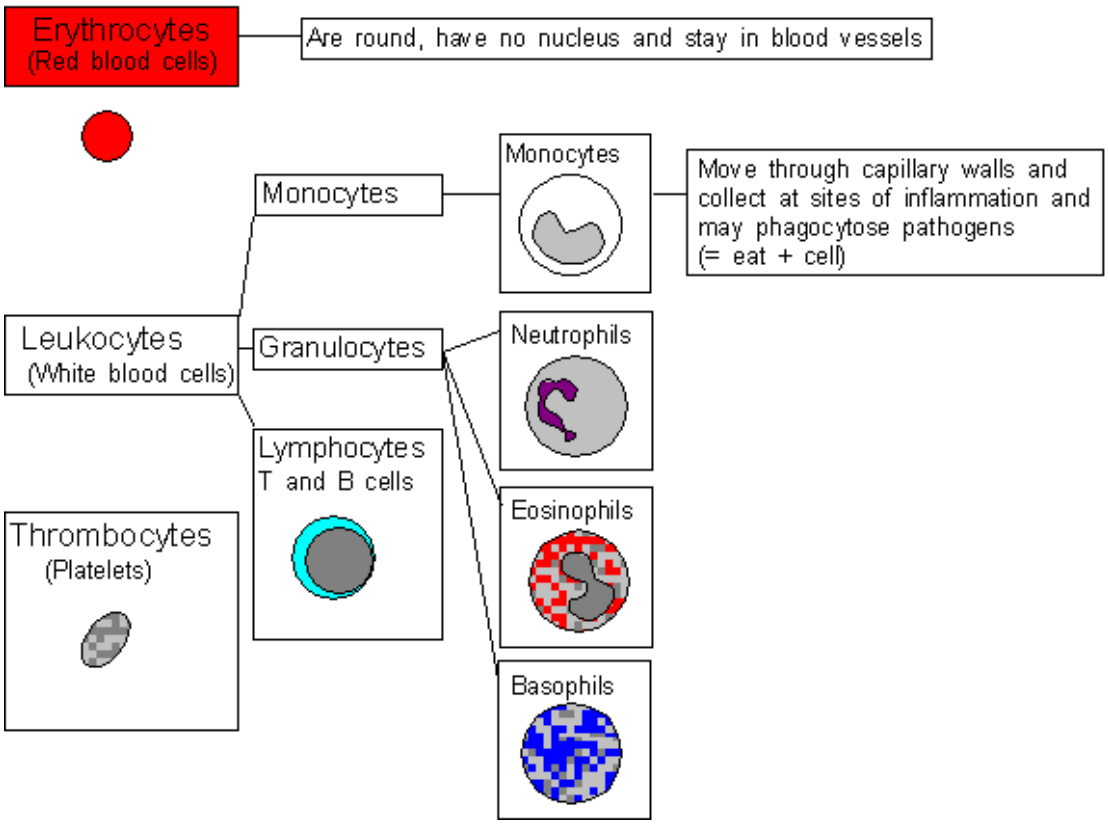
THE BLOOD

Blood can be considered a special type of connective tissue. Its fluid content contents include nutrients, wastes, salts, hormones, proteins and often medically administered substances. In addition blood transport gases, cells and heat around the body.

The details of the development of the cellular constituents of the blood from the pluripotential stem cells are detailed below.

The cellular elements of the blood



In the foetus red blood corpuscles (RBCs, erythrocytes) are made in bone marrow, liver, kidneys, spleen and muscles. In children all of the bone marrow can make red blood corpuscles but in adults the RBCs are usually made in the marrow of certain long bones and, to a lesser extent, in skull, spine and pelvis.

Red blood corpuscles have a life of 120 days (10 million RBCs are destroyed every second!) and travel through the (estimated) 60,000 miles of blood vessels in each human.

