CIRCULATING BODY FLUIDS

60% of body weight = water
2/3 intracellular
1/3 extracellular

Of extracellular:
¾ interstitial
¼ intravascular (plasma)

Composition:

- **Intravascular = interstitial** (except interstitial ⇓⇓protein)
- **Intracellular:**
  - **⇓Na ⇓Cl**
  - **⇑K**
  - **⇑Phosphate**
  - **⇑Protein**

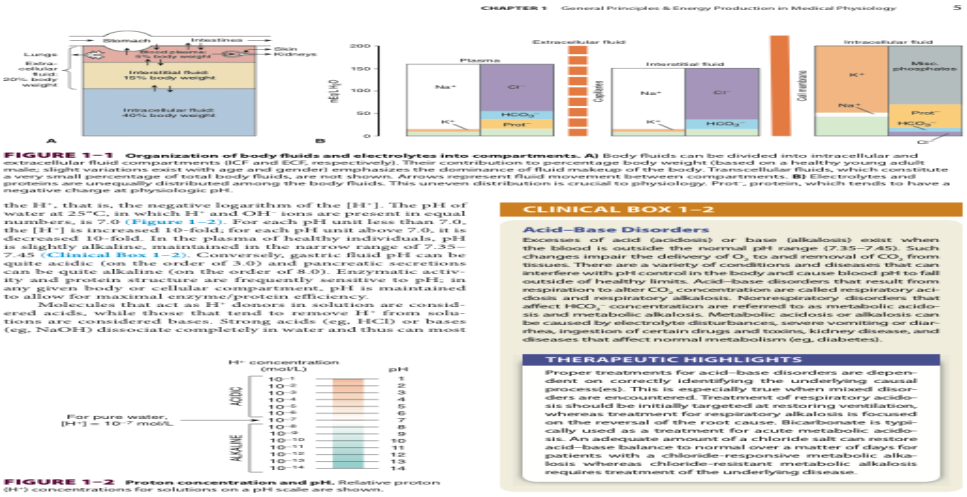


FIGURE 1–1 **Organization of body fluids and electrolytes into compartments.** **A)** Body fluids can be divided into intracellular and extracellular fluid compartments (ICF and ECF, respectively). Their contribution to percentage body weight (based on a healthy young adult male; slight variations exist with age and gender) emphasizes the dominance of fluid makeup of the body. Transcellular fluids, which constitute a very small percentage of total body fluids, are not shown. Arrows represent fluid movement between compartments. **B)** Electrolytes and proteins are unequally distributed among the body fluids. This uneven distribution is crucial to physiology. Prot⁻, protein, which tends to have a negative charge at physiologic pH.

the H^+, that is, the negative logarithm of the $[H^+]$. The pH of water at 25°C, in which H^+ and OH^- ions are present in equal numbers, is 7.0 (Figure 1–2). For each pH unit less than 7.0, the $[H^+]$ is increased 10-fold; for each pH unit above 7.0, it is decreased 10-fold. In the plasma of healthy individuals, pH is slightly alkaline, maintained in the narrow range of 7.35–7.45 (Clinical Box 1–2). Conversely, gastric fluid pH can be quite acidic (on the order of 3.0) and pancreatic secretions can be quite alkaline (on the order of 8.0). Enzymatic activity and protein structure are frequently sensitive to pH, in any given body or cellular compartment, pH is maintained to allow for maximal enzyme/protein efficiency.

Molecules that act as H^+ donors in solution are considered acids, while those that tend to remove H^+ from solutions are considered bases. Strong acids (eg, HCl) or bases (eg, NaOH) dissociate completely in water and thus can most

FIGURE 1–2 **Proton concentration and pH.** Relative proton (H^+) concentrations for solutions on a pH scale are shown.

CLINICAL BOX 1–2

Acid–Base Disorders

Excesses of acid (acidosis) or base (alkalosis) exist when the blood is outside the normal pH range (7.35–7.45). Such changes impair the delivery of O_2 to and removal of CO_2 from tissues. There are a variety of conditions and diseases that can interfere with pH control in the body and cause blood pH to fall outside of healthy limits. Acid–base disorders that result from respiration to alter CO_2 concentration are called respiratory acidosis and respiratory alkalosis. Nonrespiratory disorders that affect HCO_3^- concentration are referred to as metabolic acidosis and metabolic alkalosis. Metabolic acidosis or alkalosis can be caused by electrolyte disturbances, severe vomiting or diarrhea, ingestion of certain drugs and toxins, kidney disease, and diseases that affect normal metabolism (eg, diabetes).

