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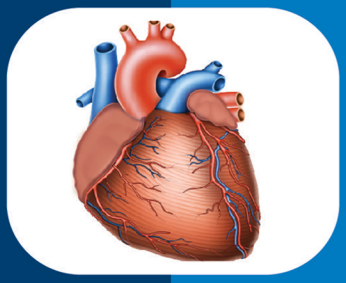
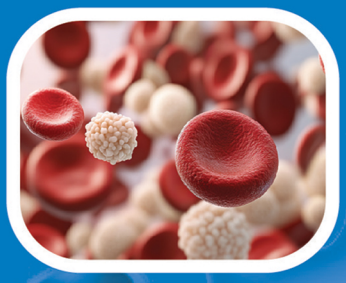
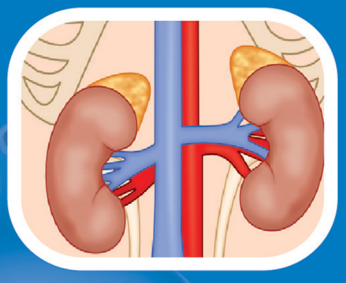


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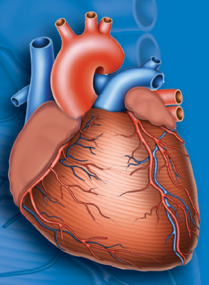

Highlights

- Fully revised and updated in accordance with 10th edition of Essentials of Medical Physiology
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Contents

Section 1: General Physiology

Section 2: Blood and Body Fluids

Section 3: Muscle Physiology

Section 4: Digestive System

Section 5: Renal Physiology and Skin

Section 6: Endocrinology

Section 7: Reproductive System

Section 8: Cardiovascular System

Section 9: Respiratory System and Environmental Physiology

Section 10: Nervous System

Section 11: Special Senses

Chapter 9

Erythropoiesis

CHAPTER OUTLINE

ERYTHROPOIESIS AND HEMOPOIESIS

Erythropoiesis is the production of red blood cells. It is defined as the process of origin, development and maturation of erythrocytes. **Hemopoiesis** is the process of origin, development and maturation of all blood cells.

SITE OF ERYTHROPOIESIS

IN FETAL LIFE

*In fetal life, erythropoiesis occurs in **three stages**.*

1. *Mesoblastic Stage*

During the first 2 months of intrauterine life, the RBCs are produced from **mesenchyme** of yolk sac.

2. *Hepatic Stage*

From third month of intrauterine life, **liver** is the main organ that produces RBCs. **Spleen** and other **lymphoid organs** are also involved in erythropoiesis.

3. *Myeloid Stage*

During the last 3 months of intrauterine life, the RBCs are produced from red **bone marrow** and **liver**.

IN NEWBORN BABIES AND CHILDREN

In newborn babies and growing children RBCs are produced only from red bone marrow.

IN ADULTS

In adults also RBCs are produced only from red bone marrow.

1. *Up to the Age of 20 Years*

RBCs are produced from red bone marrow of all bones **(long bones** and all **flat bones)**.

2. *After the Age of 20 Years*

After 20 years of age, shaft of long bones contains yellow bone marrow due to fat deposition and loses the