In the adult there are five litres of blood each cubic milliliter of which normally contains five million RBCs. The RBCs contain haemoglobin, the oxygen storage compound. Normally each 100 ml of blood contains 14.5g of haemoglobin carrying 20 mls of oxygen. The oxygen/haemoglobin dissociation curve and its significance is detailed in the Respiratory section.

Fully oxygenated haemoglobin is red but if more than 5g of haemoglobin is deoxygenated the blood and thus the tissues appear blue (cyanotic). Central cyanosis may occur if insufficient haemoglobin is oxygenated by the lungs or if systemic venous blood bypasses the lung." *Peripheral* cyanosis in the absence of central cyanosis occurs if the peripheral circulation is

slow enough to allow the tissue to collect oxygen from more than 5 g of the initially fully oxygenated haemoglobin or if peripheral tissues have an excessive demand for oxygen (as in sepsis for example). At least 30 percent of haemoglobin in the blood returning to the heart from the tissues is deoxygenated which explains why venous blood is darker than systemic arterial blood.

If the partial pressure of oxygen decreases, for example in those who live at high altitudes, the number of RBCs per cubic ml increases so that, overall, more oxygen can be carried. Similarly babies with heart defects or some patients with severe lung disease who have chronically deoxygenated blood in their systemic arterial circulation may attempt to increase their RBC count (polycythaemia). The combination of excessive redness of the complexion when associated with cyanosis produces plethora.

If the bone marrow responds vigorously to blood loss then large but immature RBCs (reticulocytes) are pumped out into the bloodstream.

Anaemia (= no blood, but in practice refers only to low haemoglobin levels) results If the bone marrow fails to produce RBCs, if the corpuscles are destroyed in the vessels (haemolysis) or if there is haemorrhage.

Causes of anaemia include:

Decreased or ineffective marrow function

- Iron deficiency
- Lack of vitamin B12 or folate
- A damaged marrow
- Infiltration by malignancy or other processes

Peripheral causes

- Blood loss
- Haemolysis (excessive or premature breakdown of RBCs)
- An overactive spleen (hypersplenism)

Hereditary anaemias

Causes include:

- Faulty synthesis or structure of haemoglobin (the haemoglobinopathies). Most are geographically or racially distributed and include sickle cell disease and thalassaemia. Both causes significant problems if sufferers are homozygous rather than heterozygous for the relevant gene
- Defects of red blood cell enzymes. Deficiency of glucose 6-phosphate dehydrogenase may present with haemolysis (breakdown of RBCs) when affected patients are given certain drugs
- Red blood cell membrane abnormalities (spherocytosis, a tendency of the red blood corpuscles to be spherical is an example).