THERAPEUTIC HIGHLIGHTS

Proper treatments for acid–base disorders are dependent on correctly identifying the underlying causal process(es). This is especially true when mixed disorders are encountered. Treatment of respiratory acidosis should be initially targeted at restoring ventilation, whereas treatment for respiratory alkalosis is focused on the reversal of the root cause. Bicarbonate is typically used as a treatment for acute metabolic acidosis. An adequate amount of a chloride salt can restore acid–base balance to normal over a matter of days for patients with a chloride-responsive metabolic alkalosis, whereas chloride-resistant metabolic alkalosis requires treatment of the underlying disease.

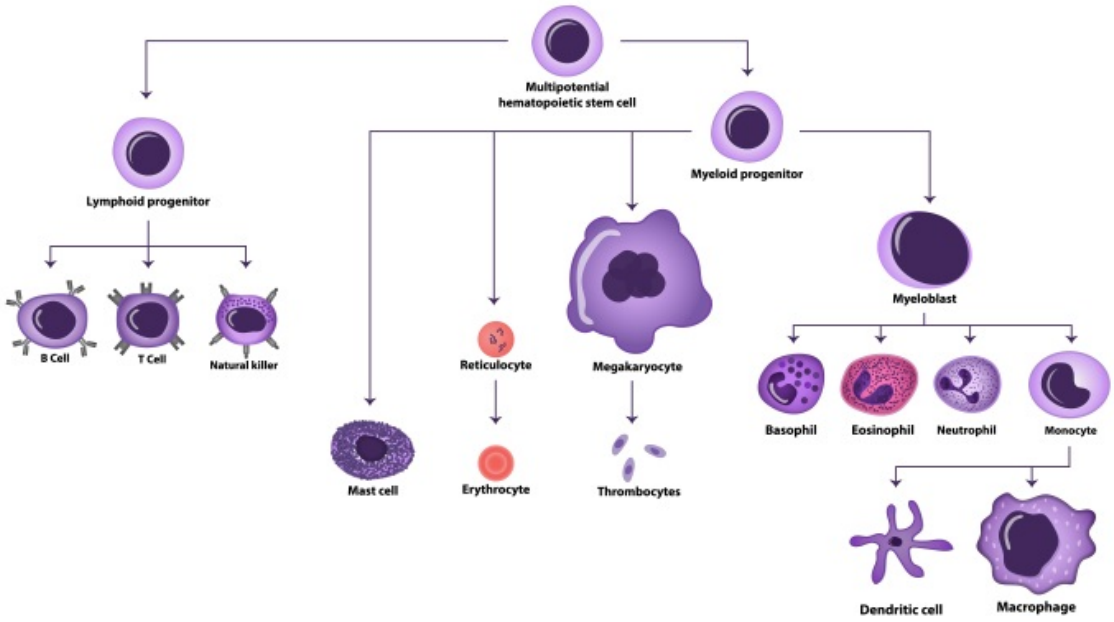
TABLE 39–2 **Principal buffers in body fluids.**

Blood	$H_2CO_3 \rightleftarrows H^+ + HCO_3^-$
	$HProt \rightleftarrows H^+ + Prot^-$
	$HHb \rightleftarrows H^+ + Hb$
Interstitial fluid	$H_2CO_3 \rightleftarrows H^+ + HCO_3^-$
Intracellular fluid	$HProt \rightleftarrows H^+ + Prot$
	$H_2PO_4^- \rightleftarrows H^+ + HPO_4^{2-}$

BLOOD:

- The cellular elements of the blood are suspended in the plasma
- The normal total **circulating blood volume is about 8% of the body weight**
    - About **55% of this volume is plasma (haematocrit 0.45)**

- BONE MARROW:
    - In the adult, RBC, WBC and platelets are formed in the bone marrow
    - In the foetus, blood cells are also formed in the liver and spleen
        - EXTRAMEDULLARY HAEMATOPOIESIS may occur in diseases in which the bone marrow becomes destroyed or fibrosed
    - Active cellular marrow is called **RED MARROW**
    - Inactive marrow that is infiltrated with fat is called **YELLOW MARROW**
    - The bone marrow is one of the largest organs in the body and is one of the MOST ACTIVE
    - HAEMATOPOIETIC STEM CELLS (HSC) are capable of producing all types of blood cells
        - They differentiate into one or another type of COMMITTED STEM CELLS (PROGENITOR CELLS)
        - These in turn form the carious differentiated types of blood cells



