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Ramadas Nayak
Rakshatha Nayak

6th Edition

Exam Preparatory Manual for Undergraduates

Pathology

With Online Additional Reading

As per the Revised Competency-based Medical Education Curriculum (NMC)

- Must-Know Content for Essential Learning
- Important Questions Highlighted in Red
- High-Yield, Exam-Oriented Presentation
- Nice-to-Know Content Available Online

Foreword
K Ramnarayan

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Contents

SECTION I: GENERAL PATHOLOGY

1. Introduction to Pathology 3

- Definitions and Terms *3*
- Role of a Pathologist in Diagnosis and Management of Disease *4*
- History and Evolution of Pathology *5*
- Maintaining Cell Populations 5

Subdivisions of Pathology *Online*
History and Evolution of Pathology *Online*
Advances in Pathology *Online*
Cell Cycle *Online*

2. Cell Injury, Cell Death, and Adaptations 10

Cell Injury 10

- Cellular Responses to Stress and Noxious Stimuli *10*
- Reversible Cell Injury *12*

Cell Death 13

- Necrosis *13*
- Apoptosis *20*
- Autolysis *24*
- Mechanisms of Cell Injury *24*

Adaptations 30

- Adaptations of Cellular Growth and Differentiation *30*

Intracellular Accumulations 37

- Lipid Accumulation *38*
- Intracellular Accumulation of Proteins *40*
- Hyaline Change *41*
- Intracellular Accumulation of Glycogen *41*
- Pigments *42*

Pathologic Calcification 45

Cellular Aging 47

Progression of Cell Injury and Death *Online*
Autophagy *Online*
Necrosis *Online*
Apoptosis *Online*
Examples of Cell Injury and Necrosis *Online*
Adaptations *Online*
Intracellular Accumulations *Online*
Pigments *Online*
Pathologic Calcification *Online*

3. Inflammation and Healing 53

Inflammation 53

- Definitions and General Features *53*

Acute Inflammation 54

- Reactions of Blood Vessels in Acute Inflammation *54*
- Leukocyte Recruitment to Sites of Inflammation *58*
- Phagocytosis and Clearance of the Offending Agent *61*
- Mediators of Inflammation *64*
- Morphological Types/Patterns of Acute Inflammation *71*
- Outcomes of Acute Inflammation *72*

Chronic Inflammation 73

- General Features *73*
- Giant Cell *79*

Systemic Effects of Inflammation 79

Tissue Repair 82

- Cell and Tissue Regeneration *82*
- Repair by Scarring *84*
- Healing of Skin Wounds *86*
- Factors Influencing Wound Healing *89*
- Abnormalities in Tissue Repair *91*

Inflammation *Online*

- *Exogenous and Endogenous Causes of Inflammation* *Online*
- *Recognition of Microbes and Damaged Cells* *Online*
- *Initiation of Acute Inflammation* *Online*
- *Types of Enzymes and their Functions in Acute Inflammation* *Online*
- *Leukocyte-Mediated Tissue Injury* *Online*
- *Inherited Defects in Microbicidal Activity* *Online*
- *Acquired Defects of Leukocyte Function* *Online*

Tissue Repair *Online*
Features of Regeneration and Scar Formation *Online*
Regulation of Cell Proliferation *Online*
Growth Factors *Online*
Angiogenesis *Online*
Deposition of Connective Tissue *Online*
Remodeling of Connective Tissue *Online*

4. Infections and Infestations 96

Mycobacterial Infections 96

- Mycobacteria *96*
- Leprosy *96*

JAYPEE BROTHERS

Spirochete Infections 103
- Syphilis *103*

COVID-19 107
Rickettsial Infections 109
Chlamydial Infections 110
Fungal Infections and Opportunistic Infections 110
Mycetoma 112
Parasitic Diseases 114
- Malaria *114*
- Cysticercosis and Hydatid Disease (Tapeworm Infections) *118*
- Filariasis *120*
- Other Infections *121*

Leprosy Online
Syphilis Online
Diphtheria Online
Whooping Cough Online
Poliovirus Infection Online
Herpesvirus Infection Online
Rabies Online
Measles Online
Malaria Online

5. Hemodynamic Disorders, Shock, and Thromboembolic Disease. 124
- Edema and Effusions *124*
- Hyperemia and Congestion *128*
- Shock *133*

Hemostasis and Thrombosis 138
- Normal Hemostasis *138*
- Thrombosis *140*
- Embolism *147*
- Infarction *153*

Edema Online
- *Myxedema* Online
- *Papilledema* Online

Hyperemia and Congestion Online
- *Differences Between Hyperemia and Congestion* Online

Shock Online
- *Superantigen-Mediated Toxic Shock* Online

Hemostasis Online
- *Endothelium and its Role in Hemostasis* Online

Thrombosis Online
- *Vaccine-Induced Thrombotic Thrombocytopenia* Online
- *Antiphospholipid Antibody Syndrome* Online
- *Venous Thrombosis* Online

Embolism Online
Infarction Online
- *Sequential Changes in Infarction* Online

6. Immunopathology, Aids, and Amyloidosis 158
Immunopathology 158
- Introduction to Immunity *158*
- Hypersensitivity Reactions: Immunologically Mediated Tissue Injury *161*
- Major Histocompatibility Complex Molecules *172*

Rejection of Tissue Transplants 173
- Transplant Rejection *173*

Autoimmune Diseases 177
- Systemic Lupus Erythematosus *179*

Acquired Immune Deficiency Syndrome 182
Amyloidosis 190

Main Components of Innate and Adaptive Immune Responses Online
Hypersensitivity Reactions Online
Major Histocompatibility Complex Online
Graft Rejection Online
Autoimmunity Online
HIV and AIDS Online
Amyloidosis Online

7. Neoplasia 201
- Nomenclature *201*
- Characteristics of Benign and Malignant Neoplasms *205*
- Acquired Predisposing Conditions *213*
- Molecular Basis of Cancer: Role of Genetic and Epigenetic Alterations *214*
- Cellular and Molecular Hallmarks of Cancer *216*

Carcinogenic Agents and their Cellular Interactions 232
- Chemical Carcinogenesis *233*
- Microbial Carcinogenesis *236*
- Radiation Carcinogenesis *239*

Clinical Aspects of Neoplasia 240
Laboratory Diagnosis of Cancer 245
- Molecular Diagnosis and Cytogenetics *247*

Examples of Benign Tumors *250*

Nomenclature Online
- *Embryonal Tumors (Blastomas)* Online

Characteristics of Benign and Malignant Neoplasms Online
Factors Determining Tumor Growth Online
Molecular Basis of Cancer Online
Oncogenes Online
Tumor Suppressor Genes Online
Familial Syndromes Online
Evasion of Cell Death Online
Limitless Replicative Potential of Cancer Cells Online
Angiogenesis Online
Cancer-Enabling Inflammation Online
Genomic Instability Online
Genetic Lesions in Cancer Online
Chemical Carcinogens Online
Oncogenic Viruses Online
Paraneoplastic Syndrome Online
Staging of Tumors Online
Laboratory Diagnosis of Cancers Online

JAYPEE BROTHERS

8. Genetic and Pediatric Diseases 253

Genetics 253
- Genetic Disorders *254*
- Single-Gene (Monogenic/Mendelian) Disorders *255*
- Chromosomal Disorders *257*

Storage Disorders 261

Diagnosis of Genetic Disorders 263

Pediatric Diseases 265
- Tumors and Tumor-Like Lesions of Infancy and Childhood *265*

Basis of Genetics Online
Chromosomal Aberrations Online
Developmental Defects Online
Storage Disorders Online
Diagnosis of Genetic Disorders Online

9. Environmental and Nutritional Diseases 268
- Environmental Pollution *268*
- Effects of Tobacco *270*
- Effects of Alcohol *271*
- Disorders due to Noise *274*
- Nutritional Diseases *274*
- Common Vitamin Deficiencies *277*
- Obesity *280*

Effects of Tobacco Online
Effects of Alcohol Online
Nutritional Diseases Online
Obesity Online

10. Basic Diagnostic Cytology 286
- Exfoliative Cytology *286*
- Cervical Cytology (Pap Smear) *287*
- Cytological Fixatives *289*
- Cytological Stains *289*
- Fine Needle Aspiration Cytology *289*
- Other Cytology Techniques *291*

Rapid On-site Evaluation Online
Molecular Cytopathology Online

SECTION II: HEMATOLOGY, TRANSFUSION AND CLINICAL PATHOLOGY

11. Introduction to Hematology and Disorders of Red Blood Cells 295
- Normal Hematopoiesis *296*
- Hematopoiesis in Disease *298*
- Anticoagulants in Hematology *300*
- Red Blood Cell Disorders *302*
- Anemia *302*

Anemias of Impaired Red Cell Production 307
- Iron Deficiency Anemia *307*
- Megaloblastic Anemia *311*
- Pernicious Anemia *313*
- Aplastic Anemia *317*

Hemolytic Anemias (Increased Red Cell Destruction) 319
- Hereditary Spherocytosis *320*
- Glucose-6-Phosphate Dehydrogenase Deficiency *323*
- Hereditary Defects in Hemoglobin *324*
- Thalassemia *325*
- β-Thalassemia Major *325*
- α-Thalassemia *329*
- Sickle Cell Anemia *330*
- Immunohemolytic Anemias *334*

Hematopoiesis Online
Bone Marrow Morphology Online
Blood Samples Used in Hematology Online
Anticoagulants Online
Red Cell Indices Online
Iron Deficiency Anemia Online
Differential Diagnosis of Microcytic Hypochromic Anemia Online
Megaloblastic Anemia Online
Macrocytic Anemia Online
Aplastic Anemia Online
Hemolytic Anemias Online
B-Thalassemia Online
Sickle Cell Anemia Online
Immunohemolytic Anemia Online
Anemia of Blood Loss Online
Approach to Hemolytic Anemia Online

12. Disorders of White Blood Cells, Lymph Nodes, and Spleen .. 342

Non-neoplastic Disorders of White Blood Cells 342
- Quantitative Disorders of Leukocytes *342*

Neoplastic Proliferations of White Blood Cells 346
- Acute Leukemia *347*
- Acute Lymphoblastic Leukemia/Lymphoma *348*
- Acute Myeloid Leukemia *351*
- Myeloproliferative Neoplasms *354*
- Chronic Myeloid Leukemia *354*

Lymph Node and Spleen 357
- Lymph Node *357*
- Non-Hodgkin Lymphomas *360*
- Hodgkin Lymphomas *367*
- Splenomegaly *374*
- Plasma Cell Neoplasms and Related Disorders *377*

