LEUCOCYTES 1

MBChB 2 lecture series

Dr Jessie N. Githang'a

Lecture outline

- Classes of leucocytes
- Review of leucopoiesis
- Normal reference ranges of leucocytes
- Functions of leucocytes
- Classification of leucocyte disorders
- Benign leucocyte disorders:
  - Leucocytosis
  - Leucopenia
  - Leukamoid and leucoerythroblastic reactions

Lecture objective

- By the end of the lecture you should know:
  - Leucopoiesis, the leucocyte classes, their reference ranges and function.
  - The classification of the leucocyte disorders and the benign leucocyte disorders.

White cells in circulation

- Normal reference range 4 – 11 x 10^9/L (3.5 – 10 x 10^9/L)
- Granulocytes (Polymorphonuclear cells)
  - Neutrophils
  - Eosinophils
  - Basophils
- Agranulocytes
  - Monocytes
  - Lymphocytes

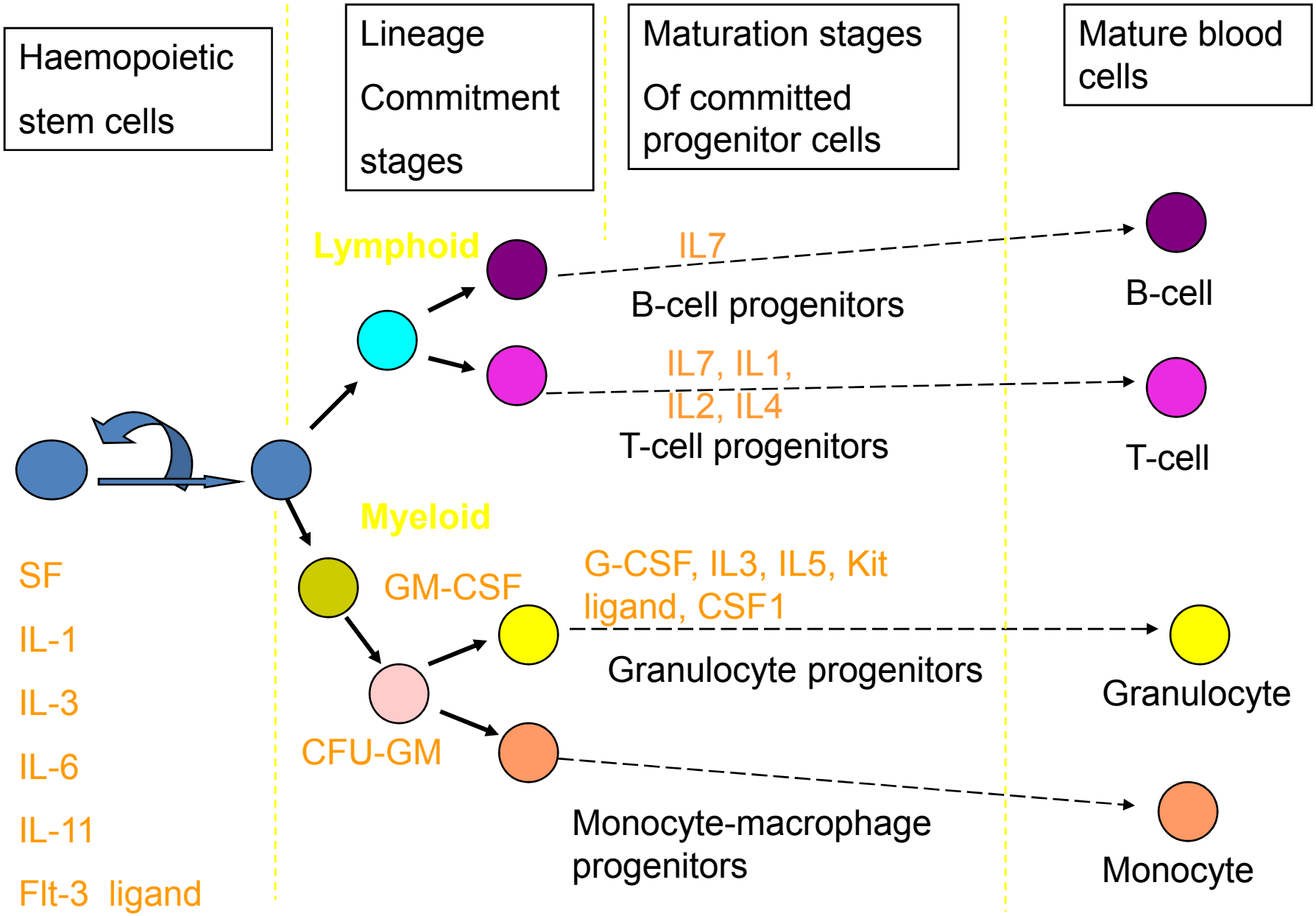


FIG 1 Leucopoiesis

PHAGOCYTES

Granulocytes + macrophages:

- Bone marrow derived cells that engulf & digest particulate matter
- Essential for host response to infection, inflammation.
- Secrete cytokines, digest senescent cells, debris.

