IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 15, Issue 6 Ser. III (Nov. –Dec. 2020), PP 23-41
www.Iosrjournals.Org

Hematopoiesis and Abnormal of Red Blood Cell Shapes in Different Diseases

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Date of Submission: 20-12-2020 Date of Acceptance: 03-01-2021

Haemopoisis

In the first few weeks of gestation the yolk sac is the main site of Hemopoiesis, from 6 weeks until 6-7 months of fetal life the liver and spleen are the main organs involved and continue to produce blood cells until about 2 weeks after birth. The bone marrow is the most important site from 6 to 7 months of fetal life and during normal childhood and adult life the marrow is the only source of new blood cells. In infancy all the bone marrow is Hemopoietic but, during childhood there is progressive fatty replacement of marrow throughout the long bones so that in adult life Haemopoietic marrow is confined to the central skeleton.

Even in these Hemopoietic areas, approximately 50% of the marrow consists of fat. The remaining fatty marrow is capable of reversion to hemopoiesis and in many diseases there is also expansion of Hemopoiesis down the long bones. More over the liver and spleen can resume their fetal Hemopoietic role so called **extramedullary** hemopoiesis.(Hoffbrand et all, 2016)

The formation of blood cells (hemopoiesis) is determined by the interaction of multiple genes and involves cytokines and other protein factors. The relative

ease with which hematopoietic cells can be studied and the development of new techniques in cell biology have enabled us to understand many of the factors determining cell renewal and differentiation. Based on this knowledge, major progress has been made in the last 15 yr in the treatment and diagnosis of many hematological disorders. In this chapter, we describe the cell types involved in normal hematopoiesis and their interactions with one another. Furthermore, the basic techniques necessary for the study of hematopoietic cells in the normal and pathological state are outlined. (Ronald Paquette, 2008)

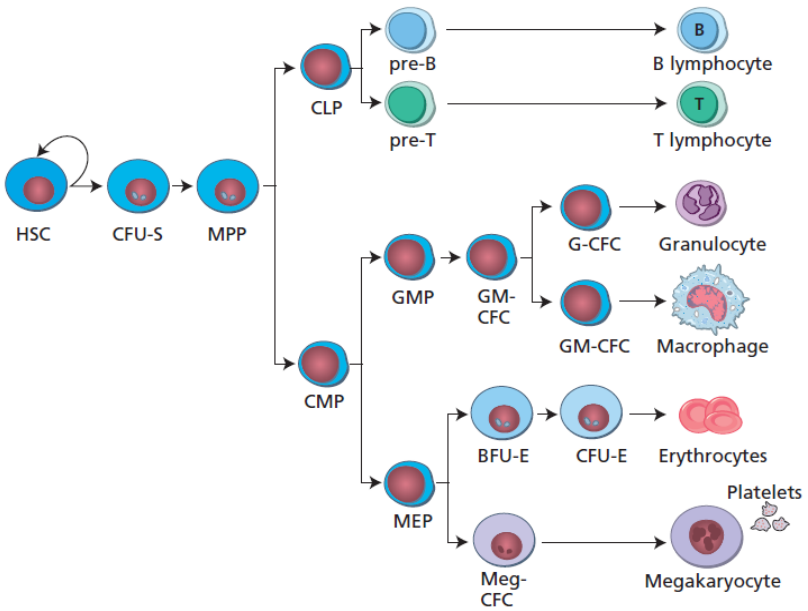


Figure: 1 Scheme of hematopoietic differentiation (Emma de Pater and Elaine Dzierzak, 2016)

Site of haemopoiesis

Fetus:	0-2 months	Yolk-sac
	2-7 months	Liver and Spleen
	5-9 months	Bone Marrow

Infants: Bone Marrow (particularly all bones)

Adults: Vertebrae, Ribs, Sternum, Skull, Sacrum, Pelvis and proximal end femur.

During the first few weeks of embryonic life, the formation of blood cells takes place in the yolk sac. Later, until the sixth or seventh month of fetal development, he liver and spleen are the major hematopoietic organs. By the time of birth, more than 90% of all new blood cells are formed in the bone marrow. Here, the progenitor cells are found, in various stages of development, situated in anatomical niches in the bone marrow from where they are then released into the marrow sinuses, the marrow circulation, and further on into the systemic circulation. During infancy and childhood, the marrow of all bones contributes to hematopoiesis. During adult life, hematopoietic marrow is restricted to certain bones e.g., pelvic bones, vertebral column, proximal ends of the femur, skull, ribs, and sternum). Even in these areas, a proportion of the marrow cavity consists of fat.

During periods of hematopoietic stress (e.g., in severe hemolytic anemias and in
Some myeloproliferative disorders), the fatty marrow as well as the spleen and
Liver can resume the production of blood cells. This situation is called extramedullary hematopoiesis. (Munker et al, 2006)

Erythropoiesis

Erythropoiesisis the generation of red blood cells carrying the to the tissues. This process, from the erythroid commitment of multipotent haemopoietic stem cells (HSCs), through the maturation of erythroblasts, to the terminal differentiation of red blood cells, is governed by complex transcriptional and epigenetic programmes, in response to extracellular signaling. Erythropoiesis normally maintains the steady state of an individual's red cell mass, producing 1011–1012 new cells per day to replace those that are lost through senescence or premature destruction. Furthermore, erythropoiesis must be able to respond rapidly to erythroid stress such as haemorrhage and haemolysis. Perhaps unsurprisingly, this system is remarkably sensitive to systemic disease, with anaemia being a common manifestation of a wide range of inherited and acquired clinical disorders. Understanding the basic biology of erythropoiesis provides a logical basis for the diagnosis and treatment of the inherited and acquired anaemias that are so frequently encountered in clinical practice. In this chapter, we outline the normal mechanisms underlying erythroid specification, differentiation and maturation, and highlight some of the ways in which this complex system may fail in erythroid diseases. (Douglas R. Higgs et al, 2016)

Substance needed for erythropoiesis

Because of the great numbers of new red blood cells that are produced each day, the marrow requires many precursors to synthesis new cells and the large amount of hemoglobin.

The following groups of substance are needed.

1-Mentals: Iron, Manganese, Cobalt.

2-Vitamins: Vitamin B 12, Folate, Vitamin C, Vitamin E, Vitamin B (pyridoxine), thiamine, riboflavin and pantothenic acid.

4- Hormones: Erythropoietin, androgen and thyroxin.

Well recognized anemias occur with B 12 or folate deficiency. Anemia's also occur with amino acid (protein), thyroxin or androgen deficiency but these may be adaptation to the lower tissue O2 consumption, rather than a direct effect of the deficiency on erythropoiesis, Anemia also occurs in the deficiency of Vitamin C (scurvy), Vitamin and riboflavin, but it is not clear whether these are purely due to an effect of these deficiency on erythropoiesis. B 6 responsive anemias also occur but these are not usually due to B 6 deficiency. (Hoffbrand A.V et all, 2005)

Iron deficiency is the most prevalent single nutritional deficiency, affecting as many as 200 million of the world's population, of the individuals with iron deficiency, 50% progress to iron deficiency anemia. While iron deficiency might be expected in developing countries with widespread social and economic deprivation, it also remains a significant problem in western nations as well. **(**Rodger L. Bick et al, 2006**)**

Erythropoietin

Erythropoiesis is regulated by the hormone erythropoietin. The erythropoietin gene contains a hypoxiaresponse element at its 3' end. Erytlu'opoietin is a heavily glycosylated polypeptide of 165 amino acids with a molecular weight of 34 kDa. Normally, 90% of the hormone is produced in the peritubular interstitial cells of the kidney and 10% in the liver and elsewhere. There are no preformed stores and the stimulus to erythropoietin production is the

Oxygen (O2) tension in the tissues of the kidney. Erythropoietin production therefore increases in anaemia, when hemoglobin for some metabolic or struchlral reason is tmable to give up O2 normally, when ah'nospheric O2 is low or when defective cardiac or pulmonary ftmction or damage to the renal circulation affects 02 delivery to the kidney.

Erytlwopoietin stimulates erytlu'opoiesis by increasing the number of progenitor cells committed to erytlwopoiesis. The transcription factors GATA1 and FOG-1 are activated by erythropoietin receptor stimulation and are important in enhancing expression of erythroid-specific genes (e.g. haem biosynthetic and red cell membrane proteins) and also enhancing expression of anti-apoptotic genes and of the transferrin receptor (CD71).