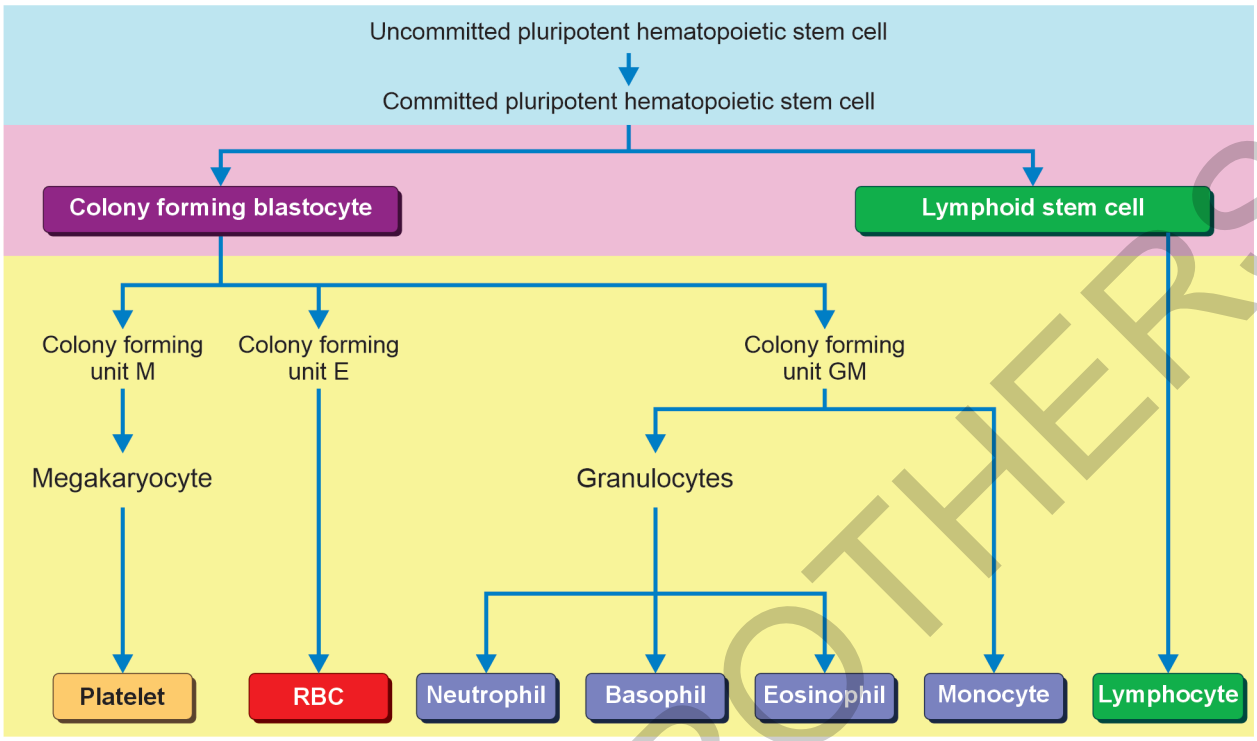

FIGURE 9.1: Stem cells. L = Lymphocyte, R = Red blood cell, N = Neutrophil, B = Basophil, E = Eosinophil, M = Monocyte, P = Platelet.

erythropoietic function. So, RBCs are produced from **membranous bones** like vertebra, sternum, ribs, scapula, iliac bones and skull bones and from the ends of long bones.

In adults, liver and spleen may produce RBCs if the bone marrow is destroyed or fibrosed. Though bone marrow is the site of production of all blood cells, comparatively 75% of bone marrow is involved in the production of leukocytes and only 25% is involved in the production of erythrocytes.

PROCESS OF ERYTHROPOIESIS

STEM CELLS

Stem cells are the primary cells capable of self-renewal and differentiating into specialized cells (Chapter 1). **Hematopoietic stem cells** are primitive cells in the bone marrow, which give rise to blood cells. Hematopoietic stem cells are called **uncommitted pluripotent hematopoietic stem cells** (PHSC). Uncommitted PHSC can give rise to all types of blood cells. In early stages, PHSC are not designed to form a particular type of cell **(Fig. 9.1)**.

When the cells are designed to form a particular type of blood cell, uncommitted PHSCs are called **committed PHSCs**. Committed PHSC is restricted to give rise to one group of blood cells.

Types of Committed PHSCs

1. **Lymphoid stem cells** (LSC) which give rise to lymphocytes and natural killer (NK) cells.
2. **Colony-forming blastocytes**, which give rise to myeloid cells. Myeloid cells are the blood cells other than lymphocytes. When grown in cultures, these cells form colonies hence the name colony-forming blastocytes.