Neutrophils

- $2 – 7 \times 10^9/L$; (40 – 75%)
- 14 days to maturation
- “Storage” pool in marrow
- Circulating pool – t ½ is 6-10 hours
- Major role is to protect host against infectious agents

Neutrophil function

- Respond to chemotactic signals and leave capillaries by margination, following which they emigrate between the endothelial cells (diapedesis/extravasation)
- Phagocytosis

Regulation of neutrophil function

- Cytokines are basic regulators of all neutrophil functions
- Neutrophils also synthesize and secrete small amounts of some cytokines including IL-1, IL-6, IL-8, TNF-, and GM-CSF
- These are pyrogenic, pro-inflammatory and neutrophil activating
- Cytokines also increase the microbiostatic and killing capacities of neutrophils against bacteria, protozoa and fungi.

Eosinophils

- $0.04 – 0.6 \times 10^9/L$ (1 – 6%)
- Produced in BM
- “Storage” pool in BM
- IL-5 key role in proliferation and differentiation
- T ½ in circulation similar to neutrophils
- Life span in tissues up to several weeks
- Localise to areas exposed to external environment
- Charcot-Leyden crystals seen in areas of eosinophil degeneration

Functions of eosinophils

- Defense against helminths
- Immunosuppression of immediate hypersensitivity reaction
- Response to certain tumours
- Activation via chemotaxis leads to phagocytosis and degranulation

Basophils

- $<0.1 \times 10^9/L$ ($\leq$ 1%)
- Mature in 7 days in marrow
- Have vasoactive & immunomodulatory chemicals in granules
  - Histamine, released by circulating basophils and tissue mast cells causes capillary and venular dilatation
- Are effector cells in certain hypersensitivity reactions (possess membrane receptors for IgE & C^l)

Monocytes

- $0.2 – 0.8 \times 10^9/L$ (2-10%)
- Monocytes circulate in the peripheral blood prior to emigration into the tissues to become tissue macrophages
  - Kupfer cells (lver)
  - Microglia (brain)
  - Mesangial cells (kidney)
  - Osteoclasts (bone)
- Phagocytosis is mediated by macrophages and polymorphonuclear leucocytes.

Lymphocytes

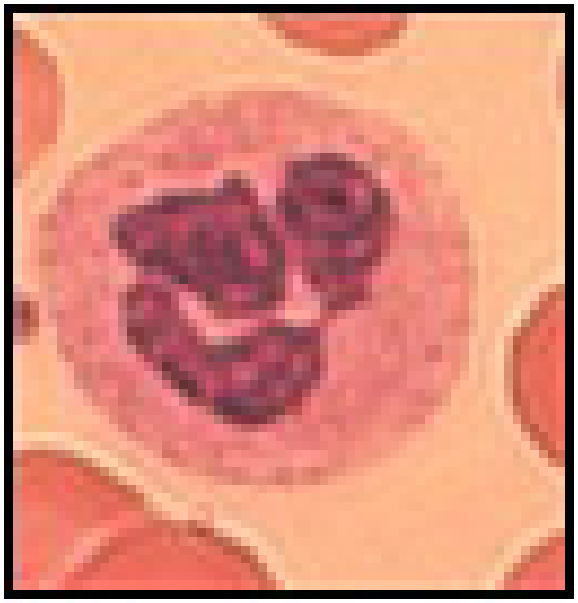
- $1.5 – 3.5 \times 10^9/L$ (20 – 40 %)
- Two broad categories of lymphocytes:
  - Small lymphocytes –T and B-cells
  - Large granular lymphocytes - Natural killer cells
- B-lymphocytes are produced within bone marrow (a primary lymphoid organ)
- T-lymphocytes are produced in the thymus (also a primary lymphoid organ)
- Secondary lymphoid tissue – Spleen, lymph nodes, adenoids, tonsils and mucosa associated tissue (MALT).

