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APPROACH TO AN ADULT PATIENT WITH A MACROCYTIC ANAEMIA

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Macrocytosis is described as an increase in the volume or size of a red blood cell (RBC). The parameter on the full blood count used to measure this, is the Mean Corpuscular Volume (MCV). An MCV >100 femtolitres (fL) is considered macrocytic. On a peripheral blood smear, a red blood cell is considered macrocytic if it is larger than the nucleus of a small mature lymphocyte. Macrocytosis may or may not be accompanied by anaemia.

The causes of a macrocytosis are broadly divided into five groups based on the mechanism:

1. Abnormalities of DNA metabolism e.g. vitamin B12 and folate deficiencies and drugs that interfere with DNA metabolism.
2. Increase in circulating immature red cells or "stressed" red cells, e.g. reticulocytosis in response to haemorrhage or haemolysis, aplastic anaemia, pure red cell aplasia, erythropoietin (EPO) effect.
3. Primary bone marrow disorders, e.g. myelodysplastic syndromes, leukaemia.
4. Lipid abnormalities, e.g. liver disease, hypothyroidism.
5. Unknown mechanism.

The following table outlines conditions which may cause a macrocytic anaemia.

Macrocytic Anaemia					
Condition	**Causes**	**Mechanism**	**Condition-specific clinical signs**	**Peripheral blood smear**	**Additional Investigations**
Vitamin B12 and folate deficiency	Nutritional deficiency • Vegans • Elderly • Alcoholism Malabsorption/GIT • Pernicious anaemia • Gluten-induced enteropathy • Gastrectomy intestinal resections Physiological deficiency • Pregnancy • Lactation Functional deficiency • Increased red blood cell turnover e.g. chronic haemolytic anaemias, sickle cell anaemia, leukaemias	Abnormality of DNA metabolism • Vitamin B12 is an essential co-enzyme and folate is a necessary substrate for DNA synthesis • Intrinsic factor (secreted by the gastric parietal cells) is required for the absorption of Vitamin B12 in the distal ileum	General signs of malnutrition Neurological symptoms • Optic atrophy • Dementia • Peripheral neuropathy • Subacute combined degeneration of the spinal cord	Oval Macrocytes Teardrop cells Neutrophil hypersegmentation Other cytopaenias /pancytopaenia	↓ Vitamin B12 ↓ Serum folate ↓ Red cell folate Positive Intrinsic factor antibodies and/or parietal cell antibodies ↑ LDH ↑ Unconjugated bilirubin

Condition	Causes	Mechanism	Condition-specific clinical signs	Peripheral blood smear	Additional Investigations
Drugs	Drugs that block/inhibit Vitamin B12 and folate absorption • Neomycin • Proton pump inhibitors e.g. omeprazole • metformin Drugs that inhibit enzymes required for DNA synthesis • Anti-epileptic e.g. phenytoin, barbiturates • Antibiotics e.g. Tetracycline • Antiretrovirals e.g. Zidovudine (AZT) • Methotrexate • Azathioprine Hydroxyurea	Abnormality of DNA metabolism • Multiple effects on folate metabolism / act as anti-metabolites for DNA synthesis		Stomatocytes Oval macrocytes Hypersegmented neutrophils Can be pancytopaenic	Folate level Vitamin B12 level ↑ LDH ↑ Unconjugated bilirubin
Liver disease	Any cause of liver disease	Lipid abnormalities • Liver disease causes increased deposition of lipids in the cell membranes of RBCs, thus increasing their size	Jaundice Enlarged or shrunken liver Signs of portal hypertension Ascites Gynaecomastia Spider angiomata	Round macrocytes Target cells Stomatocytes Rouleaux formation Acanthocytes Leucopaenia Thromobocytopaenia	Deranged Liver function tests
Alcoholic liver disease	• Direct effect of alcohol • Chronic liver disease • Nutritional	Combination of mechanisms • Direct toxic effect of alcohol on the red blood cell precursors • Co-existing nutrient deficiencies	Hepatomegaly or shrunken liver if cirrhotic Spider angiomata Dupuytren's contractures		Liver function tests ↑ GGT N/↓ Red cell folate ↓ serum vitamin B12
Asplenism or Hyposplenism	Splenectomy • Trauma • Tumour • Treatment e.g. for ITP Hyposplenism • Sickle cell disease • Coeliac disease	Lipid abnormalities • Excess RBC membrane lipids that usually are removed in the spleen are not effectively removed, resulting in larger RBCs		Howell-Jolly bodies Target cells Acanthocytes Pappenheimer bodies ± Neutrophilia, lymphocytosis or thrombocytosis	
Hypothyroidism	• Iodine deficiency • Auto-immune • Radiation • Surgical	Lipid abnormalities Erythropoietin effect • Thyroxine potentiates the action of erythropoietin, thus in deficiency there is reduced action and secretion of EPO	Dry coarse skin Hair loss Myxoedema Delayed relaxation of tendon reflexes	Hypersegmented neutrophils	Thyroid function tests ↓ T4 ↑ TSH