Late BFUE and CFUE which have erytlu-opoietin receptors are stimulated to proliferate, differentiate and produce haemoglobin. The proportion of erytlu'oid cells in the marrow increases and, in the chronic state, there is anatomical expansion of erythropoiesis into fatty marrow and sometimes into extramedullary sites In infants, the marrow cavity may expand into cortical bone resulting in bone deformities with frontal bossing and protrusion of the maxilla (p. 78). Conversely, increased 02 supply to the tissues (because of an increased red cell mass or because haemoglobin is able to release its 02 more readily than normal) reduces the erytlu'opoietin drive. Tissue hypoxia also stimulates new blood vessel formation by vascular endothelial growth factor (VEGF).

Plasma erytlu'opoietin levels can be valuable in clinical diagnosis. They are high if a hunoursecreting erythropoietin is causing polycythaernia but low in severe renal disease or polycythaemia rubra vera. or subcutaneously either 3-7 times weekly or once every 1-2 weeks depending on the indication and on the preparation used (erythropoietin alpha or beta or darbepoetin alpha, a heavily glycosylated longer acting form). The main indication is endstage renal disease (with or without dialysis). Other uses include pre-autologous blood transfusions, the anaemia of chronic disorders (e.g. in rheumatoid arthritis or cancer) and some cases of myelodysplasia or myeloma. In these conditions, often higher doses are used and the quality of life is improved. (Provan D. and Benz E.J., Shatill S.J.et al. (2005)

Blood Films

Properly prepared blood smear is essential to accurate assessment of cellular morphology. A variety of methods are available for preparing and staining blood smears (Fritsma GA et al, 2012)

A. Preparation of blood film

There are two common methods for preparation of peripheral blood films:

1. Preparation on glass slides (push or spinner)
2. Preparation on coverslips

The glass slide method is shown in Fig. 2. Blood from a fingerstick is preferable, although ethylenedia~netetraacetic acid (EDTA)-anticoagulated blood is used more frequently.

Glass slides have the advantages of

1. Ease of handling and labeling
2. Ease of smear production and staining
3. Lack of fragility-easy to store and transport

The major disadvantage of a glass slide is the irregular distribution of cells, which may cause difficulty in evaluating platelets and leukocytes. (Fermina Maria Mazzella and Gerardo Perrotta, 2000)

This technique requires at least two 3 x 1-inch (75 x 25-mm) clean glass slides. High-quality, beveled-edge microscope slides are recommended. One slide serves as the blood smear slide and the other as the spreader slide. A drop of ethylenediaminetetraacetic acid (EDTA) anticoagulated blood about 3 mm in diameter is placed at one end of the slide. Alternatively, a similar size drop of blood directly from a finger or heel puncture is acceptable. The size of the drop of blood is important. Too large a drop creates a long or thick smear, and too small a drop often makes a short or thin smear. In preparing the smear, the technician holds the pusher slide securely in front of the drop of blood at a 30- to 45-degree angle to the smear slide (Figure 1-1, A). The pusher slide is pulled back into the drop of blood and held in that position until the blood spreads across the width of the slide (Figure 1-1, B). It is then quickly and smoothly pushed forward to the end of the smear slide, creating a wedge smear (Figure 1-1, *C*). (Rodak BF et al, 2012)

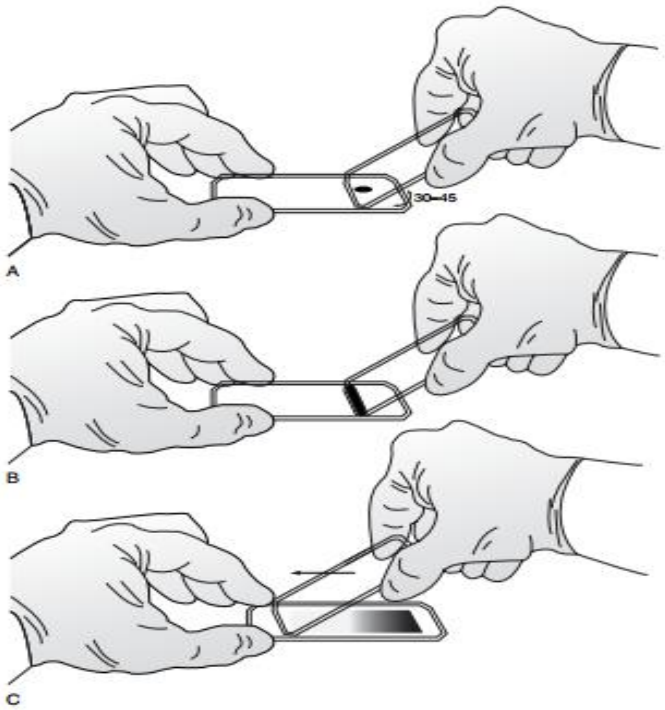


Figure 1–1 Wedge technique of making a peripheral blood smear. **A,** Correct angle to hold spreader slide. **B,** Blood spread across width of slide. **C,** Completed wedge smear. (Rodak BF et al, 2012)

A well-made peripheral
blood smear (Figure 1-2) has the following characteristics:
1. About two-thirds to three-fourths of the length of the slide is covered by the smear.
2. It is slightly rounded at feather edge (thin portion), not bullet shaped.
3. Lateral edges of the smear should be visible. The use of slides with chamfered (beveled) corners may facilitate this appearance.
4. It is smooth without irregularities, holes, or streaks.
5. When the slide is held up to light, the feather edge of the smear should have a "rainbow" appearance.
6. The whole drop is picked up and spread.

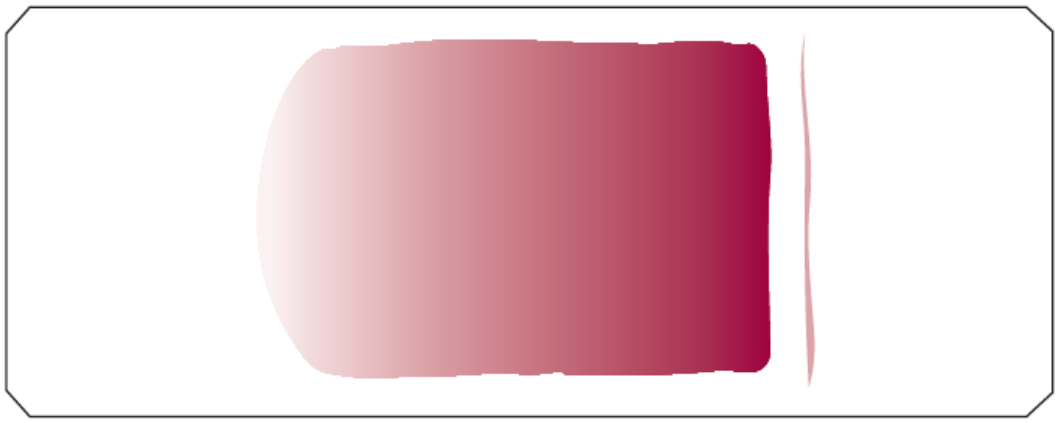


Figure 1–2 Well-made peripheral blood smear. (Keohane et al, 2012)

Staining of blood smears

The purpose of staining blood smears is to identify cells and recognize morphology easily through the microscope. Wright or Wright- Giemsa stain is the most commonly used stain for peripheral blood and bone marrow smears. These stains contain both eosin and methylene blue, and are therefore termed polychromestains.The colors vary slightly from laboratory to laboratory, depending on the method of staining.

The cells are fixed to the glass slide by the methanol in the stain. Staining reactions are pH dependent, and the actual staining of the cellular components occurs when a buffer (pH 6.4) is added to the stain. Free methylene blue is basic and stains acidic cellular components, such as RNA, blue.A well-stained slide is necessary for accurate interpretation of cellular morphology. The best staining results are obtained from freshly made slides that have been prepared within 2 to 3 hours of blood collection. (Fritsma GA et al, 2012)

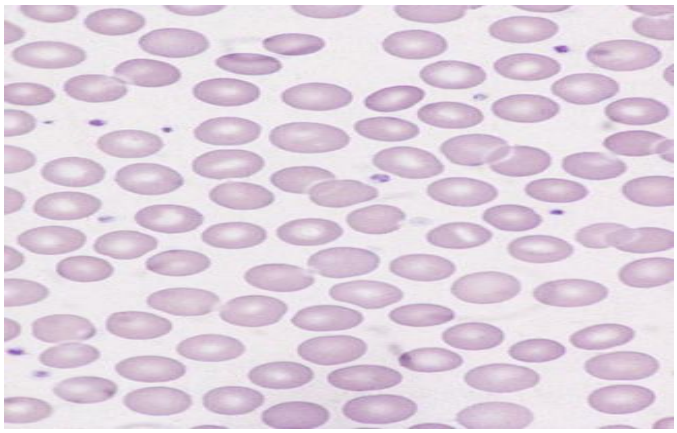
Blood film examination

Examination of the blood smear is a multistep process. Begin the smear examination with a scan of the slide using the 103 or low-power objective (total magnification = 100x). This step is necessary to assess the overall quality of the smear, including abnormal distribution of RBCs, suggesting the presence of rouleaux or autoagglutination and/or the presence of a disproportionate number of large nucleated cells, such as monocytes or neutrophils, at the edges of the smear. (Keohane et al, 2012)

Normal red cells or erythrocytes

show only slight variation in size and shape. The blood film should be examined in the area where the red cells are touching but not often overlapping. In this area many red cells have an area of central pallor which may be up to a third of the diameter of the cell. This is consequent on the shape of a normal red cell, which resembles a disc that is thinner in the CentreWhen examining red cells it is important to assess whether they are of normal size (by comparison with a small lymphocyte or a neutrophil), whether variation in shape is greater than normal and whether the area of central pallor is greater than normal.

