Calcium Metabolism

(1)

Essential physiological functions of Calcium

- Maintenance of normal excitability of Nerve & muscle
- Release of neurotransmitters / many hormones
- Muscle contraction
- coagulation of blood
- formation of bone & teeth & Production of milk
- activity of many enzymes

Mustafa

More than 98% of body calcium is found in bone

The concentration of Calcium in the plasma is approximately 2.5 mmol L^{-1}

- 1.5 mmol is ionized
- 1 " " bound to plasma proteins

Ca^{++} metabolism

- Vit. D
- Parathyroid hormone (PTH)
- Calcitonin

- Essential for normal bone development
- in animals present as Vit. D_3 (cholecalciferol)
- Deficiency
  - in children → Rickets → stunted growth, bowing of legs
  - in adults → failure of ossification (osteomalacia)
- Acts on gut & bone → to increase extracellular concentrations of Calcium & Phosphate
- It is first converted to a 25-hydroxy derivative in the liver & then in the kidney to 1,25 dihydroxy-cholecalciferol (1,25-DHCC)

If the extracellular concentrations of Calcium or phosphate are low ???

→ 1,25-DHCC acts on: (2)

① Small intestine to promote the absorption of Calcium & phosphate

② with parathyroid hormone → causes bone resorption and release of these ions from bone

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In Vit. D deficiency → insufficient calcium is absorbed in the gut & bone calcium is depleted

* If extracellular concentrations of Ca^{+2} / PO_4 are normal → most of the vitamine is transformed in the Kidney to 24,25-dihydroxy derivative (degradation product)

Parathyroid hormone (PTH)

Actions

PTH → increases ionized plasma Calcium

→ lowers plasma phosphate concentration

Acts on

bone ?? increase the rate of bone resorption by stimulating the activity of osteoclast (indirect effect) & osteocyte

longterm* effect

kidney → compensate for short term effects

Acts on the nephron tubules and increases Reabsorption of Calcium and decreases that of phosphate

indirectly on gut (increases the formation of 1,25-DHCC in the Kidney)

Remember that a major stimulus for the release of PTH is Chronic hypocalcemia in renal failure

Calcitonin

↳ a polypeptide secreted by the Parafollicular C cells of the thyroid gland

↓

It decreases plasma calcium by decreasing the rate of resorption of bone

↓

It has been suggested that calcitonin protects animals against hypercalcemia !!

↓

the physiological significance of this hormone is unclear

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Blood cell types → 3 major classes
- → Red blood cells (RBCs) (erythrocytes)
- → White blood cells (WBCs) (leucocytes)
- → platelets (thrombocytes)

All are formed in the bone marrow → a process known as **haemopoiesis**

Erythrocytes — involved in transport of O_2 & CO_2
function exclusively within the vascular system

Leucocytes — important part of defence & immune system
act mainly OUTSIDE blood vessels in the TISSUES

platelets — play a vital role in the control of bleeding (haemostasis) by a) plugging the defects in blood vessels b) activating the blood clotting cascade

Methods used to study blood & bone marrow

→ to make a smear on a glass slide

After fixation, stained by a **Polychromatic stain** (Giemsa, Wright, leishman)

(4) distinctive staining characteristics (according to the affinity of the various cellular organelles to the different stains employed)

(a) Basophilia (deep blue): affinity for the basic dye methylene blue → characteristic of DNA in nucleus & RNA in the cytoplasm e.g. Ribosomes

(b) azurophilia (purple) → affinity for azur dyes, typical of lysosomes (azurophilic granules in leucocytes)

(c) eosinophilia (Pink) → affinity for acidic dye (eosin)
particular feature for hemoglobin within erythrocytes

(d) neutrophilia (salmon Pink/lilac): characteristic of the ~~specific cytoplasmic granules~~ of neutrophil leucocytes (the dye is not of neutral pH)

White blood cells

5 types of leucocyte are normally present in the circulation → depending on their nuclear shape & cytoplasmic granules

Granulocytes
* Neutrophils
* eosinophils
* basophils

Mononuclear leucocytes
* lymphocytes
* monocytes

Granulocytes

- So named → their prominent cytoplasmic granules
- Each cell → type-specific granules (N, E, B)
- Single multilobed nucleus (old concept → multinuclear)

Polymorphonuclear leucocyte (Polymorph) ? the multilobed nucleus may assume many morphological shapes !!
→ mostly used to refer to neutrophils !!