Lymphocyte function

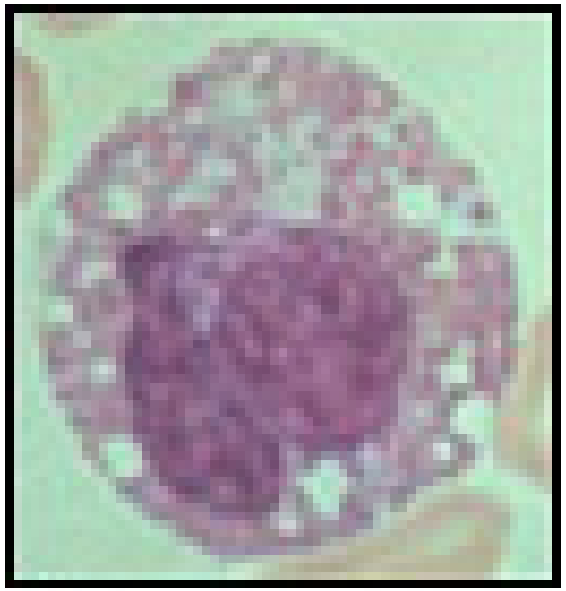
- Lymphocytes respond to presented antigens by production of:
  - **Antibodies** (by B cells)
  - **Lymphokines** (T and B cells). These have many actions including control of the adaptive immune response by secondary action on the participating cells, and, in the case of cytolytic T cells, in killing virally-infected host cells.
  - *T cells* are chiefly responsible for cell-mediated immunity whereas *B cells* are primarily responsible for humoral immunity (relating to antibodies)

- *NK cells* are a part of cell-mediated immunity (CMI) and act during the innate immune response
- They can attack host cells that display a foreign (e.g. viral) peptide on particular cell surface proteins known as MHC class I molecules

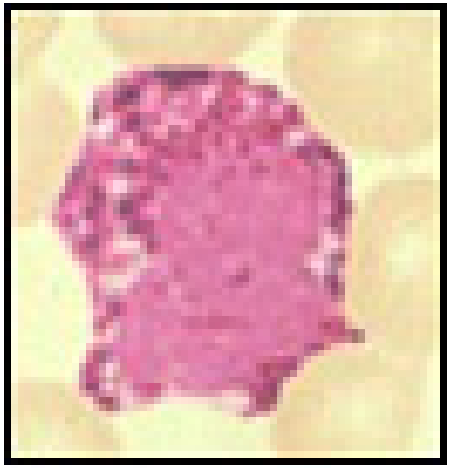
GRANULOCYTES



Neutrophil

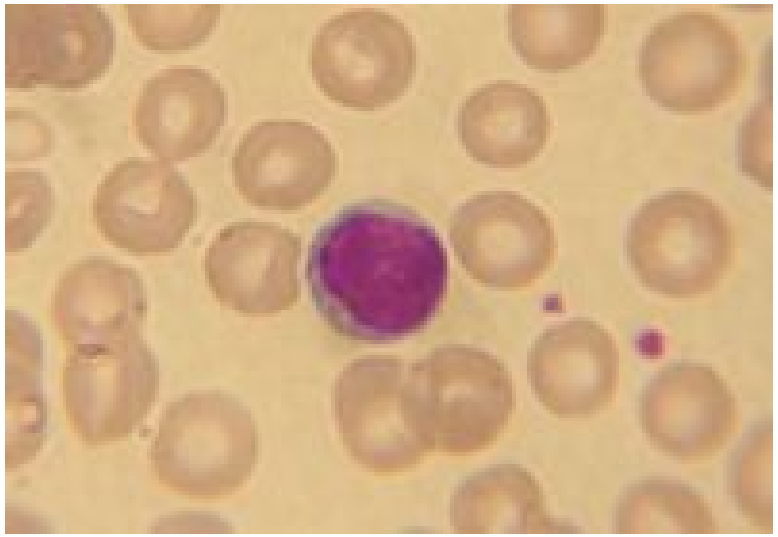


Eosinophil

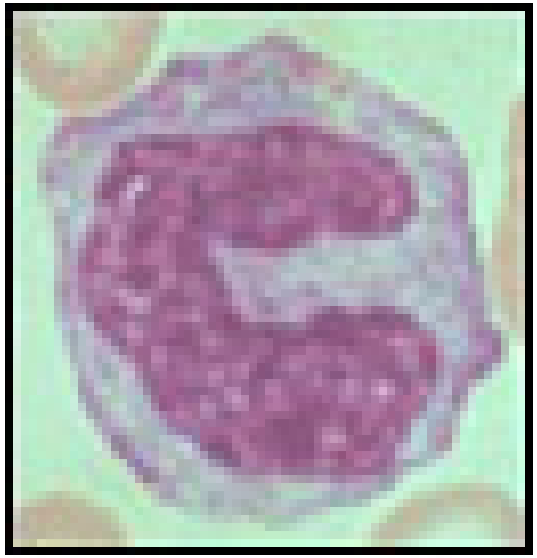


Basophil

AGRANULOCYTES



Lymphocyte



Monocyte

LEUCOCYTE DISORDERS

- Quantitative (Functional abnormality)
- Qualitative (Numerical abnormality)