WHITE BLOOD CELLS:

- GRANULOCYTES (PMN) are the most numerous of the WBCs
    - Most of these contain neutrophilic granules (NEUTROPHILS)
    - A few contain granules that stain with acidic dyes (EOSINOPHILS)
    - Some have basophilic granules (BASOPHILS)
- The other two types of cell found in peripheral blood are:

    - LYMPHOCYTES (large round nuclei and scanty cytoplasma)
    - MONOCYTES (abundant agranular cytoplasm and kidney shaped nuclei)
- Acting together, these cells provide the body with powerful defenses against tumours and viral, bacterial and parasitic infections
- GRANULOCYTES:
    - Progenitor cells (COMMITTED STEM CELLS) are stimulated to become:
        - Tissue macrophages by **GM-CSF** then M-CSF
        - Neutrophils by GM-CSF then G-CSF
        - Eosinophils by GM-CSF with IL-5
        - Basophils by IL-3 and 4

- **Granulocytes (PMNs):**
    - **Neutrophils**
    - **Basophils**
    - **Eosinophil**
    - **Mast cell**

- **Monocytes:**
    - **Macrophages**
    - **Dendritic cells**

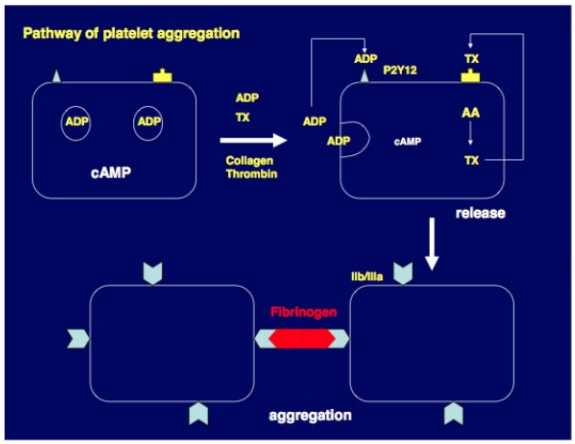
- **Lymphocytes:**
    - **T cells**
    - **B cells**
    - **NK cells**

PLATELETS:

- Small, granulated bodies that aggregate at sites of vascular injury
- They **lack nuclei**
- **Half life = 4 days**
- MEGAKARYOCYTES are giant cells in the bone marrow:
    - They form platelets by pinching off bits of cytoplasm and extruding them into the circulation
    - Between 60-75% of the platelets that have been extruded from the bone marrow are in the circulating blood and the remainder are mostly in the spleen
        - **1/3 platelets are sequestered in the spleen**
        - **Splenectomy causes THROMBOCYTOSIS**
- Membranes of platelets contain receptors for:
    - **Collagen**
    - **ADP (P2Y12)**
    - Vessel wall **VWF**

    - **Fibrinogen (IIb/IIIa receptor)**
    - **Thromboxane A2**
- Their cytoplasm contains:
    - Actin
    - Myosin
    - Glycogen
    - Lysosomes
    - Two types of granules:
        - **DENSE GRANULES**:
            - Contain the **non-protein** substances that are secreted in response to platelet activation
                - **Serotonin**
                - **ADP**
                - Other adenine nucleotides
        - **ALPHA GRANULES**:
            - Contain secreted **proteins** other than the hydrolases in lysosomes
                - **PDGF** (also produced by macrophages and endothelial cells)
                    - Stimulates wound healing and is a potent mitogen for vascular smooth muscle

- When a blood vessel wall is injured, platelet adhere to the exposed collagen and VON WILLEBRAND FACTOR in the wall via the receptors on the platelet membrane
    - The released ADP acts on the ADP receptors (P2Y12) in the platelet membranes to produce further accumulation of more platelets (PLATELET AGGREGATION)
        - Aggregation is also fostered by **PLATELET ACTIVATING FACTOR** (PAF), which is a cytokine secreted by neutrophils and monocytes as well as by platelets