Different units of colony-forming cells

1. Colony-forming unit-erythrocytes (CFU-E) which develop into erythrocytes.
2. Colony-forming unit-granulocytes/monocytes (CFU-GM) that give rise to granulocytes (neutrophils, basophils and eosinophils) and monocytes.
3. Colony-forming unit-megakaryocytes (CFU-M) which develop into platelets.

CHANGES DURING ERYTHROPOIESIS

When cells of CFU-E pass through different stages and finally become matured RBCs four important changes occur:

1. Reduction in size of cell (from the diameter of 25 to 7.2 μ).
2. Disappearance of nucleoli and nucleus.
3. Appearance of hemoglobin.
4. Change in the staining properties of the cytoplasm.

STAGES OF ERYTHROPOIESIS (FIG. 9.2)

1. *Proerythroblast: Pronormoblast*

Proerythroblast or **megaloblast** is the first cell derived from CFU-E. It is a large cell with a diameter

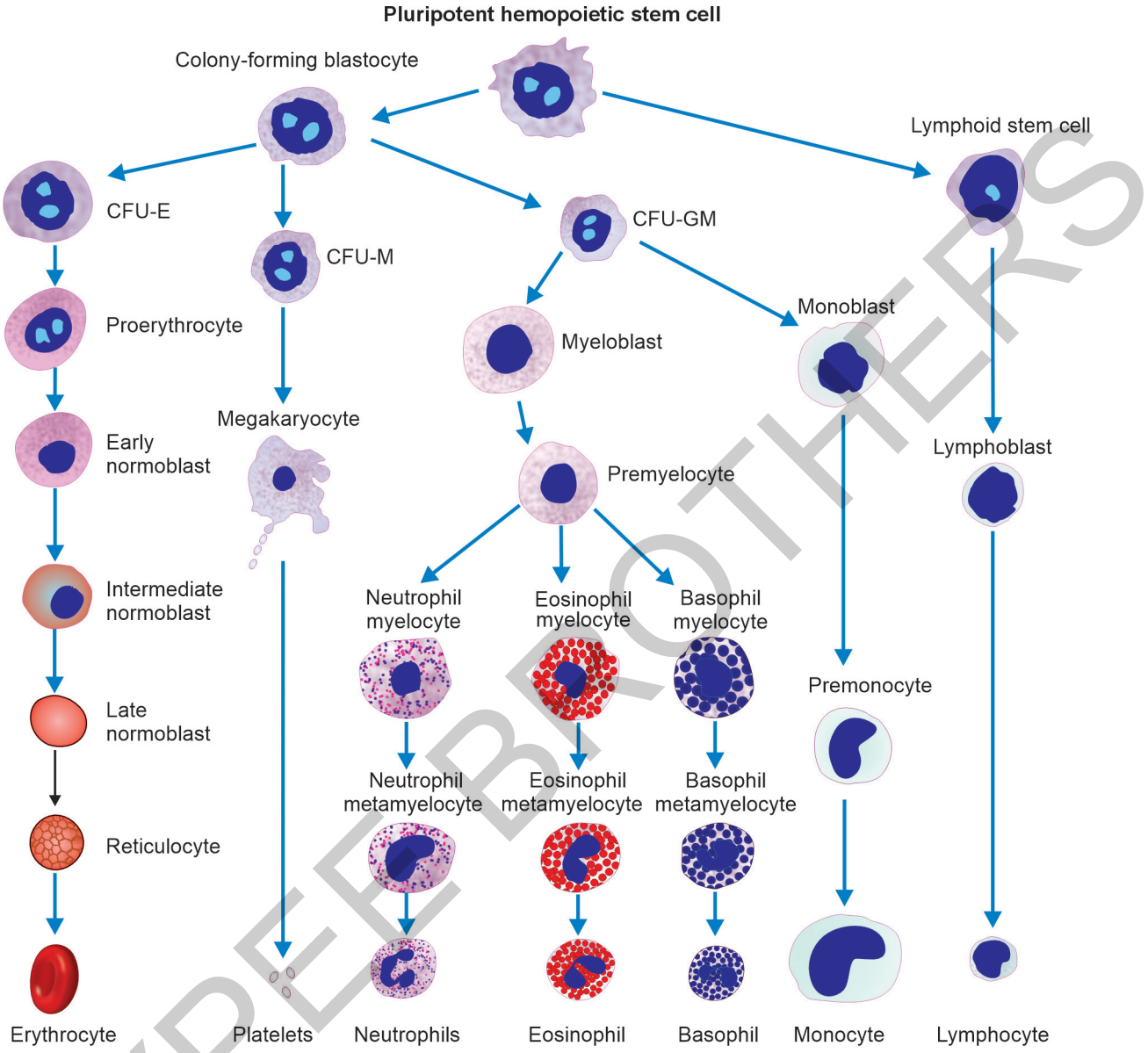

FIGURE 9.2: Stages of hemopoiesis. CFU-E = Colony-forming unit-erythrocyte, CFU-M = Colony-forming unit-megakaryocyte, CFU-GM = Colony-forming unit-granulocyte/monocyte.

of about 20 µ. Its nucleus is large and occupies the cell almost completely. Nucleus has two or more nucleoli and a reticular network. Proerythroblast does not contain hemoglobin. Cytoplasm is **basophilic** in nature.

Proerythroblast multiplies several times and finally forms the cell of next stage, early normoblast. Synthesis of hemoglobin starts in this stage. However, appearance of hemoglobin occurs only in intermediate normoblast.

2. *Early Normoblast*

Early normoblast becomes small with a diameter of about 15 µ. Nucleoli in nucleus disappear. The chromatin network gets condensed and becomes dense. Cytoplasm is basophilic in nature. So, this cell is also called **basophilic erythroblast**. This cell develops into intermediate normoblast.

3. *Intermediate Normoblast*

This cell is still smaller with a diameter of 10 to 12 µ. Nucleus is still present but, the chromatin network shows further condensation. Hemoglobin starts appearing.