Clinical Scenario for Essay Questions 381

Quantitative Disorders of Leukocytes Online
Qualitative Disorders of Leukocytes Online
Infectious Mononucleosis Online
Neoplastic Proliferations of White Blood Cells Online
Leukemia Online
Polycythemia Online

JAYPEE BROTHERS

Non-Hodgkin Lymphoma *Online*
Hodgkin Lymphoma *Online*
Multiple Myeloma *Online*

13. Bleeding Disorders: Hemorrhagic Diathesis 387

- Bleeding Disorders *387*
- Bleeding Disorders due to Vessel Wall Abnormalities *388*
- Bleeding Disorders due to Reduced Number of Platelets: Thrombocytopenia *389*
- Coagulation Disorders *392*
- Disseminated Intravascular Coagulation *396*
- Laboratory Evaluation of Bleeding Disorders *399*

Bleeding Disorders due to Vessel Wall Abnormalities *Online*
Immune Thrombocytopenic Purpura *Online*
Coagulation Disorders *Online*
Disseminated Intravascular Coagulation *Online*
Reference Ranges for Platelets and Coagulation Tests *Online*

14. Blood Banking and Transfusion 405

Blood Group System 405

- Transfusion Medicine *408*
- Blood Transfusion *409*
- Blood Components *411*
- Transfusion-Transmitted Diseases *412*
- Transfusion Reactions *413*

ABO and Rh System *Online*
Blood Components *Online*
Transfusion Reactions *Online*

15. Clinical Pathology 418

- Hemoglobin Estimation *418*
- Peripheral Blood Smear *420*
- Hematocrit (Packed Cell Volume) *424*
- Erythrocyte Sedimentation Rate *426*
- LE Cell Test *428*
- Bone Marrow Examination *428*
- Osmotic Fragility Test *430*
- Urine Analysis *432*
- Physical Examination *432*
- Chemical Examination *435*
- Microscopic Examination of Urine (Urinary Sediment) *443*

Body Fluids 445

- Pleural Fluid *445*
- Peritoneal (Ascitic) Fluid *447*
- Cerebrospinal Fluid Examination *448*
- Semen Analysis *450*
- Thyroid Function Tests *453*
- Renal Function Tests *455*
- Liver Function Tests *457*
- Tumor Marker *460*
- Liver Biopsy *460*
- Sputum Examination *461*

Hemoglobin Estimation *Online*
Peripheral Blood Smear *Online*
LE Cell *Online*
Bone Marrow Examination *Online*
Osmotic Fragility Test *Online*
Urine Analysis *Online*
Examination of CSF *Online*
Semen Analysis *Online*
Thyroid Function Tests *Online*
Renal Function Tests *Online*
Liver Function Tests *Online*
Sputum Examination *Online*
Laboratory Values of Clinical Importance *Online*

SECTION III: SYSTEMIC PATHOLOGY

16. Cardiovascular Disorders 467

Vascular Disorders 467

- Arteriosclerosis *467*
- Atherosclerosis *468*
- Aneurysms and Aortic Dissection *476*
- Aortic Dissection *479*
- Hypertensive Vascular Disease *482*
- Vascular Tumors *484*

Heart Disorders 485

- Heart Failure *485*
- Rheumatic Fever and Rheumatic Heart Disease *490*
- Ischemic Heart Disease *497*
- Angina Pectoris *500*
- Myocardial Infarction *500*
- Infective Endocarditis *512*
- Congenital Heart Disease *519*
- Cardiomyopathy *524*
- Pericarditis and Pericardial Effusion *527*
- Tumors of the Heart *529*

Arteriosclerosis *Online*
Atherosclerosis *Online*
Aneurysms and Dissection *Online*
Hypertensive Vascular Disease *Online*
Vasculitis *Online*
Heart Failure *Online*
Rheumatic Fever *Online*
Ischemic Heart Disease *Online*
Infective Endocarditis *Online*
Congenital Heart Disease *Online*
Pericarditis and Pericardial Effusion *Online*

17. Respiratory Disorders 533

Pulmonary Infections 533

JAYPEE BROTHERS

- Pneumonia *533*
- Scenario-Based Essay Question *538*
- Lung Abscess *538*

Obstructive Lung Diseases 540
- Chronic Obstructive Pulmonary Disease *540*

Tuberculosis 554

Pneumoconioses 564

Tumors of Lung 569
- Lung Carcinoma *570*

Metastatic Tumors 581

Pneumonia Online
Emphysema Online
Asthma Online
Bronchiectasis Online
Tuberculousis Online
Sarcoidosis Online
Pneumoconiosis Online
Lung Cancer Online
Acute Respiratory Distress Syndrome Online

18. Oral Cavity and Gastrointestinal Tract 586

Oral Cavity 586
- Precancerous Lesions of the Oral Cavity *586*
- Oral Squamous Cell Carcinoma *587*

Salivary Gland 589
- Salivary Gland Neoplasms *589*
- Pleomorphic Adenoma *589*

Gastrointestinal Tract 593
- Esophagus *593*
- Stomach *596*
- Intestine *610*
- Malabsorption Syndrome *611*
- Neuroendocrine Tumors *612*
- Inflammatory Bowel Disease *613*
- Premalignant and Malignant Lesions *622*
- Colorectal Adenocarcinoma *625*
- Acute Appendicitis *632*

Oropharyngeal SCC Online
Odontogenic Tumors Online
Mallory-Weiss Tears Online
Barrett Esophagus Online
Gastritis Online
Gastropathy Online
Zollinger-Ellison Syndrome Online
Gastric Adenocarcinoma Online
Gastrointestinal Stromal Tumor Online
Intestinal Tuberculosis Online
Enteric Fever Online
Shigellosis Online
Amebiasis Online
Inflammatory Bowel Disease Online
Intestinal Polyps Online
Colorectal Adenocarcinoma Online

19. Hepatobiliary and Pancreatic Disorders 637

Liver 637
- Bilirubin Metabolism *637*
- Jaundice *639*
- Hepatic (Liver) Failure *642*
- Viral Hepatitis *644*
- Alcohol-Associated Liver Disease *654*
- Cirrhosis *663*
- Portal Hypertension *666*
- Liver Abscesses *670*
- Malignant Neoplasms of Liver *671*
- Hepatoblastoma *671*
- Hepatocellular Carcinoma *672*
- Metastatic Tumors *676*

Gallbladder 677
- Cholelithiasis (Gallstones) *677*
- Cholecystitis *681*

Pancreas 684
- Pancreatitis *684*
- Pancreatic Carcinoma *690*

Interpretation of Liver Function and Viral Hepatitis Serology Panel 693

Jaundice Online
Hepatic Failure Online
Viral Hepatitis Online
Metabolic Dysfunction-associated Steatotic Liver Disease Online
Cirrhosis Online
Hemochromatosis Online
Wilson Disease Online
Malignant Biliary Tumors Online
Gallbladder Carcinoma Online
Acute Pancreatitis Online
Pancreatic Carcinoma Online

20. Kidney and Urinary Tract Disorders 697

Kidney 697
- Histology of the Kidney *697*
- Glomerular Diseases *701*
- Nephritic Syndrome *707*
- Nephrotic Syndrome *713*
- Glomerular Lesions Associated with Systemic Diseases *730*
- Diseases Affecting Tubules and Interstitium *733*
- Acute Kidney Injury *740*
- Acute Tubular Injury *741*
- Chronic Kidney Disease *744*
- Vascular Diseases of the Kidney *746*
- Cystic Diseases of the Kidney *748*
- Urolithiasis (Renal Calculi, Stones) *752*
- Urinary Tract Obstruction (Obstructive Uropathy) *754*
- Malignant Neoplasms of the Kidney *756*
- Nephroblastoma (Wilms Tumor) *761*

JAYPEE BROTHERS

Lower Urinary Tract 764
- Urothelial Tumors *764*

Common Urinary Abnormalities in a Clinical Specimen 767

Histology of Kidney Online
Glomerulonephritis Online
Pyelonephritis Online
Acute Tubular Injury Online
Horseshoe Kidney Online
Cystic Diseases of the Kidney Online
Malignant Tumors of the Kidney Online
Urothelial Tumors Online

21. Male Genital Tract Disorders 771

Testis 771
- Testicular Tumors *771*

Penis 780
- Malignant Tumors of the Penis *780*

Prostate 783
- Prostatitis *783*
- Benign Prostatic Hyperplasia *784*
- Adenocarcinoma of Prostate *788*

Cryptorchidism Online
Teratoma Online
Embryonal Carcinoma Online
Spermatocytic Tumors Online
Benign Prostatic Hyperplasia Online
Adenocarcinoma of Prostate Online
Male Infertility Online

22. Female Genital Tract Disorders 795

Cervix 795
- Inflammations of the Cervix *795*
- Premalignant and Malignant Neoplasms of The Cervix *796*

Uterus 806
- Endometriosis *806*
- Adenomyosis *808*
- Endometrial Hyperplasia *809*
- Endometrial Carcinoma *811*
- Tumors of the Myometrium *815*

Ovarian Tumors 818
- General Features *818*
- Epithelial Tumors *820*
- Serous Tumors *820*
- Mucinous Tumors *825*
- Endometrioid Ovarian Tumors *827*
- Brenner Tumors *828*
- Clinical Course, Detection, and Prevention of Ovarian Epithelial Tumors *828*
- Germ Cell Tumors *829*
- Malignant Ovarian Germ Cell Tumors *833*
- Dysgerminoma *833*
- Yolk Sac Tumor *834*
- Nongestational Choriocarcinoma of the Ovary *835*
- Mixed Germ Cell Tumors *836*
- Sex Cord-Stromal Tumors *836*
- Metastatic Tumors of the Ovary *837*

Gestational Disorders 838
- Gestational Trophoblastic Disease *838*
- Hydatidiform Mole *839*
- Invasive Hydatidiform Mole *842*
- Choriocarcinoma *842*
- Treatment and Prognostic Significance *843*

Normal Structure of Cervix Online
HPV Carcinogenesis Online
Squamous Intraepithelial Lesion Online
Invasive Carcinoma of Cervix Online
Menstrual Cycle Online
Endometriosis Online
Adenomyosis Online
Classification of Tumors of Uterus Online
Ovarian Tumors Online
Gestational Trophoblastic Disease Online
Ectopic Pregnancy Online

23. Breast Disorders 847

Female Breast 847
- Benign Epithelial Proliferations and Precursor Lesions *847*
- Proliferative Breast Disease with Atypia *849*
- Carcinoma in Situ *849*
- Invasive Carcinoma of the Breast *852*
- Types of Invasive Breast Carcinoma *857*
- Paget Disease of the Nipple *862*
- Spread of Breast Carcinoma *863*
- Stromal Tumors of the Breast *867*
- Male Breast *870*