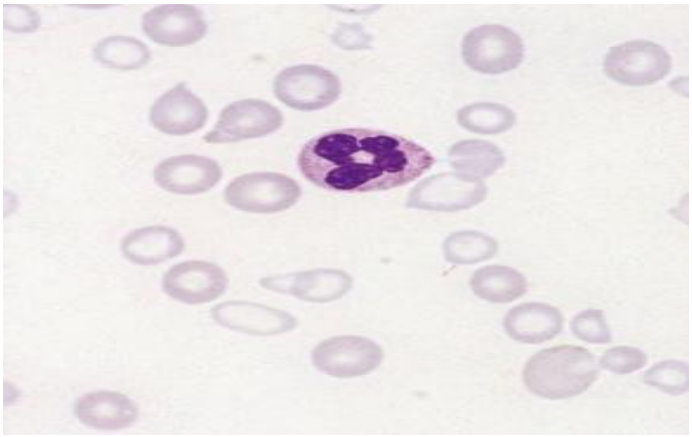
Be careful to examine the correct area of a blood film. If you examine red cells near the tail of the film they will generally lack central pallor. If you examine an area of the film that is too thick it is difficult to assess cell features accurately.



Abnormal Red Blood Cell

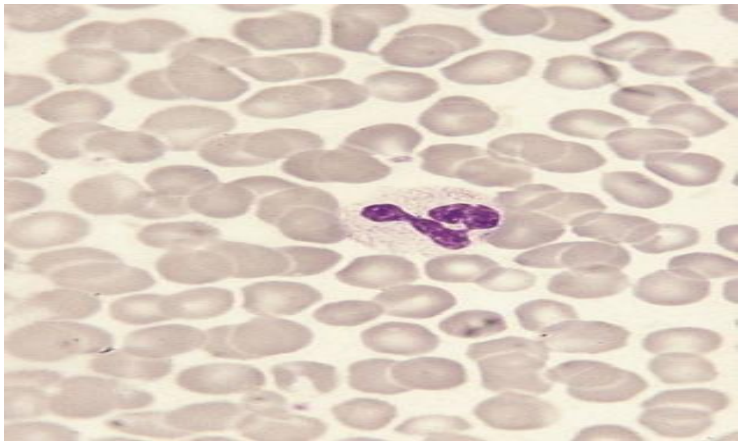
A-Anaemia

can be detected on a peripheral blood film because the reduced viscosity of the blood leads to the blood film being thinner than normal and the red cells being spaced further apart.



B-Polycythaemia

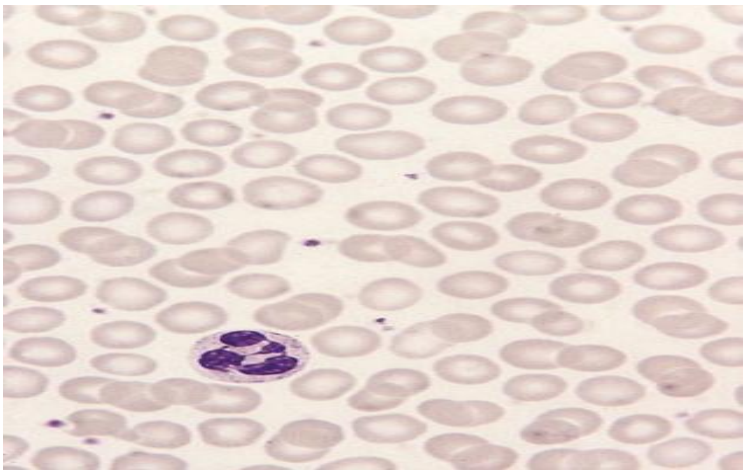
Post-transplant polycythaemia. Polycythaemia (literally many cells) refers to an increase in the haemoglobin concentration, packed cell volume and red cell count. Polycythaemia leads to increased viscosity of the blood which in turn means that the blood film is abnormally thick. It is therefore difficult to find an area where the red cells are touching without overlapping. This blood film is from a patient with a haemoglobin concentration of 20 g/dl and a packed cell volume of 0.59.



C-Microcytosis

The term microcytosis means that red cells are smaller than normal. Small red cells are referred to as microcytes. This blood film is from a blood sample with a mean cell volume (MCV) of 72 fl (normal range 82-98). There is also hypochromia, i.e. the cells have an increased area of central pallor. To compare with cells of a normal size and with normal haemoglobinization.

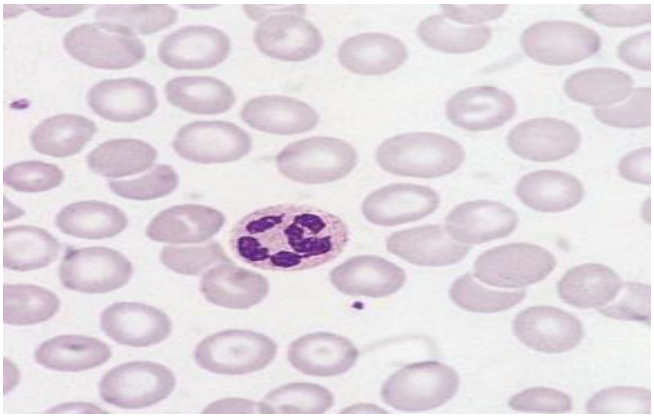
Microcytosis is most often caused by iron deficiency, severe 'anaemia of chronic disease' or thalassaemia. Cells which are microcytic are often also hypochromic. The red cells of children are smaller than those of adults but since this is a physiological phenomenon it is not referred to as microcytosis. When cells are microcytic automated full blood counters show the MCV and MCH to be reduced.



D-Macrocytosis

Macrocytosis refers to an increase in the average size of red cells. A large red cell is referred to a macrocyte. This blood film is from a patient with macrocytosis caused by liver disease. The MCV was 105 fl (normal range 82-98).

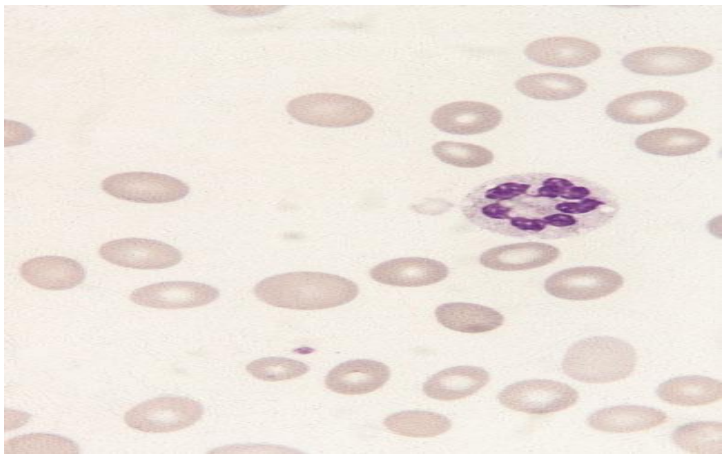
Macrocytosis is most often caused by liver disease, excess ethanol consumption, deficiency of vitamin B12 or folic acid or administrations of certain drugs. An increased proportion of young red cells can also cause macrocytosis. Neonates have much larger red cells than do older infants, children and adults but since this is a physiological feature of the neonatal period it is not referred to as macrocytosis. When cells are macrocytic automated full blood counters show the MCV and MCH to be increased.



E-Anisocytosis

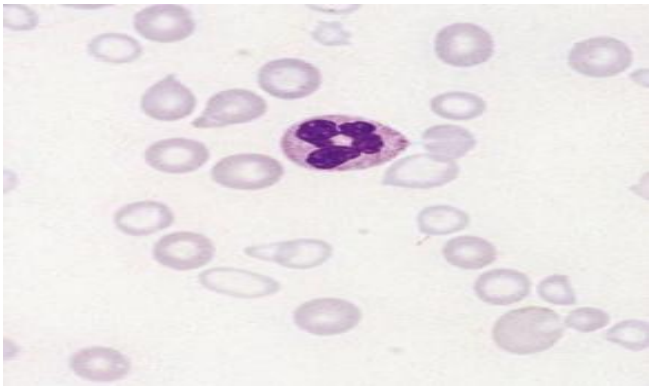
Anisocytosis refers to increased variation in the size of red cells. This image also shows anisochromasia, i.e. an increased variation in the staining of red cells. Anisochromasia indicates variation in the haemoglobin concentration between different cells.

