ANP1105B: Topic 4.1 - Blood

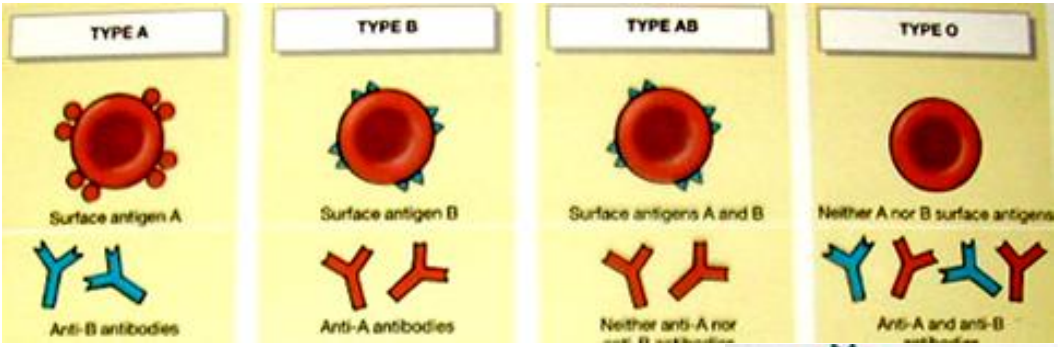
4.1.1 Describe the composition of blood (pp. 635-638)

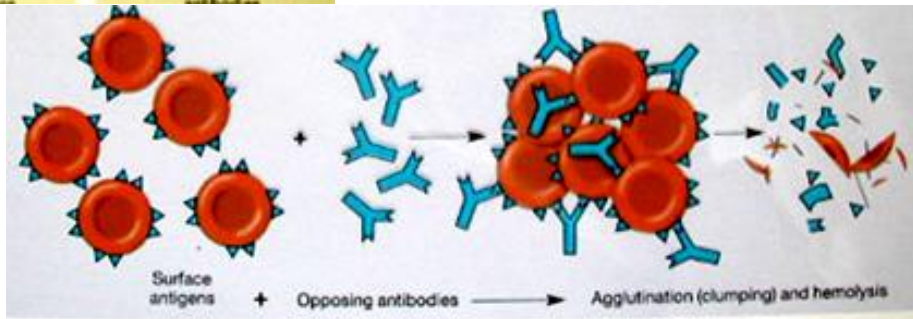
4.1.2 Erythrocytes: describe their structure, function & life cycle (pp. 638-644)

4.1.3 Hemostasis: list the principle steps and justify the role of platelets in this process (pp. 650-656) → blood clotting

4.1.4 Describe briefly the processes of clot retraction & fibrinolysis (pp.650-656)

4.1.5 Differentiate among the different blood types and explain the basis of transfusion reactions (pp. 656-658)





4.1.1.1 list the physical characteristics of blood and the types of formed elements found in blood

4.1.1.2 list and briefly describe the 3 main functions associated with blood and the circulatory system

4.1.1.3 list the physical characteristics of plasma

Blood Components

only FLUID tissue in body (formed elements suspended in **plasma**)

Formed elements:

> erythrocytes or RBCs
> leucocytes or WBCs
> platelets

Hemoglobin is also a pigment

Physical Characteristics

- colour is scarlet (O_2-rich) to dark red (O_2-poor)
- more dense, viscous than H_2O
- pH = 7.35-7.45 → Need to know
- 8% body weight (5-6 L ♂; 4-5 L ♀)

FUNCTIONS

1. Distribution: / Transport

a) oxygen & nutrients: O_2 from lungs, nutrients from digestive tract to all body cells

b) metabolic wastes: from cells to elimination sites (lungs → CO_2, kidneys → urine)

c) hormones: from the endocrine organs to their target organs

2. Regulation:

a) body temperature: distribution, conservation, dissipation

- Core temperature needs to maintain a certain temperature

b) pH in body tissues (plasma proteins, bicarbonate reserve)