Normal Anatomy of the Breast Online
Carcinoma in Situ Online
Classification of Epithelial Tumors of Breast Online
Invasive Carcinoma of Breast Online
Paget Disease Online
Fibroadenoma Online
Phyllodes Tumor Online

24. Endocrine Disorders 873

Thyroid Gland 873
- Hyperthyroidism *873*
- Graves Disease *875*
- Hypothyroidism *876*
- Thyroiditis *877*
- Diffuse and Multinodular Goiters *879*
- Thyroid Neoplasms *881*
- Thyroid Carcinoma *884*

Diabetes Mellitus 890
- Classification of Diabetes Mellitus *891*
- Type *1 Diabetes Mellitus* *891*
- Type *2 Diabetes* *893*

JAYPEE BROTHERS

- Clinical Features of Diabetes Mellitus *895*
- Chronic Complications of Diabetes Mellitus *898*
- Morphology and Chronic Complications of Diabetes Mellitus *899*
- Laboratory Diagnosis of Diabetes Mellitus *900*

Parathyroid Glands 903
- Hyperparathyroidism *903*
- Primary Hyperparathyroidism *903*
- Secondary Hyperparathyroidism *905*
- Tertiary Hyperparathyroidism *906*

Adrenal Glands 906
- Adrenal Cortex *906*
- Hypercortisolism (Cushing Syndrome) *907*
- Adrenocortical Insufficiency (Hypoadrenalism) *910*
- Adrenal Neoplasms *913*
- Tumors of the Adrenal Medulla *914*
- Neuroblastic Tumors *917*

Hyperthyroidism and Graves Disease Online
Thyroiditis Online
Diffuse and Multinodular Goitres Online
Thyroid Neoplasms Online
Diabetes Mellitus Online
- *Glucose Homeostasis* Online
- *Regulation of Insulin Release* Online
- *Complications of DM* Online
- *Laboratory Diagnosis of Diabetes* Online

Hypercalcemia Online
Hypoparathyroidism Online
Cushing Syndrome Online
Waterhouse-Friderichsen Syndrome Online
Pheochromocytoma Online
Multiple Endocrine Neoplasia Syndromes Online

25. Bones, Joints, and Soft Tissue Tumors 921

Bones 921
- Osteomyelitis *922*
- Pyogenic Osteomyelitis *922*
- Tuberculous Osteomyelitis *925*
- Healing of Fractures *926*
- Paget Disease of Bone (Osteitis Deformans) *927*
- Bone Tumors *929*
- Bone-Forming Tumors *930*
- Cartilage-Forming Tumors *933*
- Osteoclastic Giant Cell-Rich Tumors *935*
- Undifferentiated Small Round Cell Sarcomas of Bone *937*

Joints 938
- Rheumatoid Arthritis *938*
- Osteoarthritis *941*
- Gout and Gouty Arthritis *942*

Soft Tissue Tumors 946
- Molecular Basis *946*
- Tumors of Adipose Tissue *946*
- Fibroblastic/Myofibroblastic Tumors *947*
- Skeletal Muscle Tumors *948*
- Smooth Muscle Tumors *949*
- Tumors of Uncertain Differentiation *949*
- Clinical Features of Synovial Sarcoma *949*
- Peripheral Nerve Sheath Tumors *950*

Osteomyelitis Online
Pott Disease Online
Healing of Fracture Online
Bone Tumors Online
Rheumatoid Arthritis Online
Osteoarthritis Online
Gout and Gouty Arthritis Online
Soft Tissue Tumors Online

26. Skin Disorders 955
- Premalignant Epidermal Lesions *955*
- Squamous Cell Carcinoma in Situ (Bowen Disease) *956*
- Squamous Cell Carcinoma of Skin *956*
- Basal Cell Carcinoma *959*
- Melanocytic Neoplasms *963*

Melanocytic Nevus Online
Melanoma Online

27. Disorders of the Central Nervous System and Eye 969

Meningitis 969
- Acute Meningitis *969*
- Acute Pyogenic (Bacterial) Meningitis *969*
- Acute Aseptic Meningitis *971*
- Chronic Meningitis *971*

Tumors of Central Nervous System 973
- Gliomas *973*
- Embryonal Tumors *979*
- Meningiomas *981*
- Metastatic Tumors *983*

Eye 983
- Retinoblastoma *983*

Interpretation of Cerebrospinal Fluid Findings 985

Acute Pyogenic Meningitis Online
Neurosyphilis Online
Glioma Online
Pilocytic Astrocytoma Online
Ependymoma Online
Meningioma Online
Circle of Willis Online

Index ***993***

JAYPEE BROTHERS

SECTION

II

Hematology, Transfusion and Clinical Pathology

Section Outline

11. Introduction to Hematology and Disorders of Red Blood Cells
12. Disorders of White Blood Cells, Lymph Nodes, and Spleen
13. Bleeding Disorders: Hemorrhagic Diathesis
14. Blood Banking and Transfusion
15. Clinical Pathology

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CHAPTER 11

Introduction to Hematology and Disorders of Red Blood Cells

Chapter Outline

- Normal Hematopoiesis
- Anticoagulants

Red Blood Cell Disorders

- Anemia

Anemias of Impaired Red Cell Production

- Iron Deficiency Anemia
- Megaloblastic Anemia
- Aplastic Anemia

Increased Red Cell Destruction (Hemolytic Anemias)

- Hemolytic Anemias
- Hereditary Spherocytosis
- Glucose-6-phosphate Dehydrogenase Deficiency
- Hereditary Defects in Hemoglobin
- Thalassemia
  - β-Thalassemia Major
  - β-Thalassemia Minor/Trait
  - α-Thalassemia
- Sickle Cell Anemia
- Sickle Cell Trait
- Immunohemolytic Anemias

Anemia of Blood Loss

- Approach to the Diagnosis of Hemolytic Anemia

INTRODUCTION

PA13.1: Describe hematopoiesis and extramedullary hematopoiesis and the role of anticoagulants in hematology.

- **Hematology** is the **study of normal and pathologic aspects of blood and blood cells.**
- **The hematopoietic (hemopoietic) system** consists of all organs and tissues involved in hematopoiesis.

Components of the Hematopoietic System

The hematopoietic system comprises tissues responsible for the formation and maintenance of blood cells. The multipotent **hematopoietic stem cell (HSC)** is the progenitor of all the cells in the blood.

Traditionally, hematopoietic tissues are divided into:

1. **Myeloid tissues:**
   - **Bone marrow**
   - **Cells derived from bone marrow**: Erythrocytes (RBCs/Red blood cells), platelets (thrombocytes), granulocytes, and monocytes.
     - **Granulocytes**: The term granulocyte generally refers collectively to neutrophils, eosinophils and basophils.
2. **Lymphoid tissues:**
   - Thymus
   - Lymph nodes
   - Spleen

The **common lymphoid progenitor cell gives rise to B, T, and natural killer (NK) cell precursors.** They mature to form respective lymphoid cells.

Note: This division is mainly descriptive and does not accurately reflect normal physiology or disease processes.
Examples:

- Bone marrow is the source of all lymphoid progenitor cells despite containing relatively few lymphocytes.
- Long-lived plasma cells and memory lymphocytes reside within the marrow.
- Myeloid leukemias originate in bone marrow but frequently involve the spleen and lymph nodes.
- Certain red cell disorders arise from abnormalities of lymphocytes, such as autoantibody production.

Therefore, diseases of myeloid and lymphoid tissues often overlap.

Functions of Blood Cells

The formed elements of blood are red cells, white cells, and platelets. The main functions of blood cells are presented in **Table 11.1**.

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TABLE 11.1: Main functions of formed elements of blood.

Type of blood cell	*Main function*
Red blood cells	Delivery of oxygen to tissues
White blood cells	Defense against infectious organisms
Lymphocytes	Immune regulation
Platelets	Hemostasis

NORMAL HEMATOPOIESIS

Definition: Hematopoiesis (hemopoiesis) is the continuous process by which all circulating blood cells are generated from hematopoietic stem cells (HSCs).

Sites of hematopoiesis: During various phases of life, they differ **(Table 11.2)**.

Adult hematopoiesis: At birth, hematopoiesis occurs throughout the skeleton.

- Following puberty, activity progressively decreases in distal bones.
- In adults, active hematopoiesis is largely confined to the axial skeleton.
- Approximately half of the total marrow space remains hematopoietically active.

Terminology used in hematopoiesis: The meaning of the terms used in hematopoiesis is shown in **Table 11.3.**

Normal Development of Blood Cells

The hematopoietic system is a hierarchy of cells in which pluripotent hematopoietic stem cells (HSCs) proliferate and differentiate. After several steps, HSCs finally give rise to mature blood cells **(Fig. 11.1)**.

TABLE 11.3: Different terminologies used in hematopoiesis.

Terminology	
Pluripotent	Ability to generate all mature hematopoietic cells
Multipotent	Ability to produce a limited range of differentiated cell lineages appropriate to their location
Unipotent	Restricted ability to differentiate and generate one specific cell type

Q. Write a short note on the contents of bone marrow.

Hematopoietic Stem Cells (HSCs)

- HSCs occupy the highest level of the hematopoietic hierarchy.
- These cells maintain blood cell production throughout life.

Essential Properties of HSCs

1. **Pluripotency:** Ability of a single stem cell to generate every mature blood cell type.
   - Produces erythrocytes, granulocytes, monocytes, platelets, and lymphocytes
2. **Self-renewal:** Ability to generate daughter stem cells that preserve the stem cell pool.
   - Without self-renewal, stem cells would eventually become depleted. Hematopoiesis could not be sustained.

Hematopoietic stem cell niche: Self-renewing stem cells reside within specialized marrow microenvironments known as stem cell niches.

- These niches contain stromal cells and supporting extracellular factors
- **Functions:** Maintain stem cell survival, protect stem cells and regulate self-renewal.

The hematopoietic hierarchy is presented in **Flowchart 11.1**.

Clinical relevance: Granulocyte colony-stimulating factor (**G-CSF**) can mobilize HSCs from marrow niches into blood. Consequently, peripheral blood has become a major source of stem cells for transplantation.

Normal Erythropoiesis

Q. Write a short note on erythropoietin.

- Erythropoiesis is the process by which marrow hematopoietic stem cells pass through several stages.
- They proliferate, differentiate, and mature to form red blood cells (RBCs).

Stages: Various stages of erythropoiesis are shown in **Figure 11.2**.

TABLE 11.2: Different sites of hematopoiesis during various phases of life.