Causes of haemolytic anaemia

Congenital

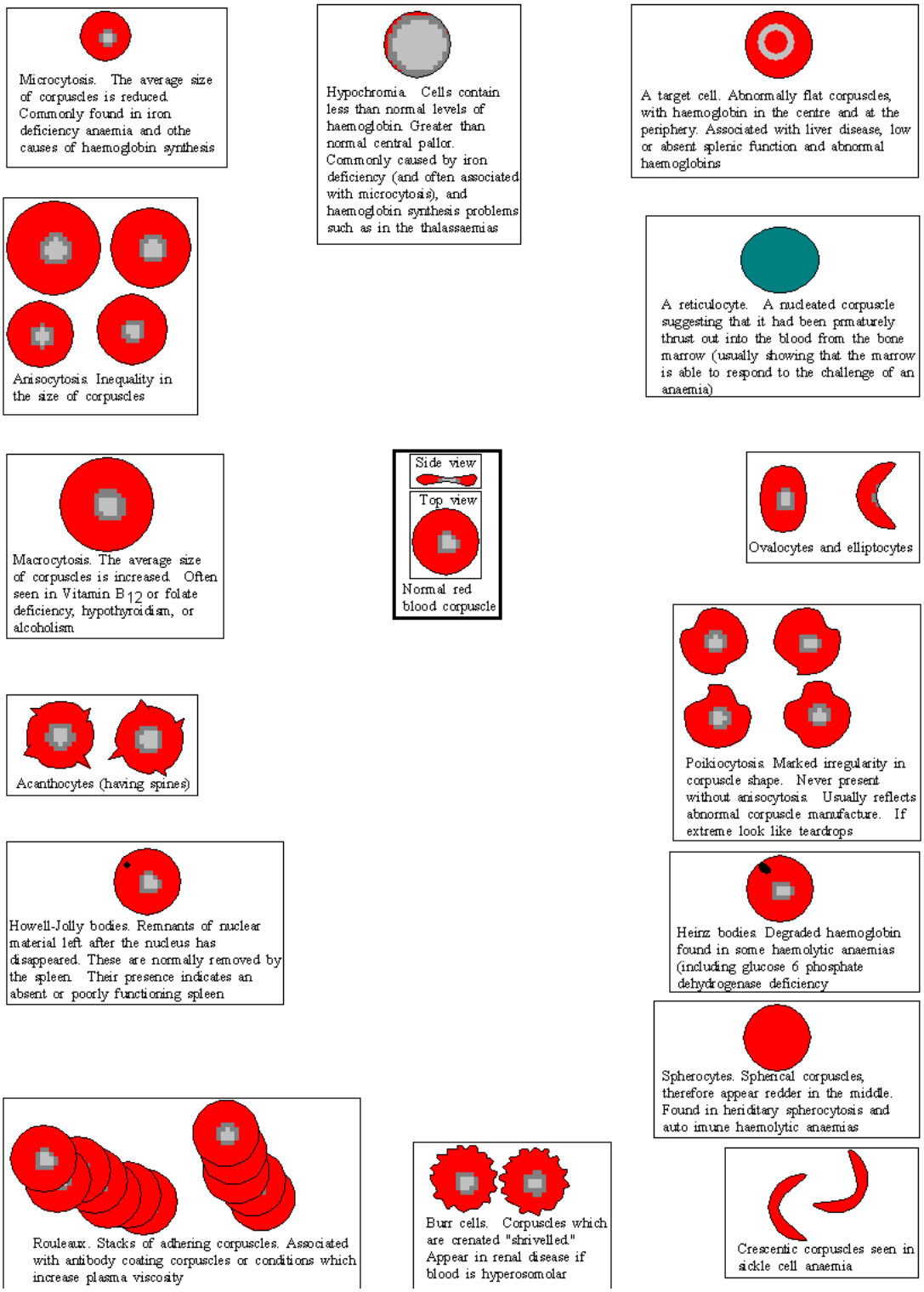
- RBC abnormalities
- Defective forms of haemoglobin
- RBC enzyme defects

Acquired

- Immune mediated
- Non-immune mediated
- Mechanical, turbulence around artificial heart valves for example
- Infections
- Drugs effects

Red blood corpuscles may exhibit various patterns on microscopy or on staining.

The appearance of red blood corpuscles in various conditions.



Iron and the blood

Iron is required for haemoglobin formation (*haem* contains iron and the *globin* is a protein). If there is insufficient iron then smaller than usual (microcytic) RBCs are produced which contain less haemoglobin then normal and which are therefore less red (hypochromic). The adult male has about 4.5g of iron in his body. Women have slightly less because of menstrual

losses or because of increased requirements in pregnancy. The diagnosis of the cause of iron deficiency anaemia (decreased iron absorption, increased RBC breakdown or excessive blood loss) may be difficult.

In iron deficiency anaemia there is:

- Reduced haemoglobin. In men less than 135g/l, in women less than 115g/l
- Reduced mean cell volume (microcytosis)
- Reduced red blood cell redness (hypochromia)
- Reduced mean cell haemoglobin
- Reduced mean corpuscular haemoglobin concentration
- Reduced serum ferritin
- Reduced serum iron and increased iron binding capacity

Iron deficiency of gastroenterological causation may result from:

- Diets low in meat (for example in the elderly or in vegans)
- Blood loss into the gut
- Gastric surgery which interferes with absorption
- Intestinal hurry which interferes with absorption
- Malabsorption

Anaemia of chronic disorders

Some chronic disorders, particularly those associated with chronic inflammatory disorders, may depress the bone marrow to produce anaemia (if this involves all cellular element of the blood this is termed pancytopenia). One major stimulus to RBC production is erythropoetin production by the kidney. If erythropoetin production is reduced, as it may be in kidney failure, then anaemia results.