Cytoplasm is already basophilic. Now, because of the presence of hemoglobin, it stains with both acidic as well as basic stains. So, this cell is called **polychromophilic** or

polychromatic erythroblast. This cell develops into late normoblast.

4. *Late Normoblast*

Diameter of this cell decreases further to about 8 to 10 µ. Nucleus becomes very small with very much condensed chromatin network and it is known as **ink-spot nucleus**.

Quantity of hemoglobin increases and cytoplasm becomes almost acidophilic. So, now the cell is called **orthochromatic** erythroblast. In the final phase of late normoblast just before it passes to next stage, nucleus disintegrates and disappears. Process by which nucleus disappears is called **pyknosis**. The final remnant is extruded from the cell. Late normoblast develops into reticulocyte.

5. *Reticulocyte*

Reticulocyte is otherwise known as **immature RBC**. It is slightly larger than matured RBC. Cytoplasm contains the reticular network or reticulum, which is formed by remnants of disintegrated organelles. Due to reticular network, it is called reticulocyte. Reticulum of reticulocyte stains with supravital stain.

In newborn babies, reticulocyte count is 2 to 6% of RBCs. The count decreases during the first week after birth. Later, reticulocyte count remains constant at or below 1% of RBCs. Number increases whenever production and release of RBCs increase.

Reticulocyte is **basophilic** due to the presence of remnants of disintegrated Golgi apparatus, mitochondria and other organelles of cytoplasm. During this stage, cells enter the blood capillaries through capillary membrane from site of production by diapedesis.

6. *Matured Erythrocyte*

The reticular network disappears and the cell becomes matured RBC and attains the **biconcave shape**. Diameter of cell decreases to 7.2 µ. A matured RBC is with hemoglobin but without nucleus.

It requires 7 days for development and maturation of RBC from proerythroblast. It requires 5 days up to the stage of reticulocyte. Reticulocyte takes 2 more days to become the matured RBC.

Important events during erythropoiesis are given in **Table 9.1**.