- Many blood proteins and other blood-borne solutes act as buffers to prevent excess or abroad changes in blood pH that could jeopardize normal cell activities. Blood also as a reservoir for the body's alkaline reserve containing bicarbonate ions

c) adequate fluid volume in the circulatory system

- Blood proteins prevent excessive fluid loss from the bloodstream into tissue space. As a result, the fluid volume in the blood vessels remain ample to support efficient blood circulation to all parts of the body

3. Protection:

a) platelets, plasma proteins, blood clotting ⇒ prevent blood loss

b) antibodies, complement, WBCs ⇒ prevent infection against foreign invaders such as bacteria and viruses

BLOOD PLASMA

- straw-coloured; 90% water + many solutes (see Table 17.1)
- *plasma proteins:* produced in liver (except gamma globulins); functional proteins which remain in blood

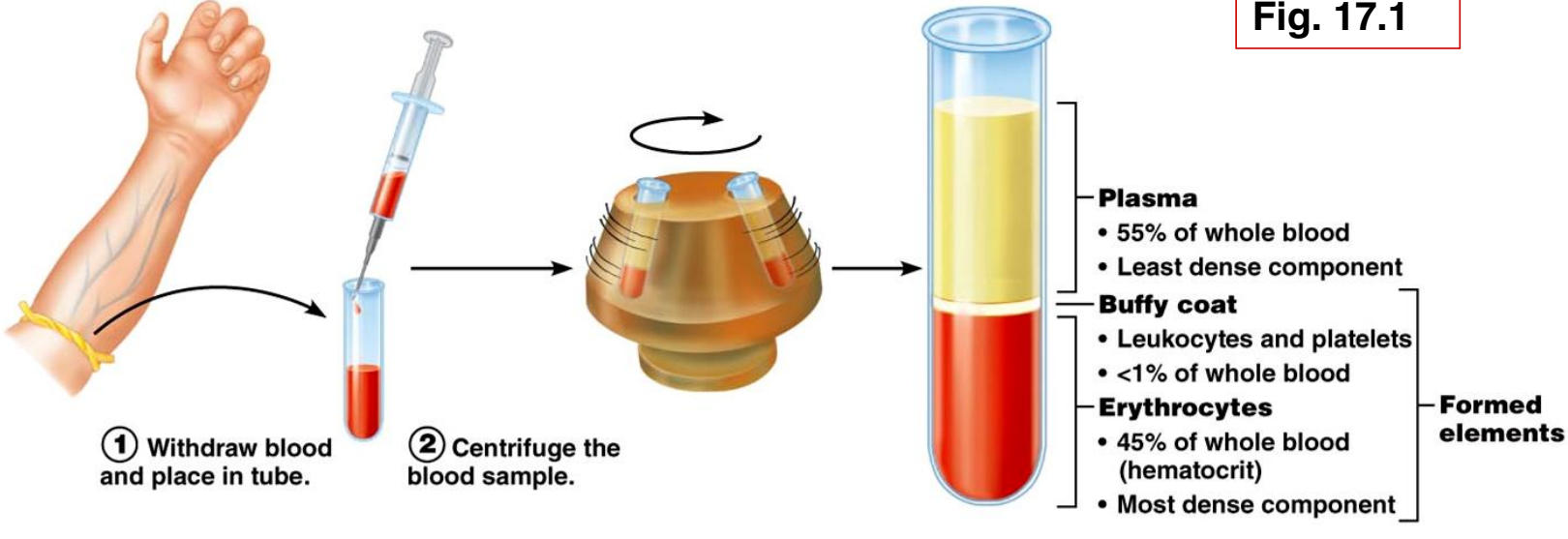
albumin: (60% of all plasma proteins) ↑ H^+

- carrier of various molecules, important blood buffer; major osmotic protein

What is the major osmotic ion??? · Sodium

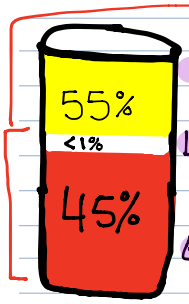
- blood constantly adjusted to keep its composition, pH within normal range

Fig. 17.1



Blood is...