Vitamin B12

Pernicious anaemia (pernicious because it develops insidiously and can be fatal if untreated) is a common cause of Vitamin B12 deficiency. Vitamin B12 in the diet is combined with an intrinsic factor secreted by the parietal cells of the stomach and the complex absorbed by the lower small gut (the terminal ileum). If the stomach fails to produce intrinsic factor (as in pernicious anaemia) or if the diet is defective in vitamin B12 (in vegans for example), or if part of the stomach has been surgically removed, or if the terminal ileum is diseased then vitamin B12 absorption is decreased and red blood corpuscles cannot develop properly. Patients becomes anaemic and their RBCs become bigger than normal (macrocytosis) and their bone marrow contains megaloblastic (large nucleated) RBC precursors. Giving vitamin B12 intramuscularly bypasses the gut and its absorption problems.

Folate deficiency

Folate deficiency may be caused by a diet poor in vegetables, malabsorption, increased demand for folate (pregnancy) or as a drug effect. A macrocytic blood picture and a megaloblastic marrow may result.

Breakdown of red blood corpuscles

Haemoglobin breakdown occurs in the reticuloendothelial system with formation of bilirubin of various types.

The white blood cells

White blood cells are not white! Apart from their nuclei and granules they are *colourless.* White blood cells, unlike red blood cells, can migrate from the bloodstream into the tissues.

Granulocytes (polymorphonuclear leukocytes, "polymorphs," pus cells, neutrophils) have lobulated nuclei, have granules in their cytoplasm, and specialize in ingesting (phagocytosing) invading pathogens).
Eosinophils increase as a response to allergic reactions of various sorts, including hay fever and invasive worm infections.
Basophils liberate inflammatory mediators such as histamine.

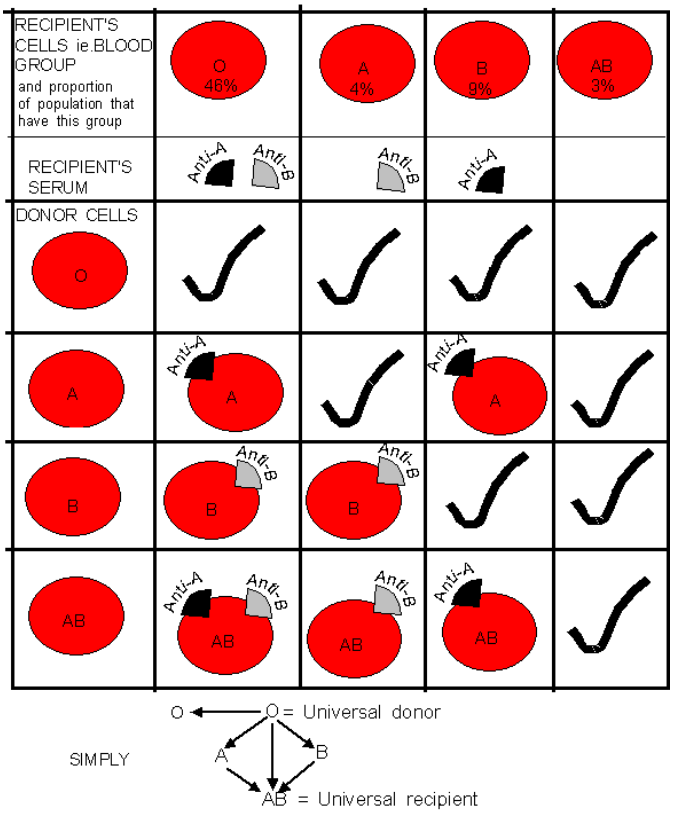
Normal neutrophil count 1.5-7.5 x 10^9/litre Normal lymphocyte count 1.5-4.0 x 10^9/litre Normal monocyte count 0.2-0.8 x 10^9/litre Normal eosinophil count 0.04-0.4 x 10^9/litre Normal basophil count <0.1 x 10^9/litre Normal platelet count 150-400 x 10^9/litre