FACTORS NECESSARY FOR ERYTHROPOIESIS

*Factors necessary for development and maturation of erythrocytes are of **three types**:*

A. STIMULATING FACTOR

1. *Hypoxia*

Hypoxia is decreased in availability of oxygen to tissues. It is the most important stimulating factor for erythropoiesis. Hypoxia stimulates erythropoiesis by inducing secretion of erythropoietin from kidney. Production of erythropoietin during hypoxia involves **hypoxia inducible factor** (HIF).

Hypoxia inducible factor

Hypoxia inducible factor is a **transcription factor** which activates transcription of genes to produce substances including erythropoietin from proteins. This factor senses the reactions of cells to hypoxia and in turn increases the erythropoietin production.

TABLE 9.1: Changes during erythropoiesis.

Stage of erythropoiesis	Diameter (µ)	Nucleus	Staining property	Important event
1. **Proerythroblast**	20	Has 2 or more nucleoli and chromatin network	Basophilic	Synthesis of hemoglobin starts
2. **Early normoblast**	15	Nucleoli disappear Dense chromatin network	Basophilic	Nucleoli disappear
3. **Intermediate normoblast**	10 to 12	Further condensation of chromatin network	Polychromophilic or polychromatic	Hemoglobin starts appearing
4. **Late normoblast**	8 to 10	Small with very much condensed chromatin Ink-spot nucleus	Acidophilic	Nucleus disappears by pyknosis
5. **Reticulocyte**	7 to 7.5	Absent	Basophilic	Reticulum is formed Cell enters capillary from site of production
6. **Matured RBC**	7.2	Absent	Acidophilic	Reticulum disappears Cell attains biconcavity

2. *Erythropoietin*

Erythropoietin or **hemopoietin** or **erythrocyte stimulating factor** is another important stimulating factor for erythropoiesis **(Table 9.2)**. This hormone is mainly secreted by peritubular capillaries of kidney (Chapter 69). A small quantity is also secreted from the liver and brain.

Hypoxia is the stimulant for erythropoietin secretion. Blood level of erythropoietin increases in anemia.

Actions of erythropoietin

Erythropoietin induces formation and release of new RBCs into circulation. After secretion, it takes 4 to 5 days to show the action.

Erythropoietin promotes the following processes:

i. Production of proerythroblasts from CFU-E of the bone marrow.
ii. Development of proerythroblasts into matured RBCs through several stages.
iii. Release of matured erythrocytes into blood.

3. *Thyroxine*

Being a general metabolic hormone, thyroxine accelerates the process of erythropoiesis at many levels. So, in hyperthyroidism, polycythemia is common (Chapter 64).

4. *Role of Sex Hormones*

Testosterone has mild erythropoietic action after puberty. The action of estrogen on erythropoiesis is not clearly understood. In animals, estrogen suppresses erythropoiesis.

5. *Hematopoietic Growth Factors*

Hematopoietic growth factors or growth inducers are the interleukins and **stem cell factor** (steel factor). All such factors induce the proliferation of PHSCs (Chapter 15). Interleukins (IL) are glycoproteins, which belong to cytokines family.

Interleukins involved in erythropoiesis are:

i. Interleukin-3 (IL-3) secreted by T-cells.
ii. Interleukin-6 (IL-6) secreted by T-cells, endothelial cells and macrophages.
iii. Interleukin-11 (IL-11) secreted by osteoblast.

6. *Vitamins*

Some vitamins also stimulate erythropoiesis. Deficiency of these vitamins causes anemia associated with other disorders.

Refer **Table 9.3** for vitamins, deficiency of which cause anemia with other disorders.

B. MATURATION FACTORS

1. *Vitamin B_{12} (Cyanocobalamin)*

Vitamin B_{12} is called **extrinsic factor** since it is obtained mostly from diet. Its absorption from intestine requires the presence of **intrinsic factor of Castle**. Vitamin B_{12} is stored mostly in liver and in small quantities in muscles. When

TABLE 9.3: Anemia associated with other disorders caused by deficiency of vitamins which stimulate erythropoiesis.