Anisocytosis is a common, non-specific abnormality which can be associated with almost any type of anaemia. It is therefore not particularly useful in making a specific diagnosis. Anisochromasia indicates a changing situation, i.e. that haemoglobin synthesis has been reduced during production of some of the circulating red cells. It is usually caused by iron deficiency or 'anaemia of chronic disease'. When there is anisocytosis automated full blood counters show an increase in the RDW (red cell distribution width), a measurement of the amount of variation in red cell size. Some instruments can also measure the variation in the degree of haemoglobinization of individual red cells. In the presence of anisochromasia such instruments show an increase in the HDW (haemoglobin distribution width).



F-Anisochromasia

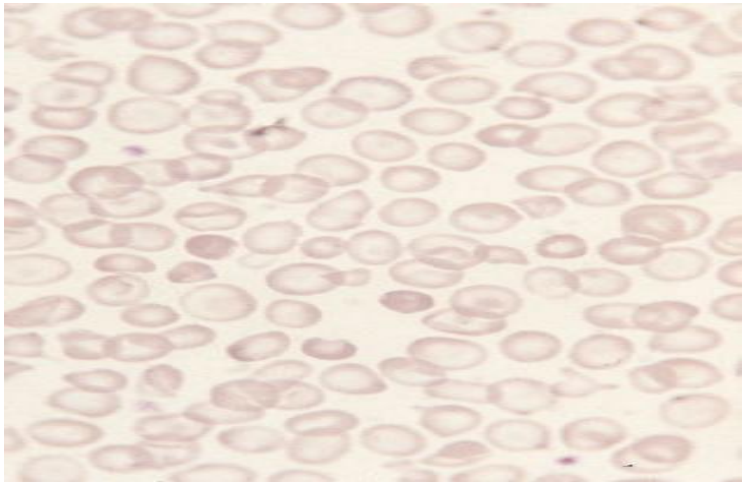
This film from an iron deficient patient shows anisochromasia, i.e. there is increased variation in staining from cell to cell. Some cells are normally haemoglobinized while others show only a thin rim of haemoglobinized cytoplasm.



G-Hypochromia

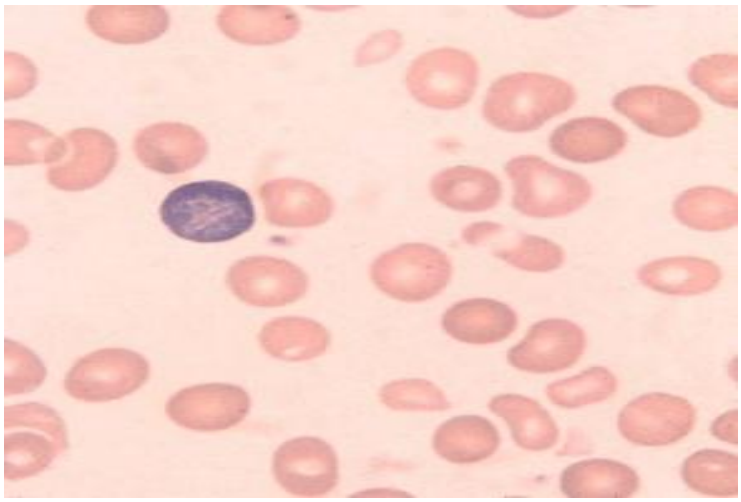
Hypochromia refers to reduced staining of red cells, indicative of a reduced haemoglobin concentration. Cells that are hypochromic are often also microcytic. In this film, from a patient with haemoglobin H disease, the great majority of cells are hypochromic.

Hypochromia indicates a defect in haemoglobin synthesis due either to a decrease in haem synthesis (in iron deficiency or anaemia of chronic disease) or to a defect in globin chain synthesis (in thalassaemia). In the presence of hypochromia automated full blood counters may show a low MCHC (mean cell haemoglobin concentration).



H-Polychromasia

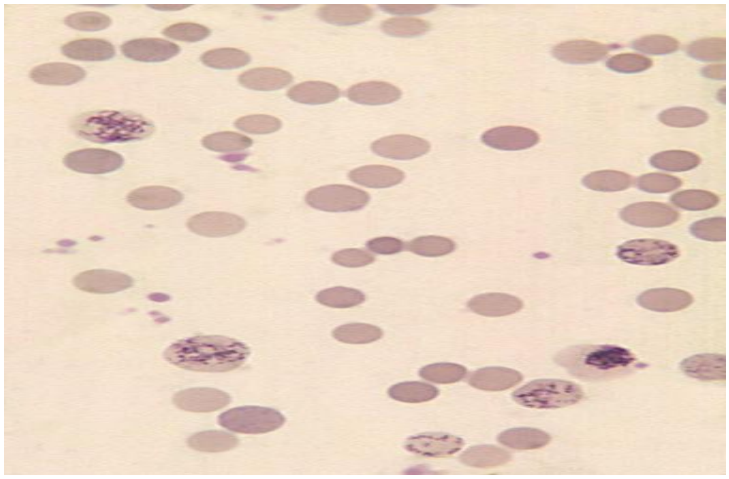
Polychromasia (literally many colours) indicates the presence of increased numbers of red cells with a bluish tinge superimposed on the red colour of haemoglobin. Polychromatic cells are cells with a blue tinge. The presence of increased numbers of polychromatic cells correlates with an increased reticulocyte count. Note that polychromatic cells are often larger than mature red cells and may then be referred to as polychromatic macrocytes.



I-Reticulocytes

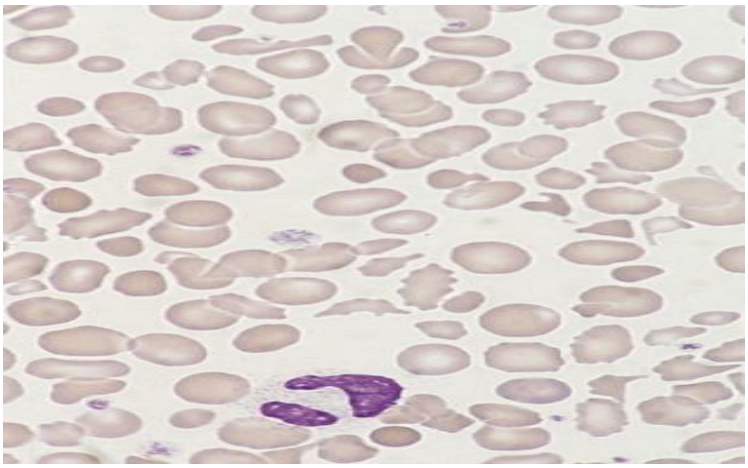
Reticulocytes are young red cells, newly released from the bone marrow. They are identified on a reticulocyte preparation rather than on a blood film stained in the normal way. Blood containing living cells is exposed to a stain such as new methylene blue. Ribosomes take up the stain and precipitate as a network or 'reticulum'.

Because reticulocytes are identified following exposure of living cells to an appropriate dye the procedure is referred to as a vital stain. An increased number of reticulocytes in the blood is referred to as reticulocytosis. Reticulocytosis indicates increased bone marrow output of red cells as occurs when there is a response to blood loss or haemolysis or when iron, vitamin B12 or folic acid is administered to a patient with a haematinic deficiency. The reticulocyte count is often expressed as a percentage of red cells but is better expressed as an absolute count. The normal range is approximately 0.5-2% or 40-140 X 109/l.



J-Poikilocytosis

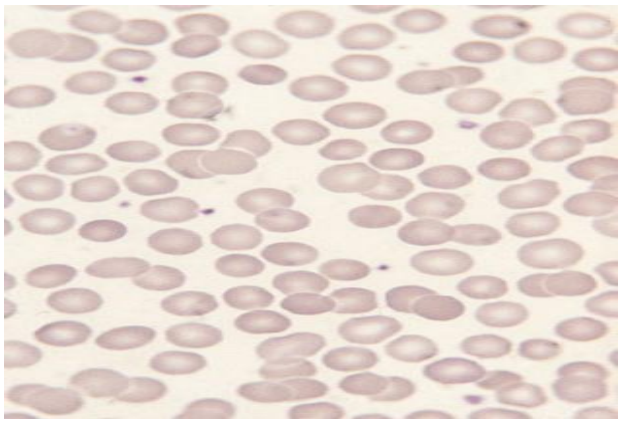
Poikilocytosis in a baby with hereditary elliptocytosis and transient neonatal poikilocytosis. Poikilocytosis means an increased variability in red cell shape. A poikilocyte is a red cell of abnormal shape. An individual may have a predominance of a particular type of poikilocyte or there may be cells of a variety of shapes.