Phase	*Period*	*Site*
Yolk sac (mesoblastic) phase	First 3 months of gestation	Yolk sac
Hepatic phase	6th–7th week of gestation until birth	Liver (chief site until birth); spleen (minor site)
Medullary (myeloid) phase	From the 5th month of gestation (main site from about the 7th month) and continuing throughout life	Bone marrow
Infants and children (up to puberty)	Birth to puberty	Bone marrow throughout the skeleton; red marrow gradually gets replaced by yellow (fatty) marrow in the long bones
Adults	After puberty	Axial skeleton predominates (vertebrae, sternum, ribs, skull, pelvis); active marrow is limited to the proximal ends of long bones (femur, humerus)

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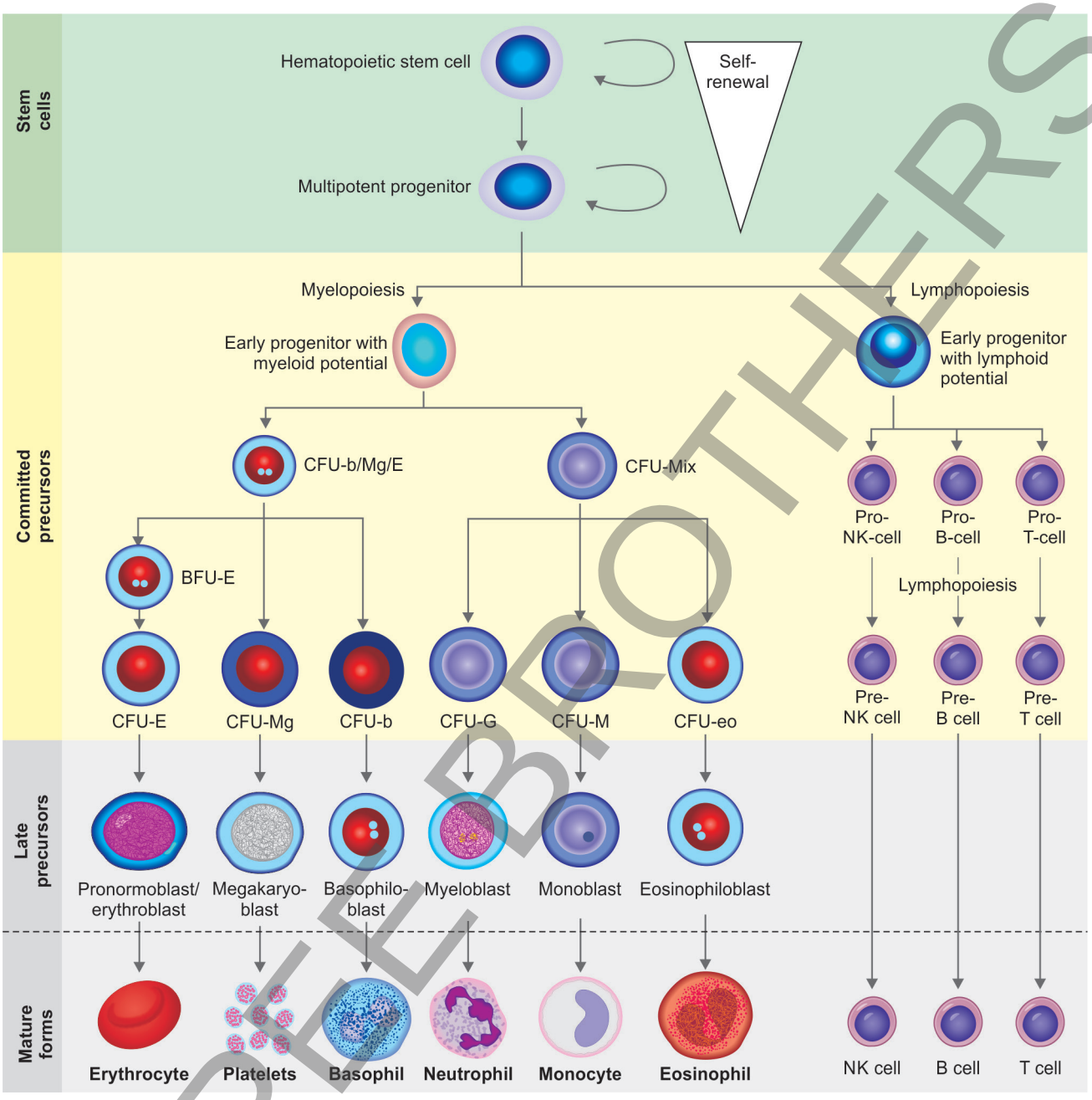

Fig. 11.1: Different stages of hematopoiesis.

(Baso: basophil; BFU: burst forming unit; CFU: colony forming unit; E: erythrocyte; Eo: eosinophil; G: granulocyte; M: macrophage; Mg: megakaryocyte; NK: natural killer).

Features of Mature RBCs

- Anucleate cells.
- **Diameter: 7–8 µm.** Similar in size to **small lymphocyte nuclei**.
- **Shape:** Round and biconcave disks.
- **Cytoplasm:** Reddish, eosinophilic.
- **Central pallor:** The center is paler than the outer rim. Occupies approximately **one-third of the total cell diameter**.
- **Life span:** Average life span of RBCs: **120 days.**

Myelopoiesis (Granulopoiesis)

- Myelopoiesis (granulopoiesis) results in the production of:
  - Neutrophils.
  - Eosinophils.
  - Basophils.
  - Monocytes.
- **Stages:** Various stages of myelopoiesis are shown in **Figure 11.3**.

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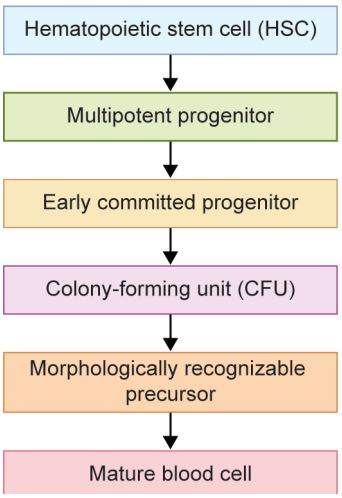
Flowchart 11.1: Hematopoietic hierarchy.



Megakaryopoiesis (Thrombopoiesis)

- Megakaryopoiesis (thrombopoiesis) is the process of **platelet formation**.
- **Stages:** Various stages of megakaryopoiesis are shown in **Figure 11.4.**

Regulation of Hematopoiesis

The production of blood cells is controlled primarily by hematopoietic growth factors.

These factors regulate the proliferation, survival, and differentiation of progenitor cells.

- **Colony-stimulating factors (CSFs):** These growth factors were initially identified for their ability to support blood-cell colony formation in culture.
- **Early-acting growth factors: These include KIT** ligand, which acts on early committed progenitors, and FLT3 ligand acts mainly on early hematopoietic stem/progenitor cells.
- **Lineage-specific growth factors** and their principal targets are presented in **Table 11.4.**

Functional Significance

These factors act through feedback mechanisms that adjust marrow output according to physiologic demand. This regulation maintains normal numbers of red cells, white cells, and platelets.

HEMATOPOIESIS IN DISEASE

Increased Hematopoietic Activity

Infections and inflammatory conditions stimulate the marrow to increase granulocyte production through growth factors and cytokines.

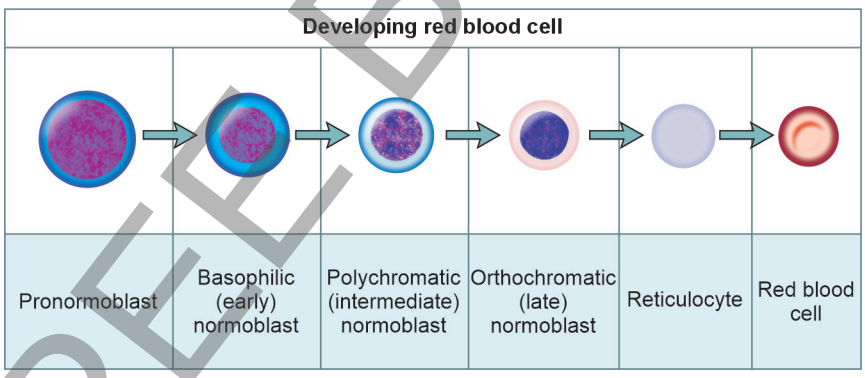


Fig. 11.2: Different stages of erythropoiesis.

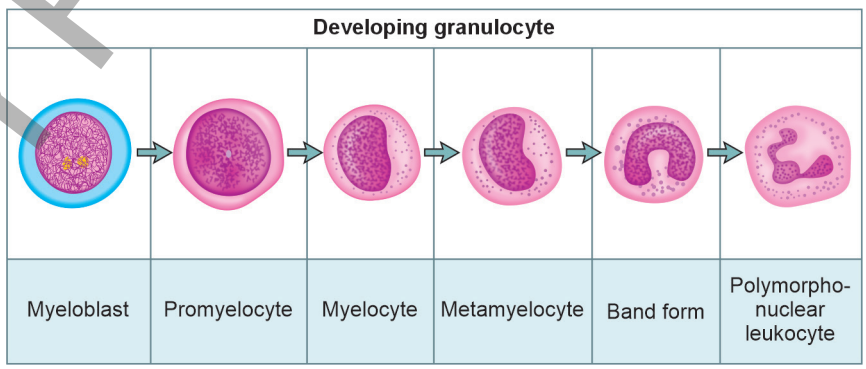


Fig. 11.3: Different stages of myelopoiesis.

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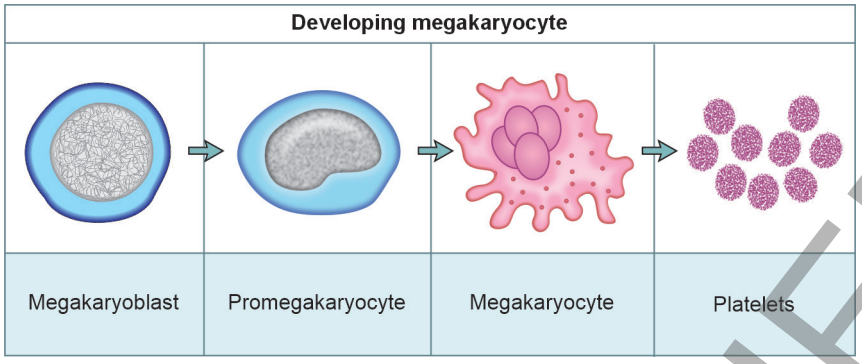


Fig. 11.4: Different stages of megakaryopoiesis.

TABLE 11.4: Lineage-specific growth factors.