Lymphocytes & monocytes → have Non-lobulated nuclei (Mononuclear !!)
↓
Agranulocytes (old term !!)
< they are not devoid of cytoplasmic granules >

Recall → lymphocytes play a key role in all immune responses → in contrast to the other leucocytes their activity is always directed against specific foreign agents

Neutrophils & monocytes → highly phagocytic & engulf microorganisms, cell debris → in a Non-specific manner

All the leucocytes perform their functions in the tissues & merely use the blood as a vehicle for transit between sites of formation → storage → activity

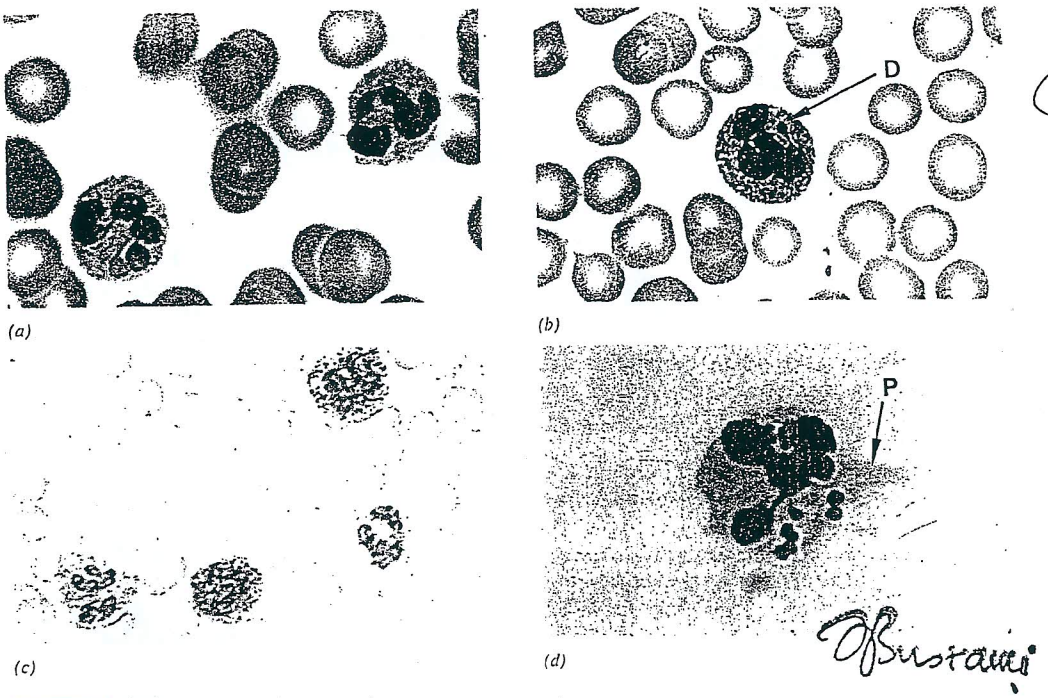

FIG 3.4 Neutrophils (a) Giemsa × 1200 (b) Giemsa × 1200
(c) Histochemical method for alkaline phosphatase × 800 (d) Giemsa × 2400

Neutrophils → the most common type of leucocyte in blood & constitute **40–75%** of circulating leucocytes

→ characterized by the **shape of the nucleus** which contains **small lobes** connected by thin filaments

↓

When **mature** → there are usually **5 lobes** connected by fine strands of nuclear material. In less mature neutrophils the nucleus is less lobulated.

Neutrophil of ♀ → the condensed quiescent **X-chromosom** or **Barr body** exists in the form of a small drumstick-shaped appendage of the nuclear lobes ⇒ visible in about **3% of neutrophils** in Peripheral blood.