→ Only fluid tissue in the body
→ Appears thick, homogeneous liquid
  → Contains cellular and liquid components on a microscope
→ Specialized connective tissue, living blood cells called formed elements, which is suspended by the non-living matrix called plasma
→ Lacks collagen and elastic fibers
→ Dissolved fibrous proteins become visible as fibrin strands during blood clotting



Plasma; contains many dissolved solutes (mostly electrolytes)

Leukocytes; help protect the body Platelets; cell fragments help stop bleeding

Erythrocytes; the RBC that transport oxygen

FORMED ELEMENTS

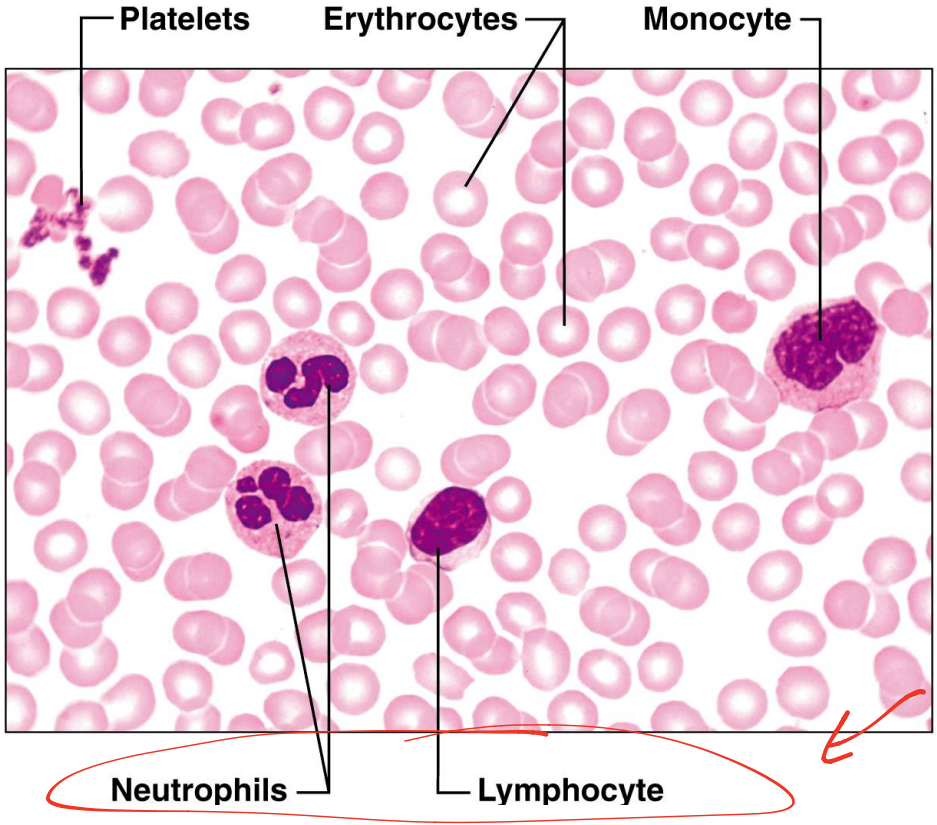
erythrocytes, leukocytes, platelets

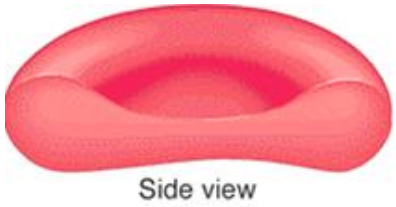
- There are the only ones that have a nuclei

Why do we say that leukocytes <u>only</u> are complete cells???

most formed elements short-lived/disposable; replaced by bone marrow

Fig. 17.2





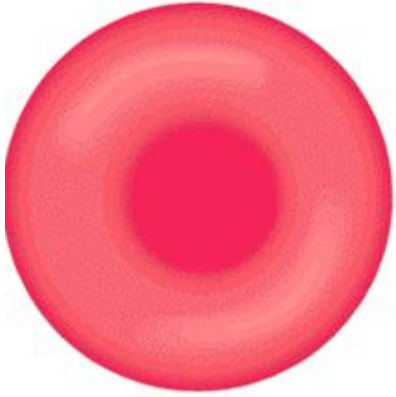


Fig. 17.3

4.1.2.1 describe the functional anatomy of an erythrocyte, the structural organization of hemoglobin