Growth factor	*Principal target*
Erythropoietin	Erythroid progenitors
GM-CSF	Granulocyte-monocyte progenitors
G-CSF	Granulocytic progenitors
Thrombopoietin	Megakaryocytic progenitors

Compensatory Changes in Anemia

1. Compensatory Hyperplasia

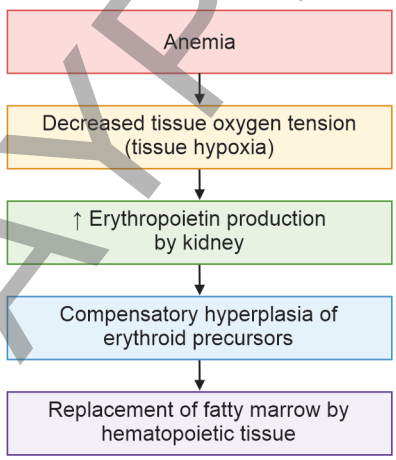
Mechanism (Flowchart 11.2)

- Anemia is associated with a **decrease in tissue oxygen tension**.
- Tissue hypoxia induced by anemia triggers **increased production of erythropoietin** from specialized cells in the kidney.
- **Exception:**
  - Anemia caused by **chronic renal failure**.
  - Anemia caused by **chronic inflammation**.

Effects of erythropoietin

- Stimulates **compensatory hyperplasia of erythroid precursors** in the bone marrow.

Flowchart 11.2: Pathogenesis of compensatory hyperplasia of bone marrow.



- Results in **replacement of fatty marrow by hematopoietic tissue**.

2. Extramedullary Hematopoiesis

- Appearance of **hematopoietic tissue outside the bone marrow** in secondary hematopoietic organs.
- Normally, cells of the **myeloid lineage** arise in the **central bone marrow (medullary cavity)**.

Mechanism of extramedullary hematopoiesis (Flowchart 11.3)

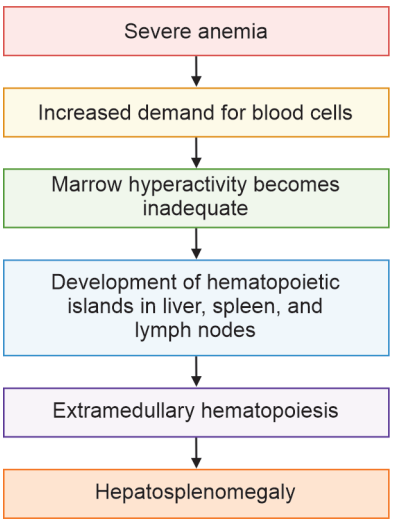
- In severe anemia, the increased demand for blood cells cannot be met by compensatory marrow hyperactivity alone.
- Hematopoietic islands develop in the liver, spleen, and lymph nodes.

Consequences: Results in **hepatosplenomegaly**.

Causes

- **Severe anemia:** Thalassemia major, sickle cell anemia.
- **Bone marrow disorders:** Myelofibrosis.

Flowchart 11.3: Mechanism of extramedullary hematopoiesis.



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ANTICOAGULANTS IN HEMATOLOGY

PA13.3: Describe collection of specimens and identify coagulants and anticoagulant bulbs, instruments.

Q. Write a short on various types of anticoagulants used in hematology. Mention their mode of action. List the uses of trisodium citrate.

- Blood coagulates when withdrawn from blood vessels.
- Anticoagulants are **substances that prevent clotting of blood**.
- They are essential for the collection, preservation, and laboratory analysis of blood samples.

Classification of Anticoagulants

I. Calcium Chelating Agents

Mechanism

- Calcium is essential for multiple steps in the coagulation cascade.
- These anticoagulants prevent coagulation by binding calcium ions.

Types

1. Ethylenediaminetetraacetic acid (EDTA)
2. Oxalates
3. Sodium citrate

II. Heparin

Mechanism

- Heparin potentiates antithrombin activity, inhibiting thrombin and factor Xa and other activated coagulation factors.
- Produces rapid anticoagulation.

Calcium Chelating Agents

1. Ethylenediaminetetraacetic Acid (EDTA)

- **Forms used:**
  - Disodium EDTA
  - Tripotassium EDTA (preferred in automated cell counters due to better solubility) ICSH (International Council for Standardization in Hematology) now recommends Dipotassium EDTA over tripotassium EDTA because it has less hyperosmolar effect on blood cells.
- **Concentration:** 1.5–2.0 mg/mL of blood (commonly 2 mg/mL)
- **Mechanism of action:**
  - Chelates calcium ions. Removes free calcium from blood.
  - Prevents coagulation.
- **Advantages:**
  - Best preservation of blood cell morphology.
  - Cell morphology remains satisfactory for several hours.
  - Cell counts remain reliable for prolonged periods.
  - **Anticoagulant of choice for routine hematology**.

Uses of EDTA

- **Cell counts:** RBC count, total leukocyte count (TLC), differential leukocyte count, absolute eosinophil count, platelet count, and reticulocyte count
- **Hematological tests:** Hemoglobin estimation, hematocrit/PCV, HbF estimation, and hemoglobin electrophoresis
- **Morphological studies:** Peripheral blood smear examination

Effects of EDTA on Blood Cells

RBC changes

- Spherocytic appearance
- Macrocytic appearance
- Crenation

WBC changes

- **Neutrophils:**
  - Separation of nuclear lobes
  - Cytoplasmic vacuoles
  - Loss of granules
- **Monocytes and Lymphocytes:**
  - Irregular nuclear lobulation
  - Cytoplasmic vacuolation

Platelet Changes

- Swelling
- Disintegration
- Pseudothrombocytopenia (false low platelet count) is a recognized clinical pitfall. It occurs in ~0.1% of the general population and must be identified promptly to avoid unnecessary diagnostic workup.

Effects of EDTA on hematological parameters are presented in **Table 11.5**.

Disadvantages: More expensive than oxalate. Not suitable for coagulation studies.

2. Oxalate

a. **Mechanism of action:** Chelates calcium ions and prevents coagulation.

Types of Oxalates

a. **Potassium oxalate:**
   - **Effect:** Shrinks RBCs. Therefore, **not suitable for** PCV, ESR, and peripheral smear.

b. **Ammonium oxalate:**
   - **Effect:** Causes RBC swelling. Therefore, **not suitable for PCV**, ESR, and peripheral smear.

TABLE 11.5: Effects of EDTA on hematological parameters.

Parameter	*Effect*
Hematocrit (PCV)	Increased
Mean cell volume (MCV)	Increased
Osmotic fragility	Increased
Total WBC count	Decreased on storage
Platelet count	Decreased on storage

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c. **Double oxalate (balanced oxalate)**
- **Composition:** Ammonium oxalate to potassium oxalate ratio = 3:2
- **Rationale:** Ammonium oxalate causes RBC swelling, and potassium oxalate causes RBC shrinkage. Combining them balances their effects.

Concentration: 2 mg/mL blood

Disadvantages
- Poor preservation of blood cell morphology.
- Toxic.
- Not suitable for blood transfusion.
- Largely replaced by EDTA.

3. Sodium Citrate

Mechanism of Action
- Binds calcium ions.
- Forms a soluble calcium citrate complex.
- Prevents coagulation.

Disadvantages
- Used as a liquid anticoagulant.
- Dilutes blood sample.
- Not suitable for cell counts and hemoglobin estimation.

Uses of Sodium Citrate
a. ***Coagulation studies***
- **Anticoagulant used**
  - 3.2% trisodium citrate dihydrate or
  - 3.8% trisodium citrate pentahydrate
- **Ratio:** 1 part citrate: 9 parts blood
- **Example:** 0.5 mL citrate + 4.5 mL blood
- **Used for:** PT, APTT, thrombin time, and coagulation factor assays

b. ***ESR (Westergren method)***
- 3.8% trisodium citrate
- **Ratio:** 1 part citrate: 4 parts blood
- **Example:** 0.4 mL citrate + 1.6 mL blood

c. ***Blood banking***
- **Previously used:** Acid Citrate Dextrose (ACD)
- **Currently used:** Citrate Phosphate Dextrose Adenine (CPDA)

Heparin
- **Mechanism of action:** Heparin works by binding to and enhancing the inhibitory activity of antithrombin against several serine proteases, most importantly factors IIa (thrombin), Xa, and IXa. Produces immediate anticoagulation.
- **Collection method:** The syringe is heparinized by coating its inner surface with heparin. Blood is then collected.

Uses
- **Hematology:** Osmotic fragility test (hereditary spherocytosis)
- **Red cell enzyme studies:** G6PD deficiency and pyruvate kinase deficiency
- **Biochemistry:** Electrolyte estimation
- **Clinical laboratory:** Arterial blood gas (ABG) analysis

Advantages: Rapid anticoagulant action. Minimal hemolysis.

Disadvantages: Expensive, causes platelet clumping, causes leukocyte clumping, not suitable for automated cell counters, produces a bluish background in peripheral smear, and anticoagulant effect is temporary.

Commonly used anticoagulants and their uses are presented in **Table 11.6**.

TABLE 11.6: Commonly used anticoagulants and their uses.

Anticoagulant	*Mechanism*	*Major uses*
EDTA	Chelates calcium	CBC, peripheral smear, Hb estimation, Hb electrophoresis
Double oxalate	Chelates calcium	Rarely used; replaced by EDTA
Sodium citrate	Forms a calcium citrate complex	Coagulation studies, ESR, blood bank
Heparin	Inhibits thrombin formation	ABG, electrolyte estimation, osmotic fragility test, enzyme studies
Antiglycolytic agent		
Sodium fluoride	Antiglycolytic action	Blood glucose estimation

(ABG: arterial blood gas; EDTA: ethylenediaminetetraacetic acid).

Sodium Fluoride
- It is antiglycolytic agent used to preserve glucose in collected blood.
- **Mechanism of action:** Acts as an **antiglycolytic agent**. Inhibits glycolysis in blood cells. Prevents utilization of glucose after collection.
- **Use: Blood glucose estimation**.

Vacutainers
Q. Write a short note on a vacutainer.
- Vacutainers are vacuum tubes used for blood collection (**Fig. 11.5 and Table 11.7**).
- Have premeasured anticoagulants.
- Ensure correct anticoagulant-to-blood ratio.
- Have largely replaced syringe collection.

Collection of Blood
Venous Blood
- **Methods:** Syringe method or Vacutainer method

Capillary Blood
- **Sites:** Finger prick or heel prick.

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Fig. 11.5: Different types of vacuum tubes.

TABLE 11.7: Common vacutainer tubes, their color, content, and uses.