1) Resting (quiescent) platelet:
   - High cAMP
   - ADP in granules
   - 2 surface receptors
     - P2Y12 (receptor for ADP)
     - Thromboxane receptor

2) Activation of platelet by exposure to collagen or thrombin:
   - Reduced intracellular cAMP
   - Release reaction - ADP released from intracellular granule
   - Released ADP can auto-activate platelet via P2Y12 receptor
   - AA –> thromboxane; which also auto-activates platelet

3) Aggregation
   - Expression of new receptor - IIb/IIIa receptor
   - IIb/IIIa receptor cross-links with fibrinogen –> platelet aggregation

- Platelet production is regulated by the **colony-stimulating factors** that control the production of megakaryocytes
- Platelet production also controlled by **THROMBOPOIETIN**:
  - A circulating protein factor
  - Facilitates megakaryocyte maturation
  - Produced constitutively in the liver and kidneys
  - There are thrombopoietin receptors on platelets
  - **When the number of platelets is low, less thrombopoietin is bound to platelets and more is available to stimulate production of platelets**
    - Thus produces a form of FEEDBACK CONTROL of platelet production
- When the platelet count is low, clot retraction is deficient and there is poor constriction of ruptured vessels
  - The resulting syndrome (THROMBOCYTOPENIC PURPURA) is characterised by:
    - Easy bruising
    - Multiple subcutaneous haemorrhages
  - Purpura may also occur when the platelet count is normal:
    - Circulating platelets are abnormal (THROMBASTHENIC PURPURA)

RED BLOOD CELLS:

- Also known as ERYTHROCYTES
- Carry haemoglobin in the circulation
- They are biconcave disks
- Manufactured in the bone marrow
- In mammals, they **lose their nuclei** before entering the circulation

- They survive in the circulation for an average of **120 days**

- RED CELL FRAGILITY:
  - Red blood cells, like other cells, shrink in solutions with an osmotic pressure greater than that of normal plasma
    - In solutions with a lower osmotic pressure they SWELL, becoming more spherical rather than disk-shaped and eventually lose their haemoglobin (HAEMOLYSIS)
    - The haemoglobin of haemolysed red cells dissolves in the plasma, colouring it red
  - In hereditary spherocytosis, the cells are spherocytic in normal plasma and haemolyse more readily than normal cells in hypotonic sodium chloride solutions
    - Spherocytes are also removed by the spleen
  - Red cells can also be lysed by drugs and infections
    - The susceptibility to haemolysis by these agents is increased by deficiency of the enzyme **glucose 6-phosphate dehydrogenase**
- ROLE OF THE SPLEEN:
  - The spleen is an important blood filter that removes spherocytes and other abnormal red cells
  - It also contains many platelets and plays an important role in the immune system
  - Abnormal red cells are removed if they are not as flexible as normal red cells and consequently are unable to squeeze through the slits between the endothelial cells that line the splenic sinuses
- HAEMOGLOBIN:
  - Red, oxygen-carrying pigment in the RBC of vertebrates is HAEMOGLOBIN
    - Globular molecule made up of four subunits
    - Each subunit contains a **haem moiety conjugated to a polypeptide**
      - Two polypeptides are alpha subunits
      - The other two are beta subunits
    - **Haem is an iron-containing porphyrin derivative**
  - CATABOLISM OF HAEMOGLOBIN:
    - When old red blood cells are destroyed in the tissue macrophage system, the **globin portion** of the haemoglobin molecule is split off and the haem is converted to BILIVERDIN
      - Enzyme involved is a subtype of haem oxygenase
      - In humans, most of the biliverdin is converted to BILIRUBIN and excreted in the bile
      - **Haem → biliverdin → bilirubin**
    - The iron from the haem is reused for haemoglobin synthesis