K-Spherocytes

Spherocytes in hereditary spherocytosis. The spherocytes are the cells that lack central pallor. Cells which have rounded up to become spherocytes have a reduced diameter in comparison with normal discocytes but the cell size is normal.

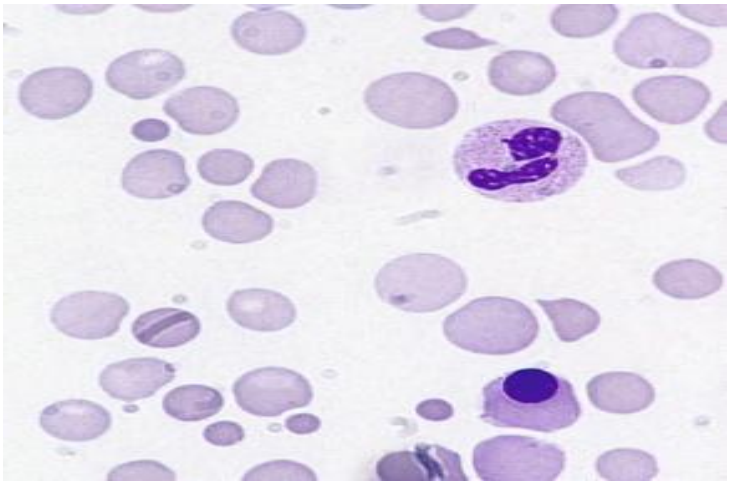
In adults the two commonest causes of spherocytosis are hereditary spherocytosis and autoimmune haemolytic anaemia. Automated instruments indicate a normal MCV and MCH but the MCHC may be increased. With some automated instruments a hyperchromia 'flag' is generated.



L-Microspherocytes

Microspherocytes resemble spherocytes in that they lack central pallor but differ in that they are smaller than normal discocytes. They result from red cell fragmentation. This photograph also shows large red cells, which are likely to be young cells, and a nucleated red cell or erythroblast.

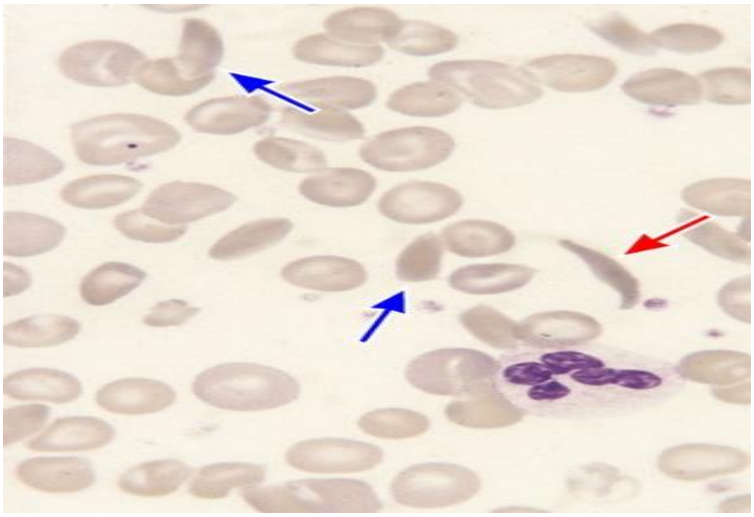
Microspherocytes result from red cell fragmentation which may be caused by mechanical damage, exposure to heat or exposure to toxic substances such as snake venoms. If microspherocytes are very numerous the MCV and MCH are reduced and the MCHC is increased. Spheroschistocyte is an alternative name for microspherocyte.



M-Sickle cell anemia

Sickle cell and boat-shaped erythrocytes in sickle cell anaemia. Sickle cells [dark red arrow] are sickle- or crescent-shaped red cells with both ends being pointed. Boat-shaped cells [dark blue arrows] are pointed at one or both ends but are not curved. Sickle cells are pathognomonic for sickle cell disease whereas boat-shaped cells are suggestive but not pathognomonic.

Sickle cells are formed by the polymerization of haemoglobin S or sickle cell haemoglobin within a red cell. Sickle-shaped erythrocytes seen in a blood film made from EDTA-anticoagulated blood represent irreversibly sickled cells since they have not reverted to normal shape on exposure to oxygen. They are pathognomonic for sickle cell disease, i.e. their presence reliably indicates that the patient has sickle cell disease. The term 'sickle cell disease' includes sickle cell anaemia, compound heterozygous states for haemoglobin S and haemoglobin C or b thalassaemia and other conditions in which significant disease results from sickling of red cells. It does not include sickle cell trait.

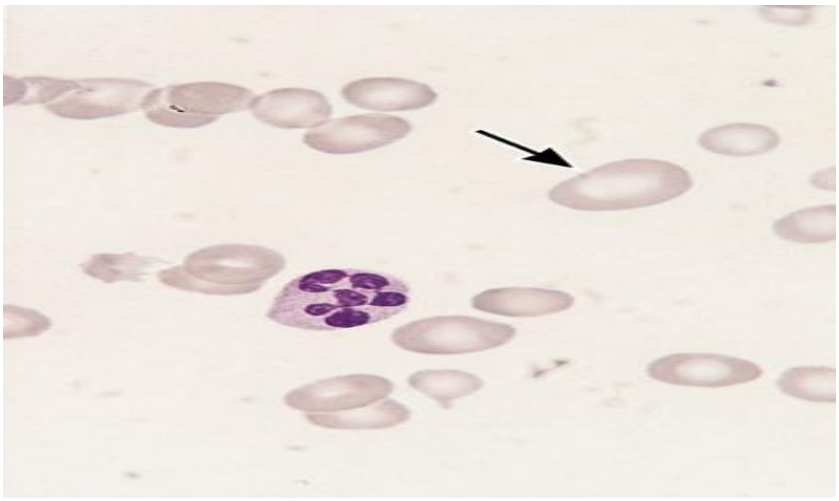


N-Megaloblastic anaemia

Macrocytosis may be caused by megaloblastic anaemia, an anaemia in which maturation of the nucleus is retarded in relation to that of the cytoplasm. In megaloblastic anaemia the most characteristic features in the

peripheral blood film are hypersegmented neutrophils and macrocytes, particularly oval macrocytes [arrow]. The neutrophil shown has six lobes and is therefore classified as hypersegmented.

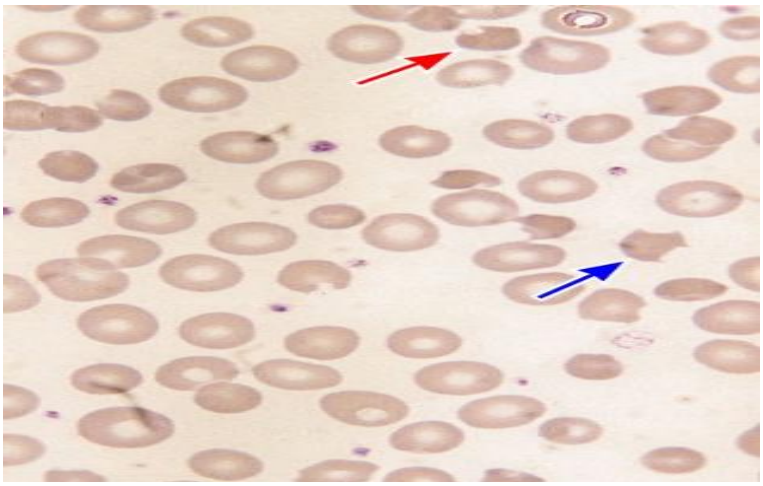
Megaloblastic anaemia is most often caused by deficiency of vitamin B12 or folic acid. Vitamin B12 is present in meat and other animal products. It combines with intrinsic factor which is secreted by the stomach. After complexing with intrinsic factor it is maximally absorbed in the distal small bowel, the ileum. Causes of vitamin B12 deficiency include a strict vegan diet, total gastrectomy, pernicious anaemia (failure of intrinsic factor secretion by the stomach) and small bowel disease or resection. Folic acid is present in fresh fruit and vegetables, liver and meat. Absorption is maximal in the proximal small bowel (the jejunum). Folic acid deficiency is usually caused by inadequate dietary intake, often associated with increased need for folate as during pregnancy or with haemolytic anaemia. Small bowel disease such as coeliac disease can also cause malabsorption of folic acid and therefore deficiency.