Condition	Causes	Mechanism	Condition-specific clinical signs	Peripheral blood smear	Additional Investigations
Reticulocytosis	• Haemorrhage • Haemolysis	Reticulocytes • Red blood cells that contain ribosomal RNA and are larger than mature RBC. Normally the percentage of circulating reticulocyte is low (0.5% – 2%). Any condition causing a marked increase in circulating reticulocytes will raise the MCV.		High reticulocyte count Fragments Spherocytes	↑ Reticulocyte count Haemolytic screen ↓ Haptoglobin ↑ Bilirubin (total and unconjugated) ↑ LDH Direct Coombs – positive
Abnormal red blood cell maturation	• Myelodysplastic syndrome (MDS) • Acute leukaemias • Aplastic Anaemia • Pure red cell aplasia	Primary bone marrow disorders Abnormal or "stressed" circulating red blood cells		Dysplastic features in one or more blood cell line Blasts Cytopaenias	Bone marrow biopsy Cytogenetic studies Flow cytometry

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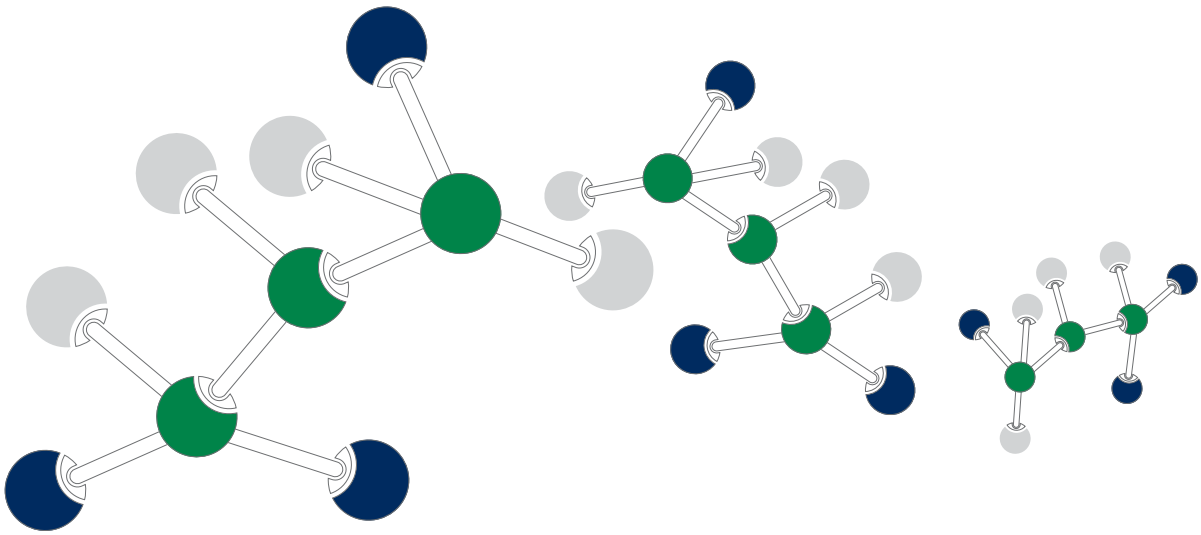