Cytoplasm contains **2 types of granules**:

- The most numerous are the specific granules (barely visible by light microscopy) which are small and take on a pinkish colour. These granules contain **Lysozyme** an enzyme complex that act against bacterial cell wall, the protein **Phagocytin** is present and also has bactericidal activity

The azurophilic granules are less numerous somewhat larger and stain a reddish purple. They are modified large lysosomes and contain the usual lysosomal hydrolases and a number of bactericidal agents including myeloperoxidase → this can be demonstrated by the peroxidase stain and is used as a marker for the primary (azurophilic) granules and for identification of leukaemia arising in neutrophil precursors

Functions of Neutrophils

Being highly motile & phagocytic → their principle function is in the (Acute inflammatory response) to tissue damage where they ingest & destroy damaged tissue & invading bacteria

↓

Neutrophils in the circulation are attracted by the presence of organisms, particularly bacteria → This process is mediated by chemotactic factors (chemotaxins) released from damaged tissue & generated by the interaction of antibodies with antigens on the surface of micro-organisms.

↓

The COATING of organisms with antibodies & complement greatly enhances neutrophilic phagocytic activity → opsonisation ←

↓

organisms which do not generate chemotaxins or become opsonised → are relatively resistant to neutrophil phagocytosis & are thus highly pathogenic

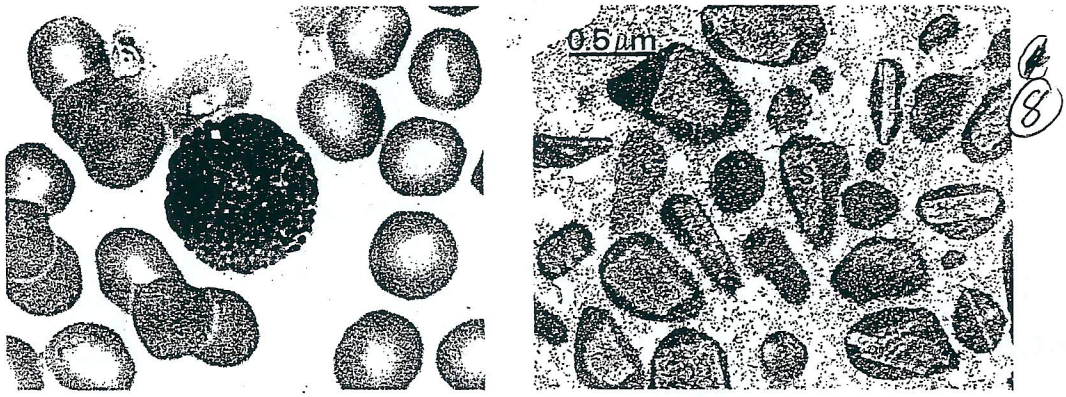

Fig. 3.6 Eosinophils (a) Giemsa × 1600 (b) Human EM × 25 000 (c) Mouse EM × 20 000 *(opposite)* (d) Rat EM × 25 000 *(opposite)*

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Eosinophils: account for **1–6%** of leucocytes in circulating blood ⇒ their numbers exhibit a marked diurnal variation, being greatest in the morning and least in the afternoon.

↓

→ The eosinophil (12–17 μm) in diameter, is larger than the neutrophil → easily recognized by its large specific granules which are stained Bright red é eosin

→ most cells have bilobed nucleus (often partly obscured by cytoplasmic granules)