Lymphocytes are produced in the bone marrow, lymph nodes and spleen and are often increased in long duration intracellular infections. Lymphocytes either form antibodies, liberate chemical messengers "kines" including inflammatory mediators, or enact cell mediated immunity.
Monocytes are phagocytic, usually increase in bacterial infections, and produce cytokines.
Platelets contribute to blood clotting. A low platelet count (thrombocytopenia) can result from decreased platelet production (including drug actions, malignancies especially if involving the bone marrow, infections and pernicious anaemia), increased platelet consumption, or an overactive spleen.

Although the *relative* proportions of the blood cellular constituents may provide diagnostic clues it is usually the *absolute* numbers of each constituent that are functionally important.

Blood groups

ABO blood groups and blood transfusions. The important entities are the agglutinins in the recipient's serum. They must not agglutinate the donor's red bloood cells



In the ABO blood group system the serum contains agglutinins which damage cells not of their group. Serum of Group A RBCs contains anti-B, serum of Group B RBCs contains anti-A, serum of Group AB contains no agglutinins (and thus can receive cells of any ABO grouping – and are thus "universal recipients") and serum of Group O RBCs contains anti-A and anti-B and can thus be given to any ABO group - the "universal donor" (the donated plasma of Group O RBCs is diluted by the recipient's plasma and does not cause significant problems by agglutinating the recipient's RBCs). Red blood corpuscles given to a patient whose serum plasma contains agglutinins to the donated RBCs (**A** -> **O**, B -> **O**, **A** -> **B**, or **B** ->**A**) causes the donated RBCs to be agglutinated to produce a systemic reaction. Transfusion reactions caused by **ABO** incompatibility depend on the RBCs being given into an environment containing antibodies to the donated RBCs. All blood grouping has depended, classically, on reacting the recipient's RBCs with known antiserum and known RBCs with the recipient's serum.

There are various other mechanisms by which blood can be grouped. Most depend on RBCs characteristics rather than spontaneously occurring plasma agglutinins as occur in the **ABO** system.

