAIDs.
- However, this benefit is lost when aspirin is added to celecoxib therapy.
- Patients who are at high risk of ulcers and require aspirin for cardiovascular prevention should avoid the use of celecoxib.
Acetaminophen (N-acetyl-p-aminophenol or APAP)

- inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties. Acetaminophen has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity.

- Acetaminophen does not affect platelet function or increase bleeding time. It is not considered to be an NSAID.
Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of NSAIDs for those patients with gastric complaints/risks, in those whom a prolongation of bleeding time is not desirable, as well as those who do not require the anti-inflammatory action of NSAIDs.

Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox.
Adverse Effects:

- It is hepatotoxic (contraindicated in patients with known liver diseases), and
- also causes hemolytic anemia and methemoglobinemia