↓

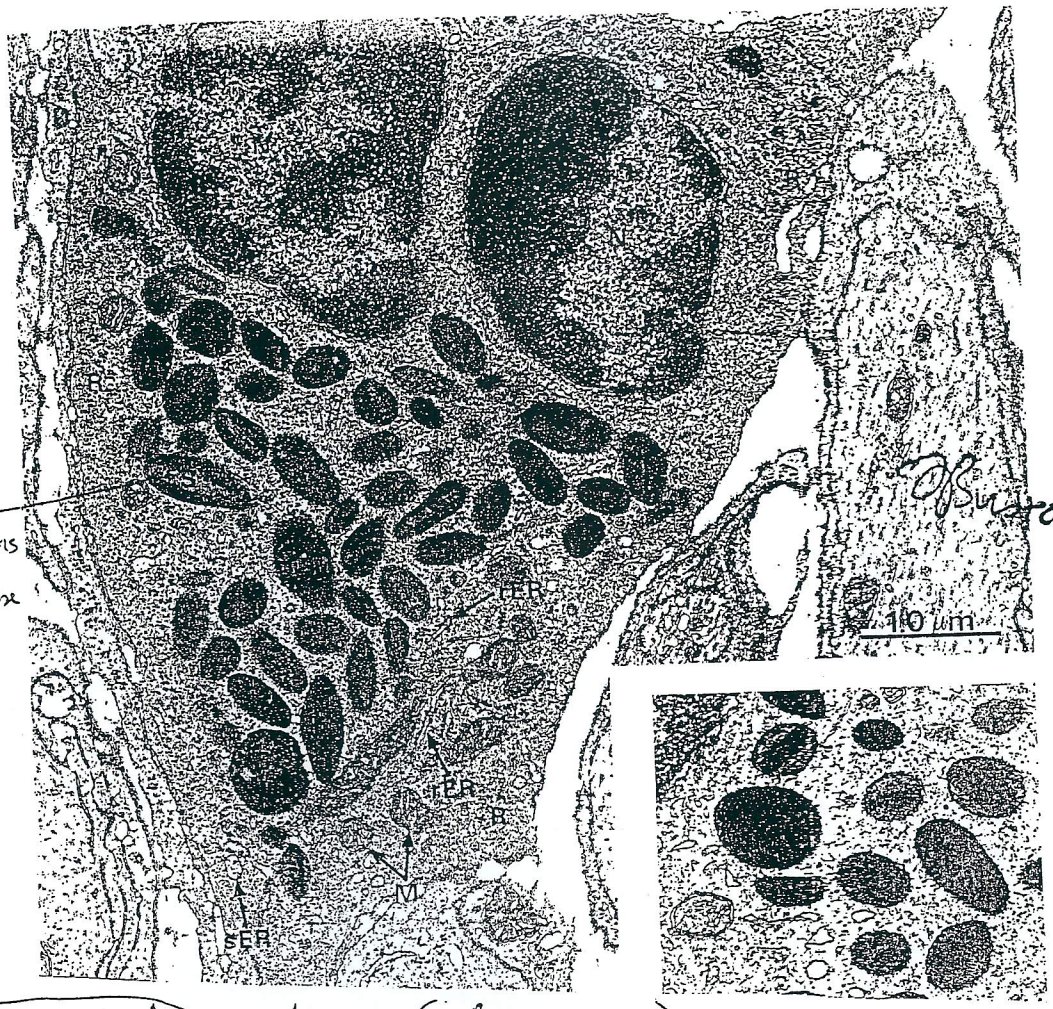
The granules are membrane-bound and shows an internal structure that has been called a crystalloid or internus (In Man it assumes various forms and is translucent

The eosinophils granules are lysosomes (including histaminase) and contain the usual lysosomal enzymes → They show a higher content of peroxidase than do the azurophilic granules of neutrophils & lack lysozyme & phagocytin

↓

Eosinophils are phagocytic cells But less bactericidal than neutrophils, however they have a particular phagocytic affinity for antigen-antibody complex

All eosinophils have receptors for IgE (important in the destruction of parasites) → this is Not present on neutrophils



Contains peroxidase

Eosinophils undergo (chemotaxis) in response to (histamine) & eosinophil chemotactic factor of anaphylaxis (ECF-A) released from basophils & mast cell.