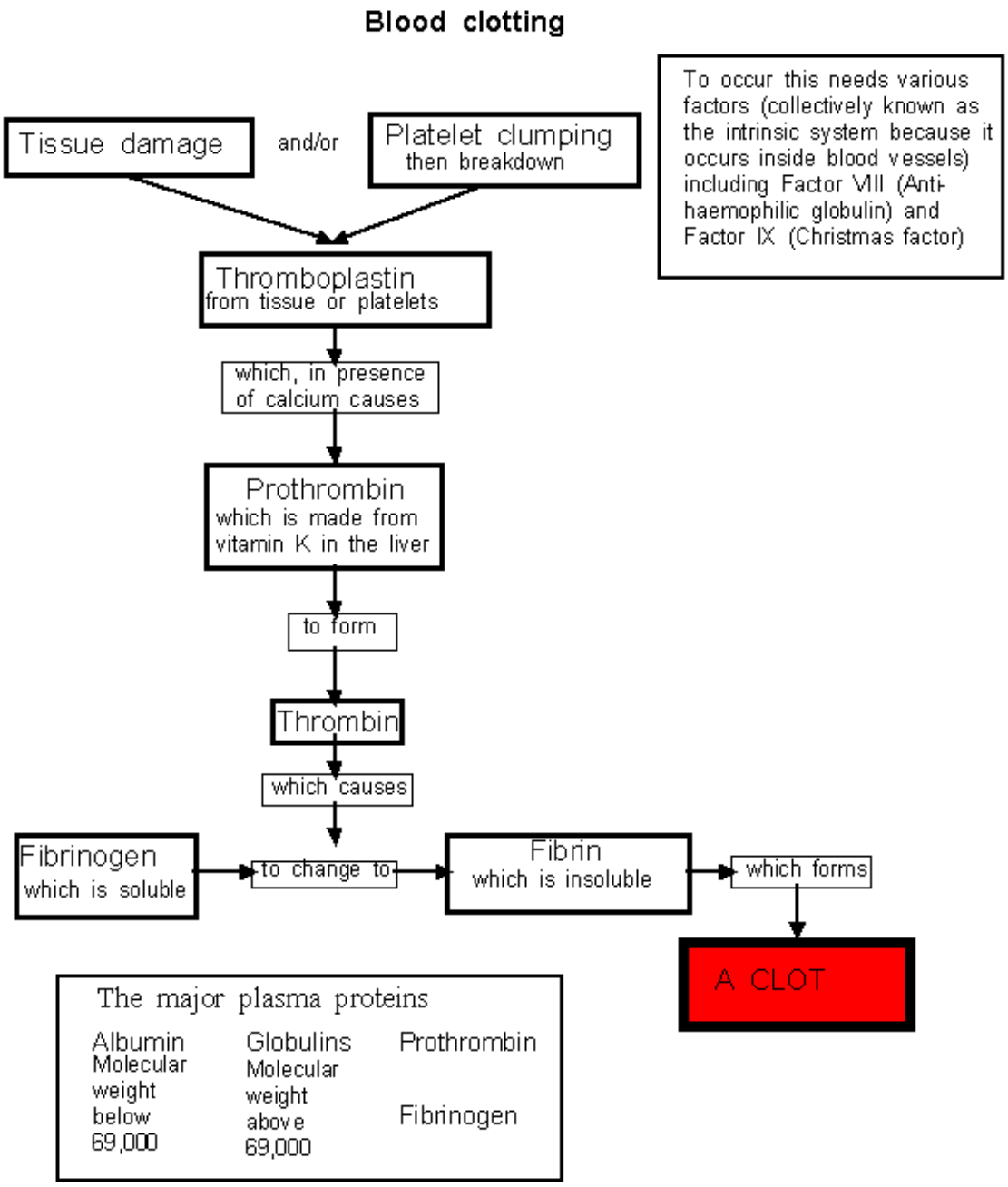
Rhesus incompatibility

If RBCs which have Rhesus positive antigens on their surface enter the bloodstream of a Rhesus negative person then this recipient will make antibodies to the Rhesus positive RBCs. Such an occurrence may occur if Rhesus positive blood is transfused into a Rhesus negative person, or at the time of childbirth if Rhesus positive foetal blood enters a maternal (Rhesus negative) circulation. If such a Rhesus negative woman has a subsequent pregnancy then the RBCs of her second or subsequent Rhesus positive foetus may be agglutinated *in utero* by maternal IgG antibody containing rhesus antibody which crosses the placenta to cause jaundice and brain damage in the foetus. To prevent this a Rhesus negative mother who has just given birth to a Rhesus positive baby is given anti-D Rhesus factor antibodies which will agglutinate the Rhesus positive foetal RBCs in her circulation before they can evoke production of anti-Rhesus antibodies.

Blood clotting

Blood clotting is essential to prevent haemorrhage from damaged blood vessels. Although plasma without cells can clot usually both plasma and cellular elements of the blood are required for effective clotting.

Below is a greatly simplified mechanism of clotting. In reality a number of intrinsic factors, including Factor VIII (anti-haemophilic globulin) and Factor IX (Christmas factor) are required to initiate or maintain clotting. Thrombus is clot in the blood vessels. Thrombi form in response to changes in the blood vessel wall to which platelets adhere with liberation of thromboplastin. This system is the *intrinsic system* (intrinsic to the blood). The *extrinsic system* refers to clotting initiated by damage to tissues outwith the blood vessels which release tissue thromboplastin. In reality there is overlap between factors and systems and other factors are also required.