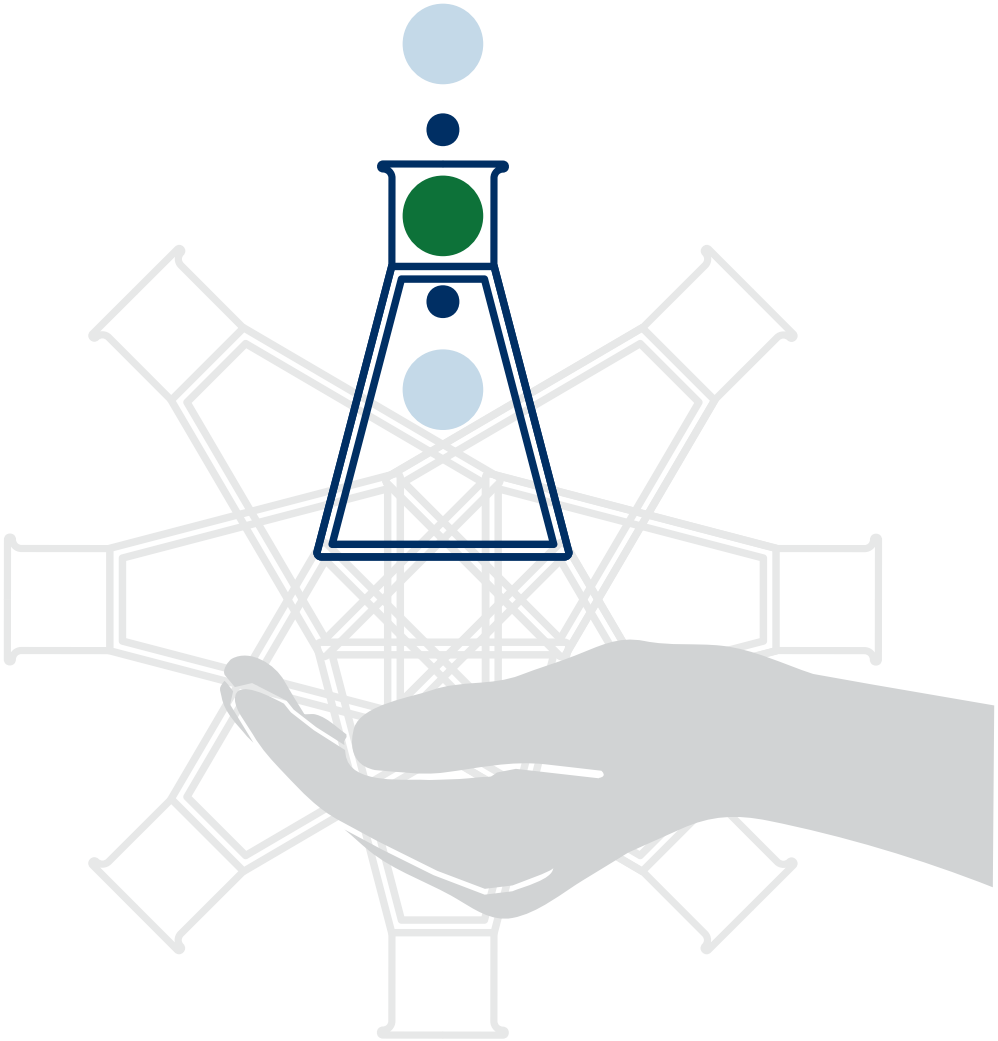

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