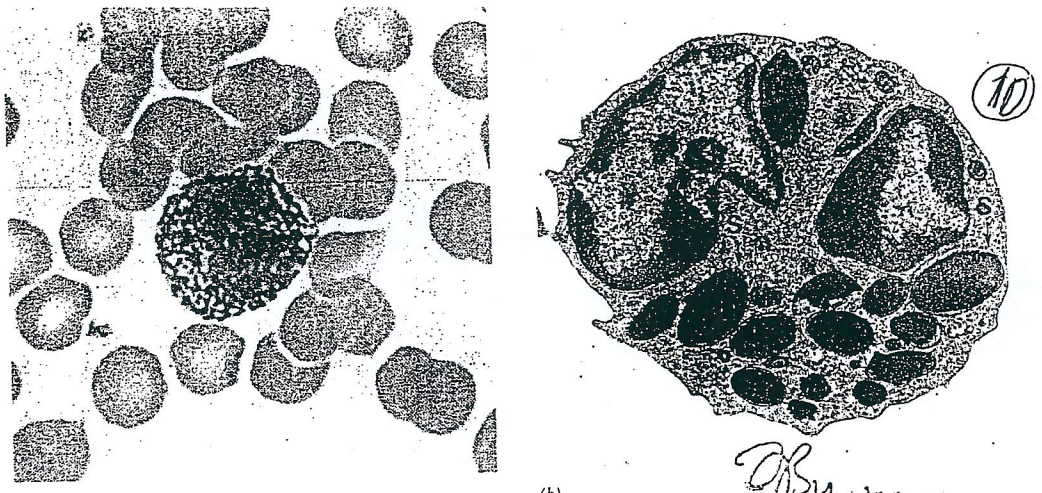
Eosinophils → ameliorate (تخفف) some aspects of hypersensitivity reactions ?? → they neutralize histamine & produce a factor → eosinophil-derived inhibitor which inhibits mast cell degranulation

Eosinophilia → ↑ No. of circulating eosinophils are found in ① many types of parasitic disease (defence against parasites is one of their principle functions) ② In some allergic disease e.g hay fever & asthma → their role here ??

From bone marrow → circulation (3-8 hours) → enters { skin, pulmonary mucosa, GI mucosa

→ local secretion

Fate & lifespan → unknown !!



(a) (b)

Fig. 3.7 Basophils (a) Giemsa × 1500 (b) EM × 10 500

Basophils

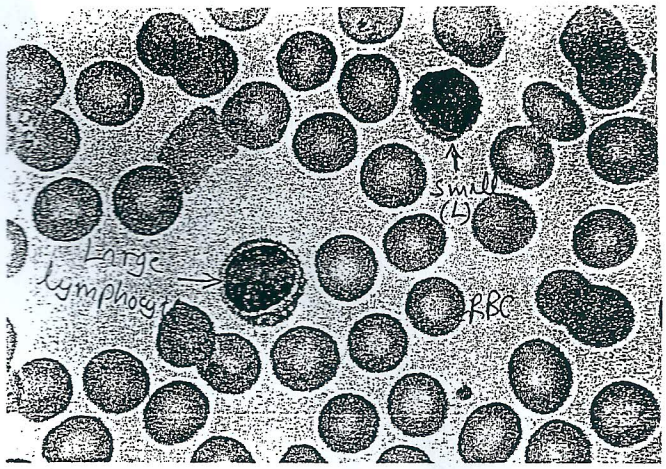
- least common leucocyte
- constitutes less than 1% of leucocytes in circulating blood.
- lifespan → unknown (few days !!)
- ~14–16 µm in diameter (intermediate between N & E)
- bilobed nucleus obscured by large densely basophilic (deep blue) specific granules which are larger but fewer in number than those of eosinophils → granules are metachromatic !! they contain proteoglycans. The granules contains heparin, histamine, eosinophil chemotactic factor of anaphylaxis (ECF-A)

Basophil & mast cells → have membrane receptors highly specific for the Fc segment of IgE which is produced by plasma cells in response to a variety of allergens

① Exposure to allergen results in antigen forming bridges between adjacent IgE molecules which triggers rapid exocytosis of granules (degranulation)

② The release of histamine & other mediators is responsible for the so called → immediate hypersensitivity (anaphylactoid) reaction characteristic of
- allergic rhinitis (hay fever)
- some forms of asthma
- urticaria
- anaphylactic shock

Basophils → account for up to 15% of infiltrating cells in allergic dermatitis & skin allograft rejection
→ Cutaneous basophil hypersensitivity



(a)

Lymphocytes

① the smallest cells in the white cell series (slightly larger than erythrocytes)

② the second most common leucocyte in circulating blood & make up 20–25% of the differential white cell count

③ increased numbers are commonly seen in viral infections

④ characterised by large round densely stained nucleus & a relatively small amount of basophilic non-granular cytoplasm

⑤ The amount of cytoplasm depends upon state of activity of the lymphocyte ⇒ In circulating blood there is predominance of small inactive lymphocytes (6–9 μm in diameter). Large lymphocytes (9–15 μm) make up about 3% of lymphocytes in peripheral blood ⇒ Represent activated B lymphocytes en route to the tissues where they will become antibody-secreting plasma cells, they also include natural killer cells