Vitamins	Effects of deficiency: Anemia associated with	
Vitamin B_3	**Pellagra**	Disease characterized by skin lesions, diarrhea, weakness, nervousness and dementia
Vitamin B_6	**Peripheral neuropathy**	Condition causing damage or disease of nerves
Vitamin C	**Scurvy**	Ancient disease characterized by impaired collagen synthesis resulting in rough skin, bleeding gum, loosening of teeth, poor wound healing, bone pain, lethargy and emotional changes
Vitamin D	**Rickets**	Bone disease. Refer Chapter 65
Vitamin E	**Malnutrition**	Deficiencies or imbalances in a person's intake of nutrients (WHO)

TABLE 9.2: Factors necessary for erythropoiesis.

Stimulating factors	Maturation factors	Factors necessary for hemoglobin synthesis
1. Hypoxia 2. Erythropoietin 3. Thyroxine 4. Hematopoietic growth factors 5. Vitamins: B_3, B_6, C, D and E	1. Vitamin B_{12} 2. Intrinsic factor 3. Folic acid	1. First class proteins and amino acids 2. Iron 3. Copper 4. Cobalt and nickel 5. Vitamins: C, B_2, B_3 and B_6

necessary, it is transported to the bone marrow to promote maturation of RBCs. It is also produced in the large intestine by intestinal flora.

Action of vitamin B_{12}

Vitamin B_{12} is essential for synthesis of DNA in RBCs. Its deficiency leads to failure in maturation of the cell and reduction in the cell division. Also, the cells are larger with fragile and weak cell membrane resulting in macrocytic anemia.

Deficiency of vitamin B_{12} causes **pernicious anemia**. So, vitamin B_{12} is called **antipernicious factor**.

2. *Intrinsic Factor of Castle*

Intrinsic factor of Castle is produced by parietal cells of the gastric glands. It is essential for absorption of vitamin B_{12} from the intestine. In the absence of intrinsic factor vitamin B_{12} is not absorbed from intestine leading to pernicious anemia.

Deficiency of intrinsic factor occurs in severe gastritis, ulcer and gastrectomy.

Hematinic principle

Hematinic principle is the principle which was earlier thought to be produced by action of intrinsic factor on extrinsic factor. It was also called **anti-anemia principle**. It is a maturation factor.

3. *Folic Acid*

Folic acid is required for the synthesis of DNA. In the absence of folic acid, synthesis of DNA decreases resulting in failure of maturation of RBCs. This leads to anemia in which the cells are larger and appear in megaloblastic (proerythroblastic) stage. Anemia due to folic acid deficiency is called **megaloblastic anemia**.

C. FACTORS NECESSARY FOR HEMOGLOBIN SYNTHESIS

Various materials are essential for the synthesis of hemoglobin in RBCs. Deficiency of these substances decreases hemoglobin synthesis leading to anemia.

1. *First Class Proteins and Amino Acids*

Proteins of high biological value are essential for hemoglobin formation. Amino acids derived from these proteins are required for synthesis of protein part of hemoglobin.

2. *Iron*

Iron is necessary for formation of heme part of the hemoglobin.

3. *Copper*

Copper is necessary for the absorption of iron from gastrointestinal tract.

4. *Cobalt and Nickel*

These two metals are essential for the utilization of iron during hemoglobin formation.

5. *Vitamins*

Vitamin C, riboflavin (B2), nicotinic acid (B3) and pyridoxine (B6) are also essential for hemoglobin formation.

Refer Table 9.3 for the factors necessary for erythropoiesis.

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K Sembulingam is a renowned person in the field of Physiology. He has a long and vast experience of teaching Physiology to undergraduate and postgraduate medical students in various institutions in India and abroad. He has served JJM Medical College and Hospital, Davanagere, Karnataka, MR Medical College, Kalaburagi, Karnataka, India; Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India; School of Health Sciences, Universiti Sains Malaysia, Kelantan, Malaysia; Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India; Sri Manakula Vinayagar Medical College and Hospital, Puducherry, India; Shri Sathya Sai Medical College and Research Institute, Nellikuppam, Tamil Nadu, India; and Madha Medical College and Research Institute, Chennai, Tamil Nadu, India.

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