Color of the top	*Contents*	*Uses*
Red	Plain tube (no anticoagulant)	Serum studies
Purple/Lavender	EDTA	Routine hematology
Light Blue	3.2% Sodium citrate	Coagulation studies
Gray	Sodium fluoride	Glucose estimation
Green	Heparin	ABG, electrolytes, enzyme studies, osmotic fragility test
Black	Citrate	ESR

Arterial Blood

- **Site:** Usually the radial artery; femoral or other sites may be used when appropriate.
- **Use:** Blood gas analysis

Complications of Venipuncture

Q. Write a short note on complications of venipuncture.

- Ecchymosis
- Hematoma
- Syncope (fainting)
- Failure to obtain blood due to a missed vein
- Difficulty locating veins in obese individuals
- Hemolysis of blood sample

Causes of Hemolysis

- Narrow bore needle
- Excessive suction during collection
- Water contamination of the syringe
- **Importance:** Hemolyzed samples are unsuitable for laboratory testing.

RED BLOOD CELL DISORDERS

- Disorders affecting the number, structure, or function of RBCs.
- Major categories:
  - **Anemia:** Decrease in circulating RBC mass
  - **Polycythemia (Erythrocytosis):** Increase in circulating RBC mass

ANEMIA

PA13.2: Define and classify anemia. Enumerate and describe the investigation of anemia.

Introduction

Q. Define anemia.

Definition: Anemia is the **reduction in total circulating red cell mass below normal limits.**

- Results in **reduced oxygen-carrying capacity** of blood, leading to **tissue hypoxia.**

Practical diagnosis: Since direct measurement of RBC mass is difficult, anemia is usually diagnosed by:

- **Decreased hemoglobin concentration (Hb): Most commonly used diagnostic criterion.**
- **Decreased hematocrit (HCT)/packed cell volume (PCV)**
- **Decreased RBC count**

Hemoglobin and hematocrit generally correlate with RBC mass, except when plasma volume is altered:

- Fluid retention causes a dilutional fall in Hb/Hct
- Dehydration leads to falsely elevated Hb/Hct

WHO criteria for anemia: For non-pregnant adults at sea level, Hb <13 g/dL in men and <12 g/dL in women is commonly used.

Classification

Q. Classify anemia/give the etiological classification of anemia.

Anemia can be classified according to RBC morphology and etiology.

Morphological Classification (Table 11.8 and Fig. 11.6)

Based on:

1. **RBC Size: Normocytic, microcytic**, or **macrocytic**
2. **Degree of hemoglobinization: Normochromic** or **hypochromic** (central pallor more than one-third of the diameter of the RBC).

Etiological Classification

Q. Etiological classification of anemia.

The etiological classification of anemia is presented in **Table 11.9**. Major categories are as follows:

1. **Blood loss:**
   - Acute hemorrhage
   - Chronic blood loss
2. **Increased RBC destruction (hemolytic anemia):**
   - Intrinsic RBC defects
   - Extrinsic causes

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TABLE 11.8: Morphological classification of anemia.

Type of anemia	*Microcytic hypochromic*	*Normocytic normochromic*	*Macrocytic*
Size of RBCs	Smaller than normal	Normal	Larger than normal
Central pallor in RBCs	More than 1/3	Normal	Normal
Mean corpuscular volume (MCV)	Reduced (<80 fL)	Normal (80-100 fL)	Increased (>100 fL)
Mean corpuscular hemoglobin concentration (MCHC)	Reduced (<30 g/dL)	Normal (31–36 g/dL)	Normal (31–36 g/dL)
Examples	Iron deficiency anemia, thalassemia, sideroblastic anemia	Acute blood loss, anemia of chronic diseases, anemia due to bone marrow failure	Deficiency of vitamin B_{12} and folic acid

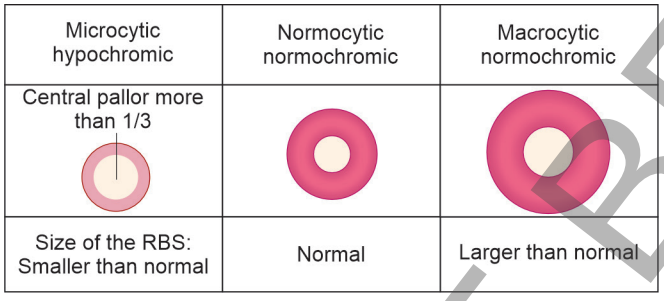

Fig. 11.6: Morphological classification of anemia.

3. **Decreased RBC production:**
   - Iron deficiency
   - Megaloblastic anemia
   - Aplastic anemia
   - Anemia of chronic disease

Anemia may be **absolute** (actual decrease in RBC mass) or **relative** (normal RBC mass with increased plasma volume). The term "anemia" is conventionally used for absolute anemia.

Classification of severity of anemia is presented in **Box 11.1.**

Clinical Features of Anemia (Fig. 11.7)

Factors Influencing Symptoms

Irrespective of the cause, anemia, when severe, presents with certain clinical features. The symptoms depend on four main factors:

1. **Speed of onset:**
   - **Rapid onset:** More symptoms
   - **Gradual onset:** Better compensation

TABLE 11.9: Etiological classification of anemia (based on pathogenesis).

Major mechanism	*Examples*
1. Blood Loss	
Acute hemorrhage	Trauma, surgery, obstetric bleeding
Chronic blood loss	Gastrointestinal bleeding, peptic ulcer, hemorrhoids, gynecological blood loss
2. Increased Red Cell Destruction (Hemolytic Anemia)	
A. Inherited Disorders	
Membrane defects	**Hereditary spherocytosis,** hereditary elliptocytosis
Enzyme deficiencies	G6PD deficiency, pyruvate kinase deficiency, hexokinase deficiency
Defective globin synthesis	**Thalassemia syndromes**
Structural hemoglobin abnormalities	**Sickle cell disease,** unstable hemoglobins
B. Acquired Disorders	
Membrane-anchor protein defects	Paroxysmal nocturnal hemoglobinuria (PNH)
Immune-mediated hemolysis	Autoimmune hemolytic anemia, transfusion reactions, and **hemolytic disease of the newborn**
Mechanical destruction	Prosthetic heart valves, microangiopathic hemolytic anemia
Physical trauma	Long-distance running, repetitive mechanical injury
Infections	Malaria, babesiosis
Toxic/Chemical injury	Snake venom, clostridial sepsis, lead toxicity
Membrane lipid abnormalities	Severe liver disease, abetalipoproteinemia
Splenic sequestration	Hypersplenism
3. Decreased Red Cell Production	
A. Inherited Disorders	
Stem cell defects	Fanconi anemia, telomerase-related disorders
Defective erythroid maturation	Thalassemia syndromes
B. Nutritional Deficiencies	
Impaired DNA synthesis	Vitamin B_{12} deficiency, folate deficiency
Impaired hemoglobin synthesis	Iron deficiency anemia
C. Acquired Disorders	
Erythropoietin deficiency	Chronic kidney disease, anemia of chronic disease

(Contd...)

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(Contd...)

Major mechanism	*Examples*
Immune-mediated marrow suppression	Aplastic anemia, pure red cell aplasia
Iron sequestration due to inflammation	Anemia of chronic inflammation
Primary marrow neoplasms	Leukemia, myelodysplastic syndrome, myeloproliferative neoplasms
Marrow infiltration	Metastatic tumors, granulomatous diseases
Infection of erythroid precursors	Parvovirus B19 infection
Miscellaneous causes	Endocrine disorders, chronic liver disease

(G6PD: glucose-6-phosphate dehydrogenase; PK: pyruvate kinase)

2. **Severity:**
   - **Mild anemia:** Usually asymptomatic
   - **Severe anemia:** Marked symptoms

BOX 11.1: Traditional classification of severity of anemia.

Grade	*Hemoglobin*
Mild	9.1–10.5 g/dL
Moderate	6–9 g/dL
Severe	<6 g/dL

3. **Age:**
   - Young individuals tolerate anemia better
   - In older people, symptoms develop earlier
4. **Underlying disease:** Symptoms may reflect the primary disorder. Example: Iron deficiency due to gynecologic disease may present with vaginal bleeding.

Presenting Features

In anemia, the lowered oxygen content of the circulating blood leads to tissue hypoxia. General clinical features are either due to tissue hypoxia or compensatory mechanisms **(Fig. 11.7)**.

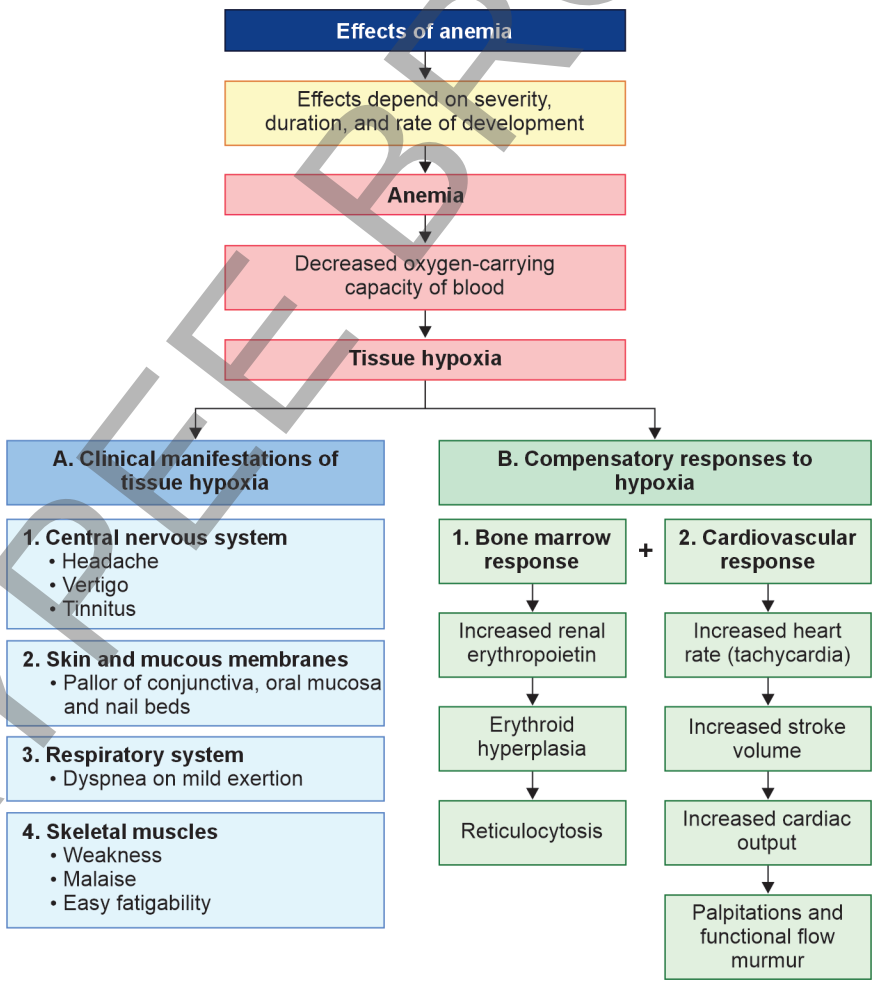

Fig. 11.7: Clinical features and effects of anemia.