↓

In the large lymphocyte → the cytoplasm is readily visible but in the small lymphocyte the cytoplasm is almost too sparse to be seen (contain few mitochondria, rudimentary Golgi apparatus, minimal endoplasmic reticulum but larg No. of ribosomes → account for basophilia (blue cytoplasm)

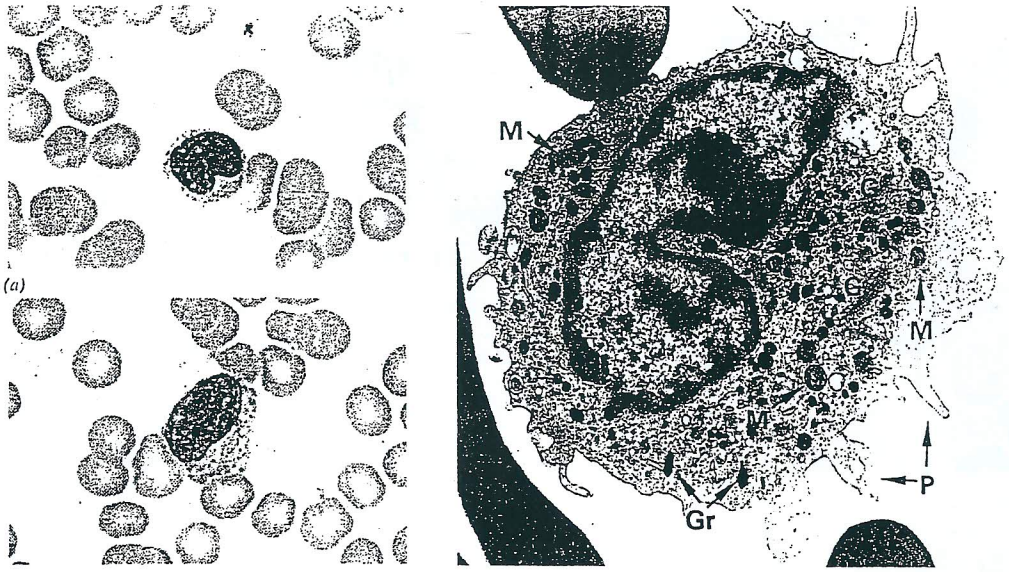


Fig. 3.9 Monocytes (a) Giemsa × 1000 (b) Giemsa × 1000 (c) EM × 20 000

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Monocytes:
- the LARGEST of white cells (up to 20 μm in diameter)
- constitute 2–10% of Leucocyte in peripheral blood
- highly motile & Phagocytic
- Precursor of MACROPHAGES found in peripheral tissues & lymphoid organs

nucleus:
- large eccentric stained less intensely than that of other leucocytes
- often with deep indentation (+) 2-3 nucleoli

cytoplasm:
- stain pale greyish-blue
- contains small pink-purple lysosomal granules
  → at EM → primary lysosomes similar to azurophilic granules of neutrophils (contain acid phosphatase & peroxidase)

Monocytes–macrophage system → monocytes migrate to peripheral tissues where they assume the role of macrophages → This has led to the concept of a single functional unit (precursors in bone marrow → circulating monocytes → tissue macrophages)

Included in this system are → Kupffer cells of liver, microglia of CNS, Langerhans cells of the skin, Antigen-presenting cells of lymphoid organs (APC), osteoclasts of bone

The system does not include : vascular endothelial cells or reticular cells & fibroblasts of lymphoid organs which may exhibit some phagocytic activity

Multinucleate giant cells → may form by fusion of macrophages or nuclear reduplication

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Monocyte function → little function in circulating blood

they migrate into the tissues & differentiate into macrophages in response to
- presence of necrotic material (necrotaxis)
- invading microorganisms (Chemotaxis)
- inflammation

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↓

- have great capacity for phagocytosis
- large content of hydrolytic enzymes

form an integral part of immunological mechanisms e.g (Antigen presentation
(final destruction of antigen)

↓

Lymphocyte activation results in the production of factors which enhance macrophage phagocytic activity