- BLOOD TYPES:
  - THE ABO SYSTEM:
    - **The A and B antigens are inherited as MENDELIAN DOMINANTS**
    - The four major blood groups are divided on this basis
      - Type A individuals have the A antigen
      - Type B have the B and type AB have both
      - Type O have neither antigen
    - **A and B antigens are actually <u>complex oligosaccharide that differ in their terminal sugar</u>**
    - **IgM antibodies against red cell agglutinogens are called AGGLUTININS**
      - **Antigens very similar to A and B are common in intestinal bacteria** and possibly in food to which newborn individuals are exposed
        - Therefore, infants rapidly develop antibodies against the antigens not present in their own cells
        - TYPE A develop anti-B antibodies
        - Type B individuals develop anti-A antibodies
        - Type O individuals develop BOTH A and B antibodies
        - Type AB develop neither
      - When the plasm of a type A individual is mixed with type B red cells, the anti-B antibodies cause the type B red cells to clump (agglutinate)
      - Blood typing is performed by mixing an individual's red cells with antisera containing various agglutinins on a slide and seeing whether agglutination occurs
  - OTHER AGGLUTINOGENS:
    - In addition to the ABO system of antigens there are other systems:
      - Rhesus
      - MNS
      - Lutheran
      - Kell
      - Kidd
      - Many others
    - THE RH GROUP:
      - The system has not been detected in tissues other than red cells
      - D is by far the most antigenic component
        - "RH-positive" normally means that the individual has agglutinogen (antigen) D
        - **85% of Caucasians are Rh positive**

- **Anti D antibodies do not develop without exposure of a D-negative individual to D-positive red cells by transfusion or entrance of foetal blood into the maternal circulation**

- HAEMOLYTIC DISEASE OF THE NEWBORN:
  - Arises when an Rh-negative mother carries an Rh-positive foetus
  - Small amounts of foetal blood leak into the maternal circulation at the time of delivery
    - Some mothers develop significant titres of anti-Rh agglutinins during the postpartum
    - During the next pregnancy, the mothers agglutinins **(IgG)** cross the placenta to the foetus
    - In addition, there are some cases of foetal-maternal haemorrhage during pregnancy and sensitisation during pregnancy
  - In any case, when anti-Rh agglutinins cross the placenta to an Rh-positive foetus, they can cause haemolysis and various forms of **haemolytic disease of the newborn (ERYTHROBLASTOSIS FOETALIS)**
    - If haemolysis is severe, the infant may **die in utero**
    - Alternatively, they may develop **anaemia, severe jaundice and oedema (HYDROPS FOETALIS)**
  - It is usually possible to prevent sensitisation from occurring the first time by administering a single dose of anti-Rh antibodies in the form of Rh immune globulin during the postpartum period
    - Such passive immunisation does not harm the mother and has been demonstrated to prevent active antibody formation by the mother

- Anti-AB agglutinins: IgM
- Anti-Rhesus: IgG

PLASMA:

- This is the FLUID PORTION OF THE BLOOD
- It is a remarkable solution containing an immense number of ions, inorganic molecules and organic molecules that are in transit to various parts of the body or aid in the transport of other substance
- If whole blood is allowed to clot and the clot is removed, the remaining fluid is called SERUM:
  - **Serum has the same composition as plasma except that its fibrinogen and clotting factors 2, 5 and 8 have been removed**

- PLASMA PROTEINS:
    - Consist of:
        - **ALBUMIN**
        - **GLOBULIN**
        - **FIBRINOGEN**
    - The capillary walls are relatively impermeable to the proteins in plasma and the proteins therefore exert an osmotic force of about **25mmHg across the capillary wall (ONCOTIC PRESSURE)**
    - The **plasma proteins are also responsible for 15% of the buffering** capacity of the blood, because of the weak ionisation of their substituent COOH and NH2 groups
        - **At the normal plasma pH of 7.40, the proteins are mostly in the ANIONIC FORM**
    - Other plasma proteins, such as ANTIBODIES and the CLOTTING FACTORS have specific functions
    - Some of the proteins function in the transport of thyroid, adrenocortical, gonadal and other hormones
        - Binding keeps these hormones from being rapidly filtered through the glomeruli and provides a stable reservoir of hormone on which the tissues can draw
        - In addition, albumin serves as a carrier for metals, ions, fatty acids, amino acids, bilirubin, enzymes and drugs

LYMPH:

- Lymph is tissue fluid that enters the lymphatic vessel
- It drains in to the venous blood via the thoracic and right lymphatic ducts
- It contains clotting factors and clots on standing in vitro
- In most locations, it also contains proteins that traverse capillary walls and return to the blood via the lymph
- **Its protein content is generally lower than that of plasma** but lymph protein content varies with the region from which the lymph drains
- Water **insoluble fats are absorbed from the intestine into the lymphatics** and the lymph in the thoracic duct after a meal is milky because of its high fat content
- **Lymphocytes enter the circulation principally through the lymphatics** and there are appreciable number of lymphocytes in the thoracic duct lymph