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BOX 11.2: General scheme of routine investigation of anemia.

Routine investigations:

- Estimation of hemoglobin and packed cell volume (hematocrit) (*refer* Chapter 15)
- Complete blood counts (CBC): RBC, WBC, and platelet counts
- Peripheral smear examination (*refer* pages 422-424)
- Red cell indices
- Reticulocyte count
- Erythrocyte sedimentation rate (*refer* pages 426-427)
- Bone marrow examination (*refer* pages 428-430)
- Special investigations: Depends on the type of anemia (*refer to* individual types of anemia)

Features Due to Tissue Hypoxia

- **General symptoms:** Weakness, malaise, easy fatigability, and lethargy
- **Respiratory:** Dyspnea on exertion
- **Skin and Mucosa:** Pallor of conjunctiva, tongue, and nail beds

  Pallor + Icterus → Suggests **Hemolytic anemia**
- **CNS features:** Headache, vertigo, tinnitus, dizziness, dimness of vision, lack of concentration, and faintness
- **Severe hypoxia:** Angina pectoris, renal hypoperfusion, oliguria, and anuria

Features Due to Compensatory Mechanisms

- **Cardiovascular system:** Tachycardia, palpitations, flow murmur, hyperdynamic circulation, cardiomegaly, and dyspnea on exertion
- **Severe cases:** Congestive cardiac failure
- Impaired concentration ability.

Investigations of Anemia

The general scheme of routine investigation of anemia is listed in **Box 11.2**.

Complete Blood Count (CBC/Hemogram) (Table 11.10)

Q. Write a short note on complete blood counts (CBC) (hemogram).

Various parameters obtained in automated cell counters are listed in **Table 11.11**.

Q. Write a short note on various parameters obtained in automated cell counters.

Red Cell Indices

Q. Write a short note on red cell indices.

- Red cell indices are laboratory parameters used to characterize anemia and identify its cause.
- Quantitative measurements of RBC size and hemoglobin content.
- Useful for morphological classification and differential diagnosis of anemia.

TABLE 11.10: Complete blood counts.

RBC Parameters
◆ Hemoglobin
◆ RBC count
◆ Hematocrit (HCT)/packed cell volume (PCV)
◆ Reticulocyte count
◆ Peripheral smear
◆ RBC morphology
WBC Parameters
◆ Total leukocyte count
◆ Differential leukocyte count
Platelet Parameters
◆ Platelet count
◆ Platelet morphology
Others
◆ Hemoparasites
◆ Any abnormal/atypical cell

TABLE 11.11: Various parameters obtained in automated cell counters.

Red cell indices	◆ Mean platelet volume (MPV)
◆ Mean corpuscular volume (MCV)	◆ Hematocrit (Hct)/packed cell volume (PCV)
◆ Mean corpuscular hemoglobin (MCH)	◆ Total leukocyte count
◆ Mean corpuscular hemoglobin concentration (MCHC)	◆ RBC count
◆ Red cell distribution width (RDW)	◆ Platelet count
	◆ Reticulocyte count
	◆ Differential leukocyte count (3-part or 5-part)

Q. Write a short note on mean corpuscular volume.

Mean Corpuscular Volume (MCV)

- Average volume of an RBC.
- **Normal range: 80–100 fL**
- **Significance:** Most important index for morphological classification **(Table 11.12)**.

Mean Corpuscular Hemoglobin (MCH)

- Average hemoglobin mass per RBC.
- **Normal range: 27–32 pg**

Mean Corpuscular Hemoglobin Concentration (MCHC)

Q. Write a short note on mean corpuscular hemoglobin concentration.

- Average concentration of hemoglobin within packed RBCs.
- **Normal range: 31–36 g/dL.**

TABLE 11.12: Use of MCV in the morphological classification of anemia.

MCV (mean corpuscular volume)	*Type*
<80 fL	Microcytic
80–100 fL	Normocytic
>100 fL	Macrocytic

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TABLE 11.13: Significance of RDW.		
Condition	*MCV*	*RDW*
Iron deficiency anemia	↓	↑
Thalassemia trait	↓	Normal

Red Cell Distribution Width (RDW)

Q. What is RDW? What is its significance?

- Coefficient of variation of RBC volume.
- Quantitative measure of **anisocytosis (i.e., variation in size of RBCs).**
- **Normal range: 11.5–14.5%**
- **Significance of RDW (Table 11.13): A RDW reflects variation in RBC volume (anisocytosis).**
  - **Low MCV + High RDW → Iron deficiency anemia**
  - **Low MCV + Normal RDW → Thalassemia trait**

Reticulocyte Count

Q. Write a short essay on reticulocytes, their morphology, staining methods, normal values, and their importance/utility.

- **Immature non-nucleated RBCs** containing residual RNA.
- They are slightly larger than the mature RBCs. They continue to synthesize hemoglobin after losing their nucleus.
- Reticulocytes stain ***polychromatically with Romanowsky stains,*** and hence, the term ***"polychromatophil"*** is used to indicate their presence in peripheral smear.

Methods of reticulocyte count: Visual method or automated method

Stains Used

- **Supravital stains: New methylene blue** and **brilliant cresyl blue.** When blood is briefly incubated in supravital stains, the RNA is precipitated **(Fig. 11.8)** as a dye-ribonucleoprotein complex

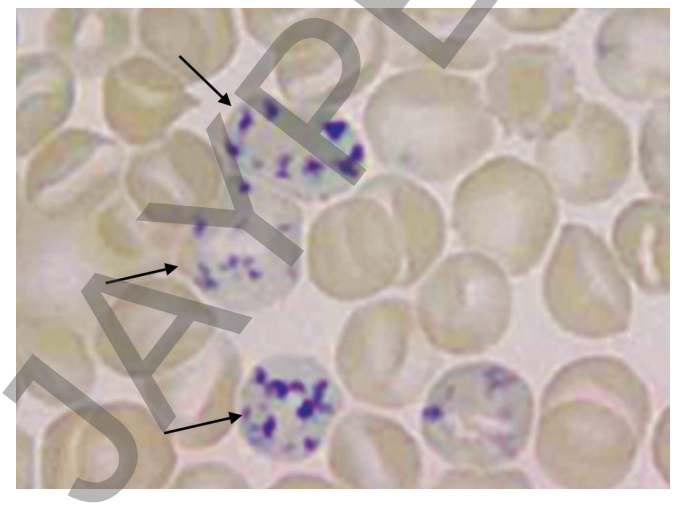

Fig. 11.8: Smear shows a reticulocyte (arrows) with blue filamentous/granular material (new methylene blue).

- **Normal values:** Reticulocyte count is expressed as a percentage of total red cells.
  - **Adults:** 0.5–2.5%
  - **Newborns (cord blood):** 1–7.0%

Importance

- Measures marrow erythropoietic activity.
- Distinguishes:
  - Regenerative anemia
  - Nonregenerative anemia

Causes of Reticulocytosis

Q. List the conditions in which reticulocyte count is increased.

Reticulocyte count is increased in:

- Hemolytic anemia
- Hemolytic crisis
- Acute hemorrhage
- Response to iron therapy
- Response to folate therapy
- Response to vitamin B_{12} therapy

Note: Reticulocytosis generally becomes evident within several days and peaks during the first 1–2 weeks after effective therapy.

Causes of Reticulocytopenia

Reticulocyte count is decreased in:

- Aplastic anemia
- Pure red cell aplasia
- Fanconi anemia
- Myelofibrosis
- Aplastic crisis (Parvovirus B19)

Special Investigations

Depending on the differential diagnosis, several other blood tests may be necessary to evaluate anemia. These include the following:

- **Iron studies:** These include serum iron levels, total iron-binding capacity (TIBC), transferrin saturation, and ferritin concentrations. This investigation will help to **distinguish among microcytic anemia** caused by iron deficiency, chronic inflammation, or thalassemia.
- **Serum and red cell folate and vitamin B_{12} concentrations**: These are low in megaloblastic anemia caused by folate and vitamin B_{12} deficiency, respectively.
- **Hemolysis workup:** Unconjugated bilirubin, LDH (lactate dehydrogenase), and haptoglobin
- **Hemoglobin analysis:** Hemoglobin electrophoresis
- **Immunological tests: Coombs (AHG) test**

Bone Marrow Examination

Tests performed on peripheral blood are usually sufficient to establish the cause of many types of anemia. But when anemia is accompanied by thrombocytopenia and/or granulocytopenia, it is more likely to be associated with marrow aplasia or infiltration. In such cases, a marrow

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examination is usually necessary. It is discussed on pages 428-430.

Indications

- Unexplained anemia
- Pancytopenia
- Suspected marrow infiltration
- Suspected marrow aplasia

ANEMIAS OF IMPAIRED RED CELL PRODUCTION

Most anemias due to decreased erythropoiesis result from inadequate dietary intake of nutrients, particularly iron, vitamin B_{12}, and folic acid.

IRON DEFICIENCY ANEMIA (IDA)

PA14.1: Describe iron metabolism and the etiology, investigations, and differential diagnosis of microcytic hypochromic anemia.

Anemia due to deficiency of iron causing defective hemoglobin synthesis → microcytic hypochromic anemia.

- **Iron deficiency anemia (IDA)** is the most common nutritional deficiency disorder worldwide.
- Results from inadequate iron availability for hemoglobin synthesis.
- Characterized by **microcytic hypochromic anemia**.
- Clinical manifestations are due to:
  - Anemia itself (reduced oxygen-carrying capacity of blood)
  - Depletion of iron-containing enzymes in tissues

Iron Metabolism

Normal Iron Balance

- **Total body iron:** Adult male: ~3.5–6 g and adult female: ~2.5 g
- Iron balance is maintained mainly by **regulation of intestinal absorption**.
- There is **no regulated pathway for iron excretion**.
- **Daily iron loss**: About **1–2 mg/day**. Through shedding of intestinal epithelial cells, skin epithelial cells, sweat, urine, hair, and nails.

Distribution of Iron

Iron is an essential metal present in the human body. The total body iron content is divided into functional and storage compartments. Iron in the body is extensively recycled between the functional and storage pools.

Functional Iron

- Present **mainly in hemoglobin, myoglobin, and iron-containing enzymes**

Storage Iron

- Approximately 20–30% of body iron.
- Present as **ferritin** and **hemosiderin**

TABLE 11.14: Serum ferritin and conditions associated.