Calcium in blood specimens is often removed or complexed to prevent clotting in laboratory specimens *in vitro* or to prevent clotting in blood required for transfusion. Heparin (which occurs naturally in the body and which can only be given by injection) can be used to inhibit clotting by inhibiting the formation of thrombin from prothrombin and by inhibiting the formation of fibrin from fibrinogen. The major action of most oral anticoagulants is to reduce the formation of prothrombin.

Commonly used tests of clotting

The blood count (including the platelet count) and blood film examination are basic firstline investigations.

The bleeding time is measured by the time to bleeding cessation after pricking of an ear lobe with removal of blood every 15 seconds. The modern version involves making two standardized cuts on the forearm. The usual value is 2-6 minutes. The bleeding time is essentially a measure of platelet capacity to stop bleeding by forming plugs in small vessels and of vessel integrity. The test is dependent on platelet numbers, and the function and integrity of small vessels.

The clotting time (usually less than one minute) is the time that blood, kept at body temperature, takes to stop flowing. It is essentially a test of clotting mechanisms

The activated partial thromboplastin time is a test of *intrinsic* clotting mechanisms. Measurement of specific clotting factors may be necessary for a definitive diagnosis

The prothrombin time assesses the *extrinsic* mechanisms

The thrombin clotting time is a measure of thrombin/fibrinogen status (the speed of clotting depends on the concentration of thrombin added). It is useful for detecting fibrinogen and its degradation products. D-dimer tests are used for estimating fibrinogen degradation products.

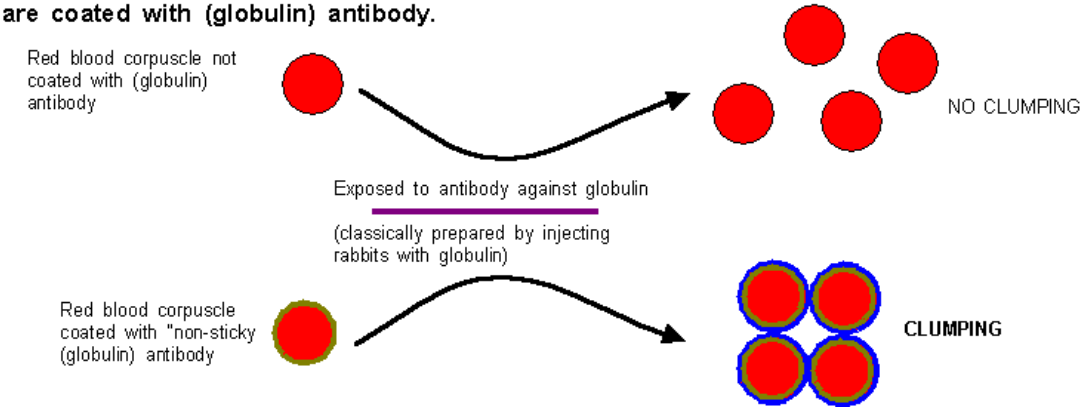
Disseminated intravascular coagulation

Disseminated intravascular coagulation is a paradox. Intravascular *clotting* causes consumption of clotting factors, particularly fibrin, which results in *haemorrhage*. Additionally the body's response may entail excessive attempts to dissolve fibrin in existing clots by production of an enzyme, plasmin, which may cause haemorrhage by reducing clotting elsewhere. In disseminated intravascular coagulation the fibrin levels are low, fibrin degradation products are high and the platelets are low. Fragmentation of RBCs may also be seen.