O-Keratocyte

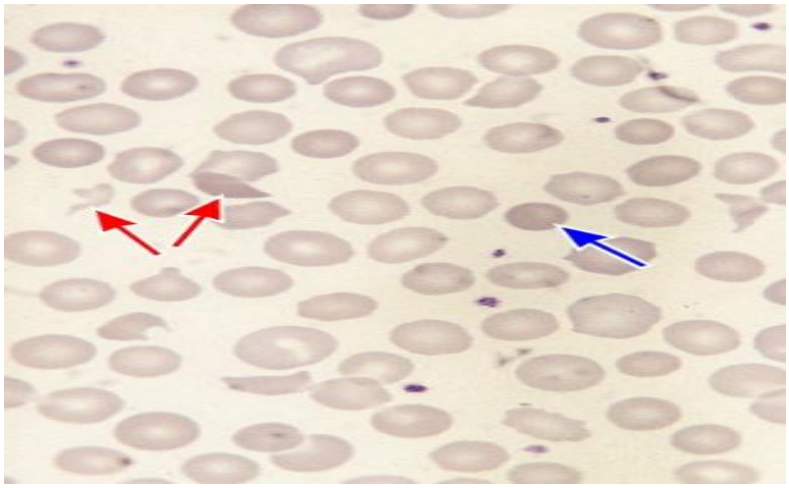
Keratocytes or horned cells are erythrocytes with a pair of spicules or 'horns' surrounding a gap in the cell outline. There may be a single pair of spicules [red arrow] or two pairs of spicules [blue arrow]. Keratocytes can result from removal of a Heinz body from a cell (this case) or from red cell fragmentation. To view keratocytes resulting from fragmentation of red cells.

Keratocytes are sometimes referred to as 'bite cells' because one mechanism of their formation is removal of a Heinz body by splenic macrophages. This picturesque term is appropriate in this context but in general it is better to use purely descriptive terminology rather than terminology which implies knowledge of the underlying mechanism since this may not always be certain.



P-Schistocytes

Schistocytes are fragments of erythrocytes, also referred to as 'fragments' or 'red cell fragments'. Schistocytes are usually small and angular [dark red arrows] but microspherocytes [dark blue arrows] are also schistocytes.



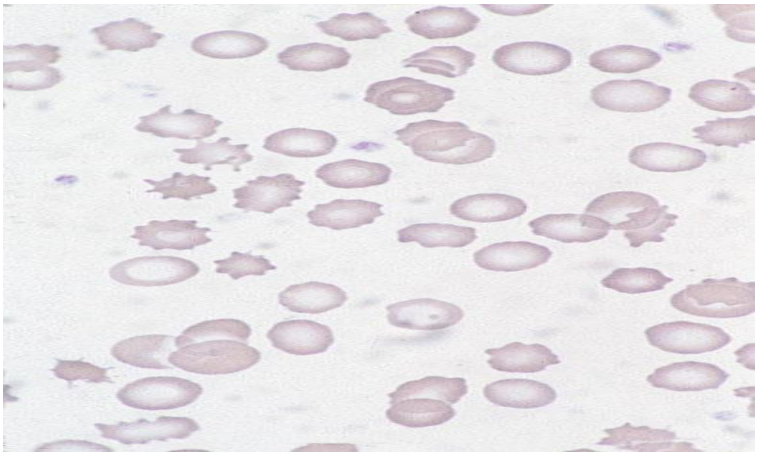
Q-Echinocyte

The presence of schistocytes may indicate an intrinsic abnormality of the red cell, which makes it more likely to fragment. Red cell fragmentation can also result from the exposure of cells to abnormal conditions, such as heat or mechanical trauma, or from contact with fibrin strands or damaged endothelium. If there is fragmentation of red cells within the microvasculature leading to anaemia the term 'microangiopathic haemolytic anaemia' is used.

An echinocyte is an erythrocyte with a large number of short blunt spicules (10-30), regularly distributed over the surface of the cell. The presence of echinocytes is referred to as echinocytosis. In this case the abnormality was caused by chronic renal failure but much more often echinocytes represent a storage artefact indicating that EDTA-anticoagulated blood has been stored for too long before the blood film was made.

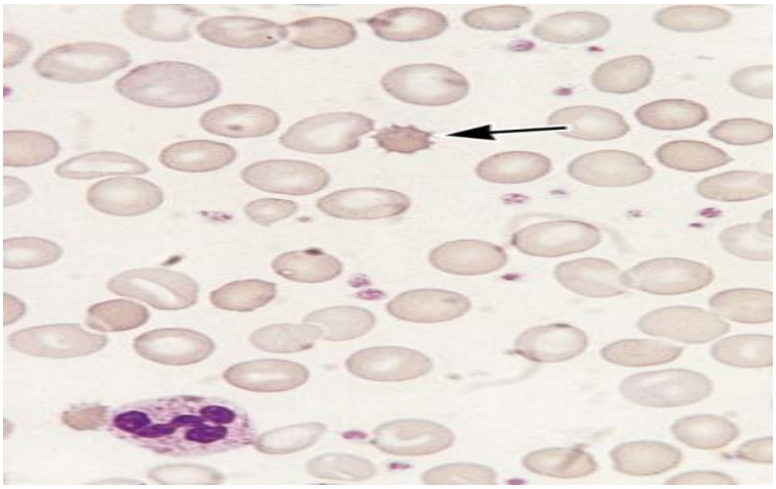
The only common cause of echinocytosis is storage artefact. Uncommon causes include renal failure, liver failure and several rare red cell enzyme deficiencies. Echinocytosis may be reversible on suspending red cell in normal plasma.

NOTE: The term 'burr cell' is not recommended to describe an echinocyte or any other abnormal erythrocyte since the term has been used to describe a number of different types of poikilocyte. The designation 'crenated cell' which is commonly used is acceptable since it is unambiguous.



R-Sphero-echinocyte

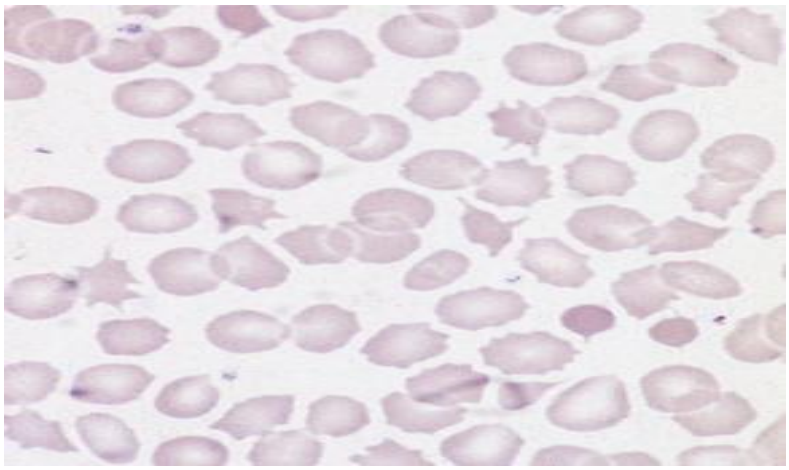
A sphero-echinocyte is a rounded erythrocyte covered with a large number of short spicules. It can indicate that a spherocyte, e.g. in hereditary spherocytosis, has undergone an echinocytic change. In the case illustrated the sphero-echinocyte [arrow] was a transfused cell in a patient who had been transfused with bank blood at the end of its shelf-life.



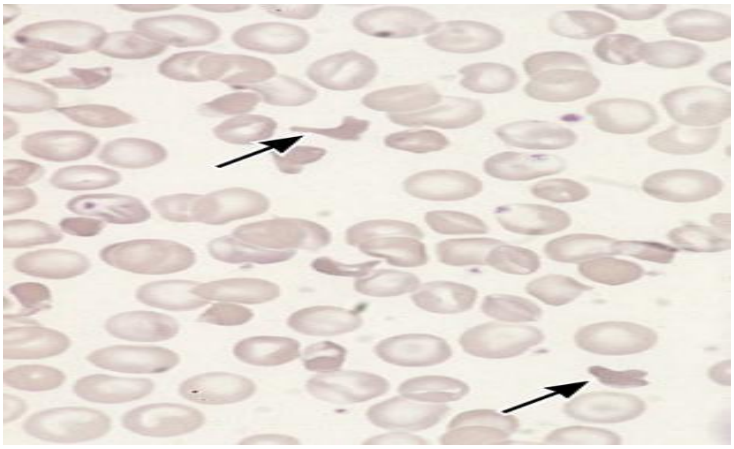
S-Acanthocyte

An acanthocyte is an erythrocyte that is irregular in shape and is covered with a small number of spicules (2-20) which vary in length and thickness. The spicules are irregularly distributed over the surface of the red cell. The presence of acanthocytes is referred to as acanthocytosis.