- Quantitative
  - Leucopenia
  - Leucocytosis
- Physiologic or pathologic variations in leucocyte counts

LEUCOPENIA.

- WBC <4.0 $\times 10^9$/L (3.5)
- White cell counts below the **lower normal limit**
- May affect any class of the WBC series, singly or in combination
- Physiological
- Pathological

Physiologic leucopenia :

- In Africans low total Wbc, low neutrophil counts

Pathological causes of leucopenia:

- May be due to reduced production in BM or increased destruction or combination of both (e.g. HIV)
- Reduced production:
  - As part of pancytopenia
  - Drugs
  - BM replacement
  - Agranulocytosis
  - Familial cyclic neutropenia
  - Hereditary (eg Kostmann's syndrome)

- Increased destruction:

  - Drugs eg : Steroids cause ↓Lymphocytes, ↓eosinophils (but increase in neutrophils)
  - Hypersplenism
  - Viral infections (incl HIV - multifactorial)
  - Some protozoal infections
  - Typhoid fever

LEUCOCYTOSIS.

- Increased leucocyte counts above the upper normal limits (>4x10^9/L)
- Leucocytosis
  - Physiologic
  - Pathological → Reactive (Benign)
    → Neoplastic

  Leucocytosis can affect any class of the WBC, singly or in combination.

Causes of leucocytosis

NEUTROPHILIA >7.5 $\times 10^9$/L

- Physiologic - newborn, pregnancy, exercise, high altitude.

- Pathologic (reactive)-
  - Pyogenic infections (abcesses, septicaemia).
  - Other inflammatory conditions - acute rheumatic fever, burns, thrombosis.
  - Chemical poisoning, drugs
  - Metabolic e.g. renal failure.
  - Malignant disease e.g. cancers of various organs
  - Burns

LYMPHOCYTOSIS (>3.5 $\times 10^9$/L)

- Viral infections – Many viruses including Infectious mononucleosis, inf. Hepatitis, Acute infectious lymphocytosis.
- Pertussis (*Bordetella pertussis*)
- Chronic infections -T.B., brucellosis.
- Thyrotoxicosis.
- Toxoplasmosis, other Protozoal infections.

MONOCYTOSIS > 0.8 x 10^9/L.

- Protozoal inf. - malaria, kala-azar, trypanosomiasis.
- Rickettsial inf.- typhus
- Bacterial inf.-T.B., bacterial endocarditis, brucellosis, syphilis.
- Collagen vascular diseases –SLE, Rheumatoid arthritis, P.A.N.
- Misc. - ulcerative colitis, regional enteritis e.t.c.

EOSINOPHILIA > 0.6 x 10^9/L

- Allergic disorders, atopy.
- Parasitic infections.
- Drugs
- Skin disorders.
- Cancer esp. with necrosis or metastatic
- Infectious e.g. scarlet fever.
- Inherited.
- Misc. e.g. radiation, Loeffler's syndrome, hypereosinophilic syndrome, etc.

BASOPHILIA > 0.1 x 10^9/L

- Haematologic/oncologic disorders e.g. CML, MF, Polycythaemia vera.
- Infections - varicella, chronic sinusitis.
- Endocrine - hypothyroidism.
- Drugs.
- Misc. e.g. nephrosis, radiation.

Leukamoid Reaction

- Extremely high leucocyte counts seen in **non-leukaemic** conditions e.g. in acute infections, intoxications, malignancy
- May be associated with immature forms -left shift
- Various types of leukamoid reaction:
  - Granulocytic (neutrophilic) leukamoid reaction
  - Lymphocytic leukamoid reaction
- Associated changes in neutrophilic leukamoid reaction:
  - Toxic granulation, Vacuolation, Dohle bodies.
  - ↑NAP (LAP)

Leucoerythroblastic Reactions.