The plasma proteins

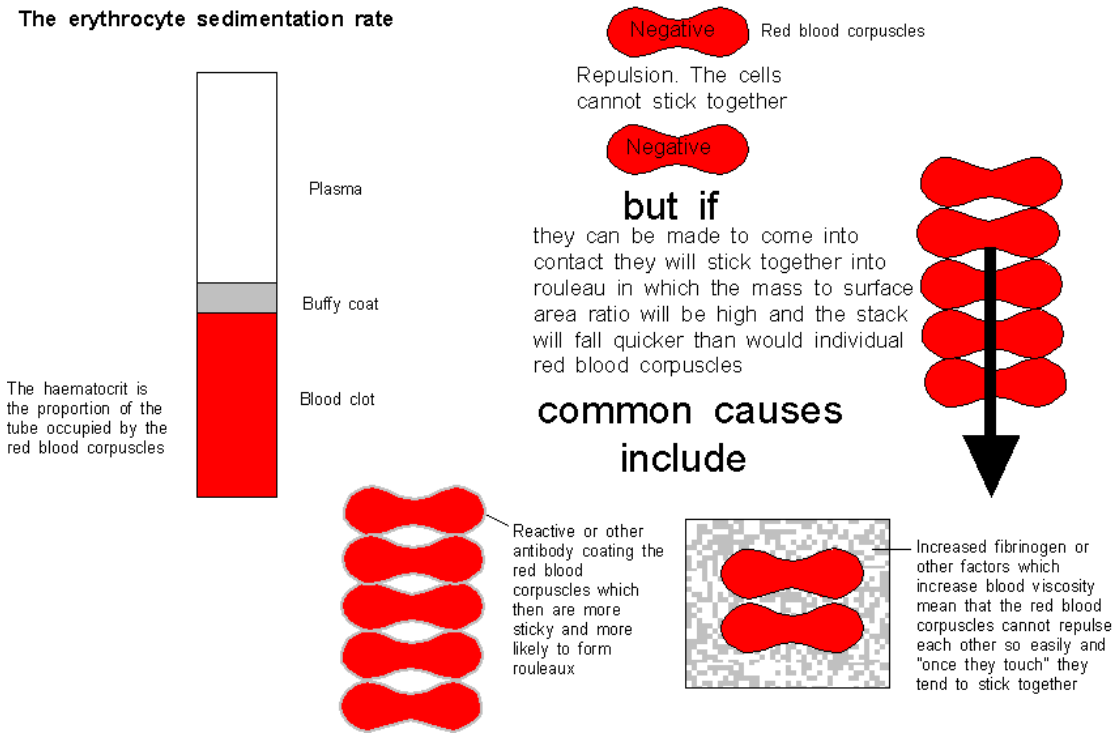
The direct antiglobulin (Coombs') test) detects antibodies on RBCs which are found in most cases of immune mediated anaemia associated with antibodies of various sorts which cause the red blood corpuscles to have a shortened lifespan. The osmotic significance of plasma proteins is detailed elsewhere.

The principle of the (direct) Coombs test to detect whether red blood corpuscles are coated with (globulin) antibody.



The Erythrocyte sedimentation rate (ESR)

If clotting is prevented RBCs sink, and the distance they sink at the end of one hourcan be measured (the erythrocyte sedimentation rate) and eventually constitutes a layer 40-47 percent of the total column height (the haematocrit or packed cell volume). The white cells form a shallow layer on top of the red corpuscles (the buffy coat), leaving the plasma above.



Normally the slight negative charge on each RBC prevents them from clumping together. However if they are pushed together they may then clump and form rouleaux (stacks of RBCs) which fall down the column of plasma quicker than would individual RBCs because their mass to surface area ratio increases. The erythrocyte sedimentation rate thus depends on the viscosity of blood (which may be increased by an increase in globulins or increases in fibrinogen). If RBCs are coated by antibody, particularly reactive antibodies produced by the liver in response to inflammation, their stickiness may increase and thus their propensity to from rouleaux. If RBCs cannot easily clump together to form rouleaux (for example if there are abnormally shaped corpuscles) then the erythrocyte sedimentation rate may remain normal in conditions in which it is usually high.