The common causes of acanthocytosis are splenectomy (case illustrated) and severe liver disease. In neonates acanthocytosis may be seen in association with haemolytic anaemia, referred to as infantile pyknocytosis and probably related to vitamin E deficiency. Rare causes include abetalipoproteinaemia and various inherited abnormalities of the red cell membrane (McLeod phenotype, In(Lu) phenotype and acanthocytosis with choreoathetosis). Smaller numbers may be seen in anorexia nervosa and hypothyroidism. Acanthocytosis is irreversible. Acanthocytes have also been referred to as 'pyknocytes' and as 'spur cells'. NOTE: The term 'burr cell' is not recommended to describe an acanthocyte or any other abnormal erythrocyte since the term has been used to describe a number of different types of poikilocyte.



T-SC poikilocyte

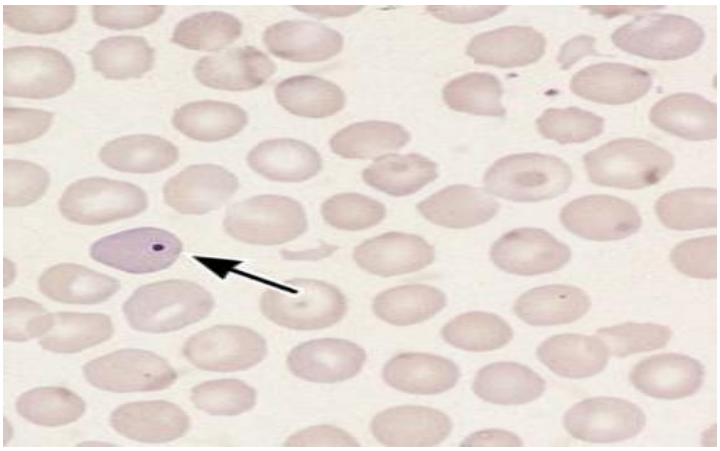


U-Howell-Jolly bodies

Patients with compound heterozygosity for haemoglobin S and haemoglobin C often have characteristic poikilocytes [arrows] resulting from the simultaneous polymerization of haemoglobin S and crystallization of haemoglobin C. They are of complex shapes with some curves and some straight edges. To compare an SC poikilocyte with sickle cells and boat-shaped cells.

Howell-Jolly bodies [arrow] are small nuclear fragments within erythrocytes. Their staining characteristics resemble those of the nucleus of a mature erythrocyte. They are round in shape and are sited closer to the edge of the cell than the centre.

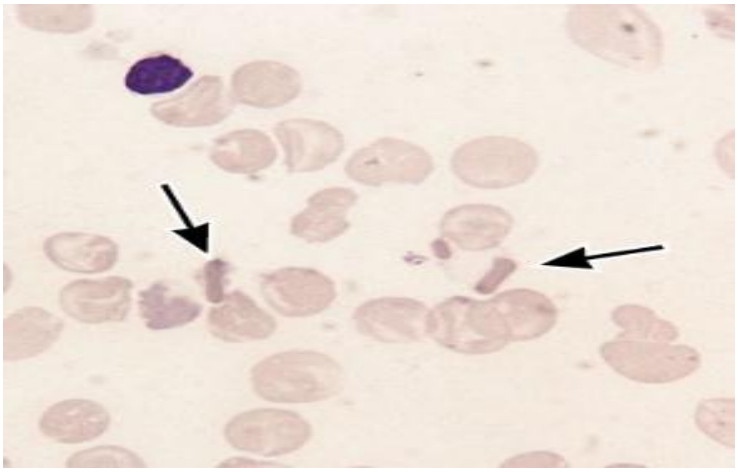
Howell-Jolly bodies indicate absence or reduction of splenic function. When erythropoiesis is normal they are formed in erythroblasts in small numbers. However they are removed by the pitting action of splenic macrophages so that they are not seen in the peripheral blood of normal subjects. Increased numbers of Howell-Jolly bodies are formed if there is megaloblastic erythropoiesis. If the spleen is also hypofunctioning they may then be very numerous in the peripheral blood.



V-Haemoglobin C crystal

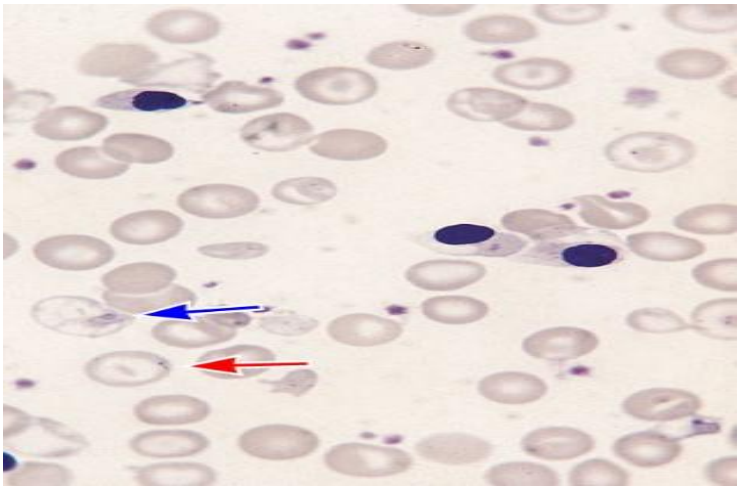
Haemoglobin C crystal. Haemoglobin C is prone to crystallize, forming crystals with straight parallel edges [arrows]. They are usually rhomboidal or hexagonal. Usually all the haemoglobin in the cell crystallizes so that the cell appears otherwise empty of haemoglobin.

aemoglobin C crystals may be seen in haemoglobin C disease, sickle cell/haemoglobin C compound heterozygosity and haemoglobin C/bthalassaemia compound heterozygosity.



W-a Chain precipitates

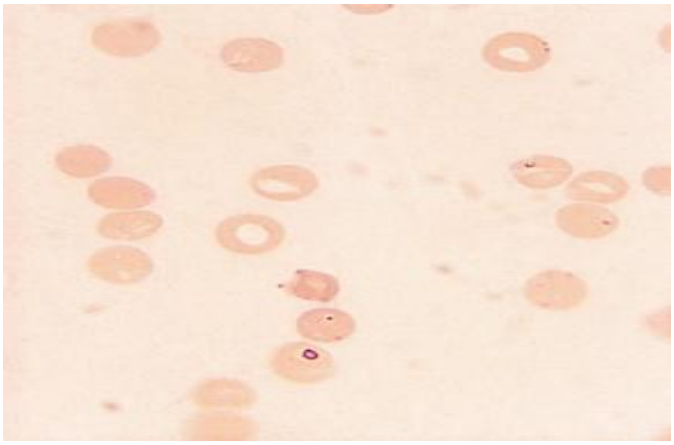
When synthesis of b globin chain is reduced excess a chains may precipitate in erythroblasts or mature erythrocytes. a chain precipitates [blue arrow] have the same staining characteristics as haemoglobin and appear as an irregular mass within a hypochromic red cell. They are seen in patients with b thalassaemia major.



X-Heinz bodies

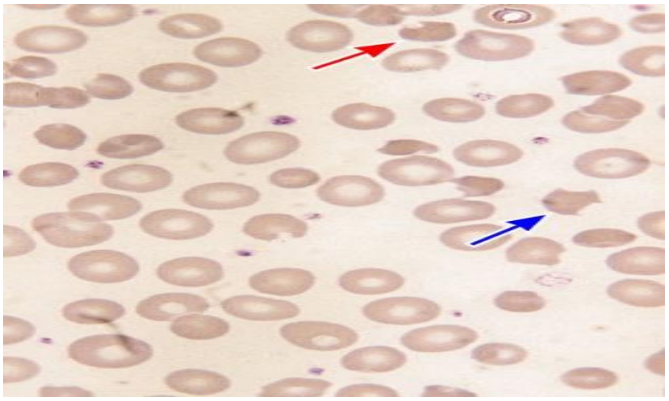
Heinz bodies are red cell inclusions that are seen only after a specific vital stain, a Heinz body stain, has been performed. They stain pale pink or purple, are attached to the red cell membrane and sometimes protrude through the membrane. Heinz bodies cannot be seen on a routinely stained blood film. However when they are present the routine blood film usually shows irregularly contracted cells and keratocytes. Sometimes there is a protrusion of the red cell membrane.

Heinz bodies represent denatured haemoglobin. They are attached to the red cell membrane by sulphydryl bonds. They are present when red cells have been exposed to oxidant stress (e.g. certain drugs), during acute haemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency and in some patients with an unstable haemoglobin. Haemolytic anaemia characterized by the presence of Heinz bodies is sometimes referred to as a 'Heinz body haemolytic anaemia'. Heinz bodies should not be confused with Howell-Jolly bodies with which they have no relationship.