- Leucoerythroblastic reaction (in PB)
  - Left shift in the granulocyte series associated with nucleated red cells in the peripheral blood.

  Is often assocoated with anaemia
- **Causes:**
  - Marrow invasion by tumour
  - Miliary T.B.
  - Severe haemolysis
  - Multiple myeloma
  - Myelofibrosis

QUALITATIVE DISORDERS.

- Variation in morphology and/or function. Counts may be normal

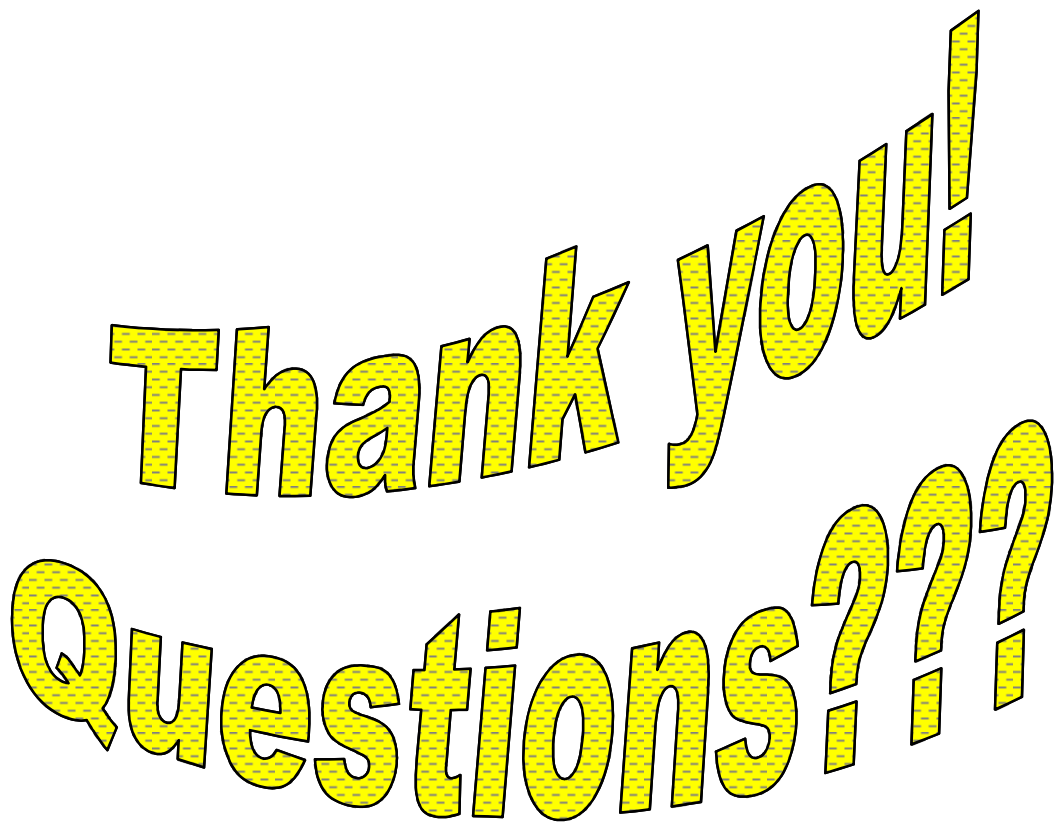
Granulocytes:

- Pelger-Huet forms: Bilobed nucleus
- Chediak-Higashi: Giant leucocyte granules
- Chronic granulomatous disease: Defective neutrophil killing of intracellular bacteria
- May-Hegglin abnormality: Dohle bodies

Lymphocytes.

Abnormalities of function associated with immunodeficiency states e.g.

- Congenital hypogammaglobinaemia (B-cell),
- Di George syndrome (T-cell)
- Mucocuteneous candidiasis (T-cell)
- Acquired hypogammaglobinaemia.


Thank you!
Questions???

Phagocytosis

- **Phagocytosis** is mediated by macrophages and polymorphonuclear leucocytes
- It involves the ingestion and digestion of the following:
  - microorganisms
  - insoluble particles
  - damaged or dead host cells
  - cell debris
  - activated clotting factors

There are several stages of phagocytosis:

- Chemotaxis
- Adherence
- Pseudopodium formation
- Phagosome formation
- Phago-lysosome formation
  - Lysosome contains hydrogen peroxide, active oxygen species (free radicals), peroxidase, lysozyme and hydrolytic enzymes. This is known as the **oxidative burst**, and leads to digestion of the phagolysosomal contents, after which they are eliminated by exocytosis.