Condition	*Ferritin level*
Normal serum ferritin	15–300 µg/L
Iron deficiency	<12–15 µg/L
Iron overload	Up to 5000 µg/L

Ferritin

- Protein–iron complex (apoferritin + iron)
- Water-soluble major storage form of iron.
- Found in liver, spleen, and bone marrow macrophages
- A small amount circulates in serum. Serum ferritin reflects body iron stores (**Table 11.14**).
- **Low serum ferritin:** Earliest biochemical marker of iron deficiency.

Hemosiderin

- Aggregate of partially degraded ferritin. Insoluble storage form
- Seen as cytoplasmic granules.
- Stored mainly in liver, spleen, and bone marrow macrophages
- **Iron overload:** Iron stored predominantly as hemosiderin.
- **Prussian Blue (Perl's stain):** Demonstrated by **Prussian Blue stain**. Appears blue-black due to reaction with potassium ferrocyanide.

Iron transport between functional and storage pools

- Storage iron can be mobilized when body iron requirements increase, such as after blood loss.
- Transfer of iron between storage and functional pools is mediated by **transferrin**.
- Transferrin is a plasma iron-binding protein synthesized in the liver.
- In normal individuals, **transferrin is approximately one-third saturated with iron**.
- Average serum iron levels: Males: **120 µg/dL** and females: **100 µg/dL**
- **Main function of transferrin**:
  - Delivers iron to cells, especially **erythroid precursors**.
  - Supplies iron required for **hemoglobin synthesis**.
- Erythroid precursors possess high-affinity transferrin receptors.
- Iron uptake occurs through **receptor-mediated endocytosis**.

Daily Dietary Iron Requirement

- The daily requirement are 8 mg/day for adult men and 18 mg/day for women aged 19–50 years.
- Approximately **1 mg of iron** must be absorbed daily to maintain normal iron balance.
- Only **10–15%** of ingested iron is absorbed.

Iron Absorption in the Duodenum

Sites: Duodenum and proximal jejunum

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Dietary sources: The diet contains iron either in the form of **heme** contained in animal products **and/or nonheme** iron in vegetables. The regulation of iron absorption in the duodenum differs for nonheme and heme iron.

Nonheme Iron Absorption

- Derived from vegetables.
- Most luminal nonheme iron exists as **Fe^{3+} (ferric iron)**.
- Ferrireductases reduce Fe^{3+} to **Fe^{2+} (ferrous iron)**.
- Fe^{2+} is transported across the apical membrane by **Divalent Metal Transporter 1 (DMT1)**.
- Frequently, **less than 5%** of dietary nonheme iron is absorbed.

Heme Iron Absorption

- Heme iron enters enterocytes through incompletely characterized transporters.
- Within the cytoplasm, heme is metabolized to release **Fe^{2+}**.
- Released Fe^{2+} joins the common intracellular iron pool.
- Heme iron is derived from animal products and is **highly bioavailable**.

Fate of Iron Within Duodenal Cells

After entering enterocytes, Fe^{2+} follows one of two pathways:

1. **Storage pathway:** Iron is stored as **mucosal ferritin**.
2. **Transport to blood: Ferroportin** transports Fe^{2+} across the basolateral membrane.
   - Iron oxidases **hephaestin** and **ceruloplasmin** convert Fe^{2+} to Fe^{3+}.
   - Fe^{3+} rapidly binds transferrin.
   - Transferrin delivers iron to red cell progenitors in bone marrow.

Hepcidin: Master Regulator of Iron Absorption

Q. Write a short note on the role of hepcidin in iron homeostasis.

Source

- Hepcidin is a peptide synthesized and released by the **liver**.
- Production increases when **intrahepatic iron levels rise**.

Effects of High Hepcidin

When the body has adequate iron stores, hepatocytes increase hepcidin production. Actions of hepcidin

- Inhibits iron transfer from enterocytes to plasma.
- Traps iron within duodenal cells as mucosal ferritin.
- Decreases iron absorption into the blood.
- Suppresses iron release from macrophages.
- **Reduces iron available for hemoglobin synthesis**.

Effects of Low Hepcidin

When the body iron begins to drop, the liver decreases hepcidin production and increases iron absorption.
Actions of low hepcidin:

- Facilitates intestinal iron absorption.
- Enhances mobilization of iron from macrophages.

Etiology and Pathogenesis of Iron Deficiency Anemia

Q. Discuss the causes (etiology/etiopathogenesis) of iron deficiency anemia.

Causes of Iron Deficiency (Table 11.15)

Iron deficiency results from:

1. **Dietary lack of iron**
2. **Impaired absorption**
3. **Increased requirement**
4. **Chronic blood loss**

1. Dietary Iron Deficiency

- Rare in high-resource countries.
- Dietary iron is present as both heme and non-heme iron; the relative contribution varies with diet.
- More common in low-resource countries because:
  - Food is less abundant.
  - Most dietary iron is present in poorly absorbable inorganic plant forms.

TABLE 11.15: Causes of iron deficiency anemia.

1. Dietary Deficiency *Common in:* ◆ Milk-fed infants ◆ older people with a poor diet ◆ Low socioeconomic groups ◆ Vegans/strict vegetarians
2. Impaired Absorption *Causes:* ◆ Celiac disease (sprue) ◆ Steatorrhea ◆ Chronic diarrhea ◆ Partial/total gastrectomy ◆ Gastritis
3. Increased Requirement Occurs in: Infancy, childhood, adolescence, pregnancy, and lactation
4. Chronic Blood Loss **The most common cause in developed countries** **Gastrointestinal:** ◆ Peptic ulcer ◆ Hemorrhoids ◆ Hookworm infestation ◆ Gastric carcinoma ◆ Colonic carcinoma ◆ Ulcerative colitis ◆ Aspirin-induced bleeding **Female Genital Tract:** ◆ Menorrhagia ◆ Metrorrhagia ◆ Uterine carcinoma **Urinary Tract:** ◆ Hematuria ◆ Tumors **Respiratory Tract:** ◆ Hemoptysis

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High-risk groups for dietary iron deficiency

a. **Infants:** High risk due to the very low iron content of milk.
   - Human breast milk contains approximately **0.3 mg/L** of iron.
   - Cow's milk contains about twice as much iron. The bioavailability of iron in cow's milk is poor.
b. **Poverty:** May consume suboptimal diets because of socioeconomic factors.
c. **Older adults:** Often consume restricted diets with little meat.
   - **Causes:** Limited income and poor dentition
d. **Vegans:** Lack heme iron in the diet.

2. Impaired Iron Absorption

Causes

- **Intestinal disorders:** Sprue, other causes of fat malabsorption (steatorrhea), chronic diarrhea
- **Gastrectomy:** Acidity normally enhances iron uptake. Reduced acidity diminishes absorption.
- **Dietary factors:** Certain dietary constituents may either enhance or inhibit iron absorption.

3. Increased Iron Requirement

High-risk groups

- **Growth periods:** Growing infants, children, adolescents
- **Premenopausal females:** Increased physiological iron requirements.
- **Pregnancy:** Requirement increases significantly.
- **Females in low-resource countries:** Multiple closely spaced pregnancies increase risk substantially.

4. Chronic Blood Loss

- The most **common cause in developed societies**
- Chronic blood loss is the leading cause of iron deficiency.

Sources of blood loss

- External hemorrhage
- Gastrointestinal tract bleeding
- Urinary tract bleeding
- Genital tract bleeding

Adult males and postmenopausal females

- Iron deficiency in these groups must be attributed to gastrointestinal blood loss until another cause is proven.
- Failure to investigate may lead to missed:
  - Gastrointestinal cancer
  - Other bleeding lesions

Clinical significance: Investigation of unexplained iron deficiency anemia may reveal occult bleeding sources such as cancer.

Pathogenesis of Iron Deficiency Anemia

Iron deficiency anemia (IDA) results from iron deficiency, which impairs **heme synthesis**. Irrespective of the cause, iron deficiency develops insidiously and is divided into three stages **(Flowchart 11.4)**.

Flowchart 11.4: Various stages of iron deficiency anemia.

Stage 1 (Depletion of iron stores)
Iron is adequate to maintain normal hemoglobin levels
Only serum ferritin decreased
Absence of stainable iron in bone marrow

↓

Stage 2 (Iron deficient erythropoiesis)
Decrease of serum iron
No anemia (Hb, MCV, and MCH within normal range).
Bone marrow shows iron-deficient erythropoiesis

↓

Stage 3 (Iron deficiency anemia)
Low serum iron, serum ferritin. Impaired hemoglobin production.
Morphologically, **first reduction in the size (microcytic) and later an increase in the central pallor (hypochromia) of RBCs**

Laboratory Findings

Q. Discuss the laboratory findings/investigations in iron deficiency anemia.

Q. Describe the peripheral blood picture and bone marrow findings in iron deficiency anemia.

Peripheral Blood

- **Hemoglobin:** Decreased
- **Hematocrit (PCV):** Decreased
- **Red cell indices:** MCV, MCH, and MCHC are reduced in IDA.
  - **MCV:** <80 fL (normal 82–98 fL)
  - **MCH:** <25 pg (normal 27–32 pg)
  - **MCHC:** <27 g/dL (31–36 g/dL)
  - **RDW: Increased** and >15%. A rising RDW may occur during evolving iron deficiency, but low serum ferritin is a more direct indicator of depleted iron stores.
- **Reticulocyte count:** Low or normal. Inappropriately low for the degree of anemia

Q. Write a short note on peripheral smear findings in iron deficiency anemia.

Peripheral Smear (Figs. 11.9A and B)

- **RBCs: Microcytic** (small) and **hypochromic** (pale).
  - **Microcytic:** Normal, mature RBCs are anucleate cells measuring 7–8 µm in diameter, similar in size to small lymphocyte nuclei. Microcytic RBCs in established IDA are **smaller than normal RBCs and smaller than the nuclei of small lymphocytes.**
  - **Hypochromic:** Normal red cells with sufficient hemoglobin show a zone of central pallor measuring about one-third of the cell diameter. In established iron deficiency, **the zone of pallor is enlarged, producing hypochromasia.** In severe anemia, central pallor occupies 2/3 to 3/4 of the cell, leaving only the peripheral rim of hemoglobin visible (ring/pessary cells).
  - **Moderate anisocytosis** (variation in size) and **poikilocytosis** (variation in shape).
  - **Severe cases:** Some of the RBCs are very thin and oval and are called pencil/cigar-shaped cells.
  - **Characteristic cell: Pencil cell**
- **WBCs:** Usually **normal**; eosinophilia may be seen in hookworm infestation.

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