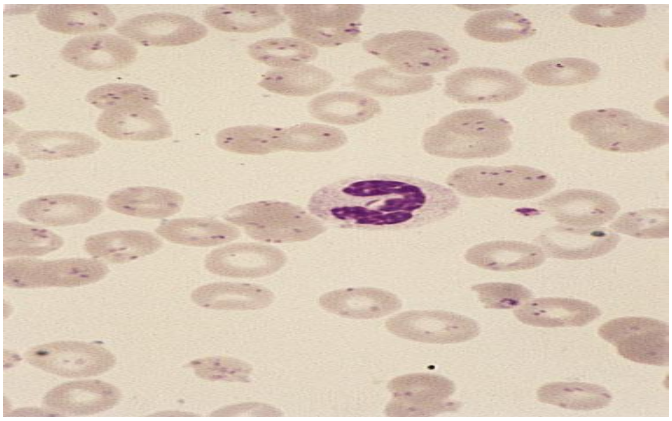
Y-Oxidant-induced haemolytic anaemia

Oxidant drugs and chemicals can cause acute oxidant-induced haemolytic anaemia. This blood film from a patient exposed to dapsone shows macrocytosis, irregularly contracted cells and keratocytes [red and blue arrows]. Polychromasia and hemighosts may also be seen. When haemolysis is acute the Heinz body preparation is positive. There may also be methaemoglobinaemia.



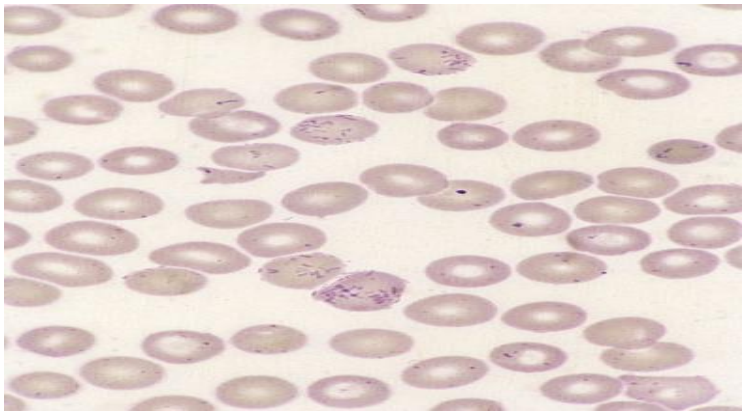
Z-Bartonellosis or Oroya fever

Blood film in bartonellosis showing multiple small rod-shaped bacilli associated with erythrocytes. There may be associated spherocytosis. Bartonellosis or Oroya fever is a very rare cause of acquired haemolytic anaemia. This disease, which occurs in South America, is caused by the organism Bartonella bacilliformis.



1-Whipple's disease

Blood film in Whipple's disease. Whipple's disease is a very rare cause of haemolytic anaemia. In hyposplenic subjects the causative bacillus, Tropheryma whippelii, may be seen associated with the surface of red cells.



2-Microangiopathic haemolytic anaemia

Blood film showing the features of microangiopathic haemolytic anaemia in haemolytic uraemic syndrome. There are schistocytes including one microspherocyte. For a list of important causes of microangiopathic haemolytic anaemia. mportant causes of microangiopathic haemolytic anaemia

Haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura and related thrombotic microangiopathies, Following certain infections (e.g. E. coli, Shigella) and vaccinations, HIV infection

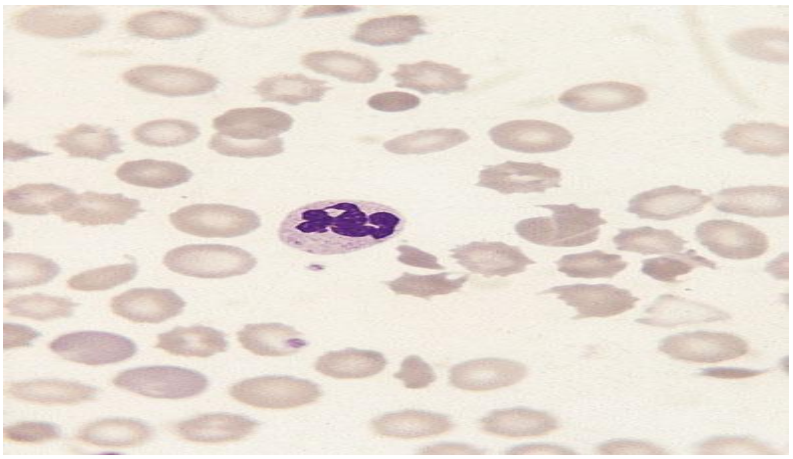
Associated with pregnancy or hormone administration

Familial

Associated with certain chemotherapeutic agents and other drugs

Associated with certain renal diseases (e.g. pregnancy-associated hypertension, malignant hypertension, renal allograft rejection)

Associated with chronic intravascular coagulation, e.g. with certain carcinomas



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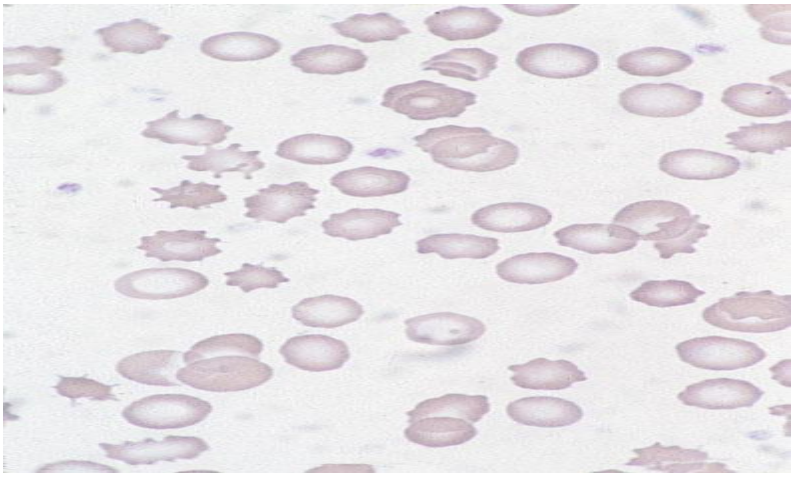
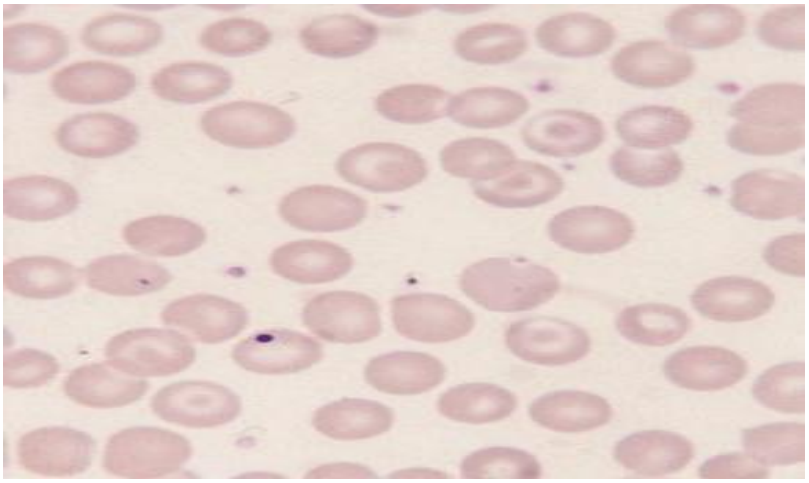


4-Target cell

get cells are erythrocytes that, in stained blood films, resemble a target. They have an area of increased staining in the centre of the normal area of central pallor. In three dimensions, target cells are found to be bell-shaped. Target cells are a feature of hyposplenism (this case), obstructive jaundice, liver disease and various haemoglobinopathies. Target cells in obstructive jaundice or liver disease are either normal in size or enlarged and are well haemoglobinized. Target cells following splenectomy or in hyposplenism are of normal size and normally haemoglobinized. Target cells in haemoglobinopathies and thalassaemias are often reduced in size and may be poorly haemoglobinized.



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Acknowledgment

-I wish to express my sincere thanks to the lord of the universe (ALLAH), blessing and peace be on the prophet (MUHAMMAD)
(Allah peace and pray be upon him)
We would like to express gratitude & thank to my supervisor Assist. Prof. Dr. Zrar Saleem Marzany & all Medical Microbiology department academic staff, our dear families and all our lovely friends …
We would like to express gratitude & thank to Bashdar & Bawar

Bashdar Sdiq Mahmood. "Hematopoiesis and Abnormal of Red Blood Cell Shapes in Different Diseases.*"IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*, 15(6), (2020): pp. 23-41.