- ~7.5 μm diameter; biconcave discs (no nucleus) = "bags of hemoglobin"; other proteins maintain PM, regulate cell shape

  > *eg: spectrin – what is the function of this protein?*

- RBCs transport O_2 from lungs to tissues; transport 20% of CO_2 back to lungs

Specialized characteristics that optimize function:

(i) small size & biconcave shape ➢ large SA to V ratio

(ii) >97% non-water composition is hemoglobin

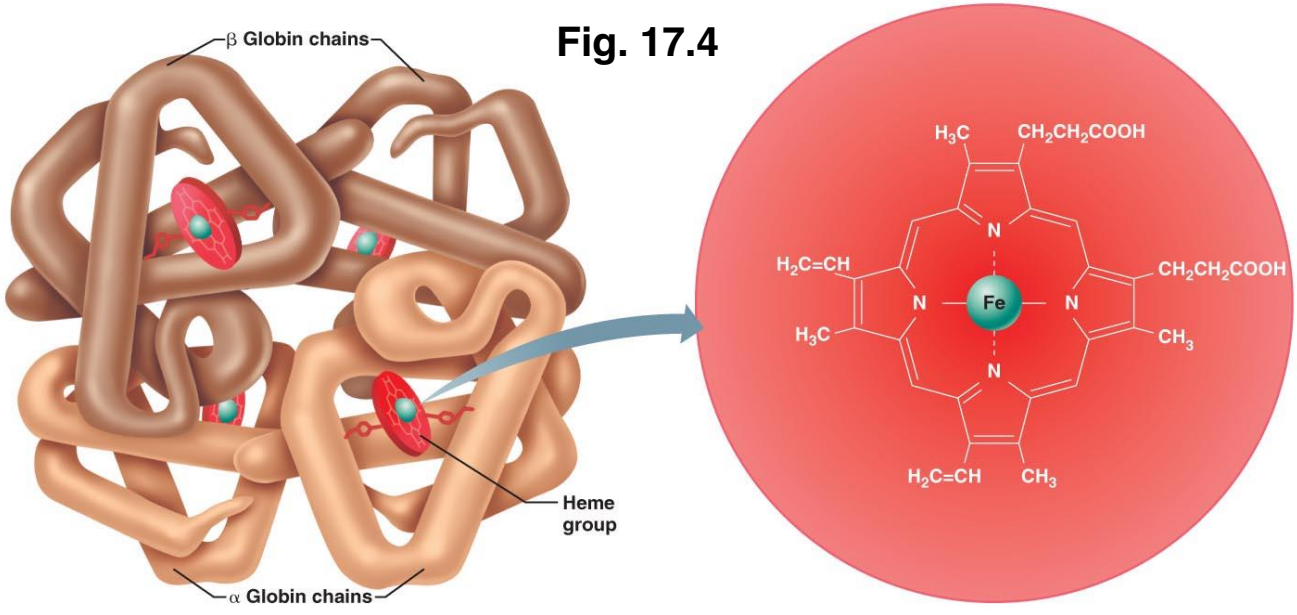
(iii) no mitochondria; generate ATP anaerobically

- major factor contributing to blood viscosity; women have lower RBC count (4.3-5.2 x 10^6 cells/μl) than men (5.1-5.8 x 10^6 cells/μl)
- rate of blood flow inversely affected by RBC count

low rate ↓ High RBC count ↑

hemoglobin = protein globin bound to red heme pigment

Fig. 17.4



(a) Hemoglobin consists of globin (two alpha and two beta polypeptide chains) and four heme groups.

(b) Iron-containing heme pigment.

- globin = 4 polypeptide chains (2α & 2β); 4 Fe-containing central heme groups
- each Fe can reversibly bind one molecule of oxygen (4 per Hb molecule; each RBC contains 250 million Hb molecules!!)
- Hb contained in erythrocytes:
  > keeps it from fragmenting and being lost
  > keeps it from contributing directly to osmotic pressure & blood viscosity
- oxyHb a different shape and colour than deoxyHb
  bright red color — purple-blue color
- O_2 combines with heme group, but CO_2 combines with globin part ➤ carbaminohemoglobin

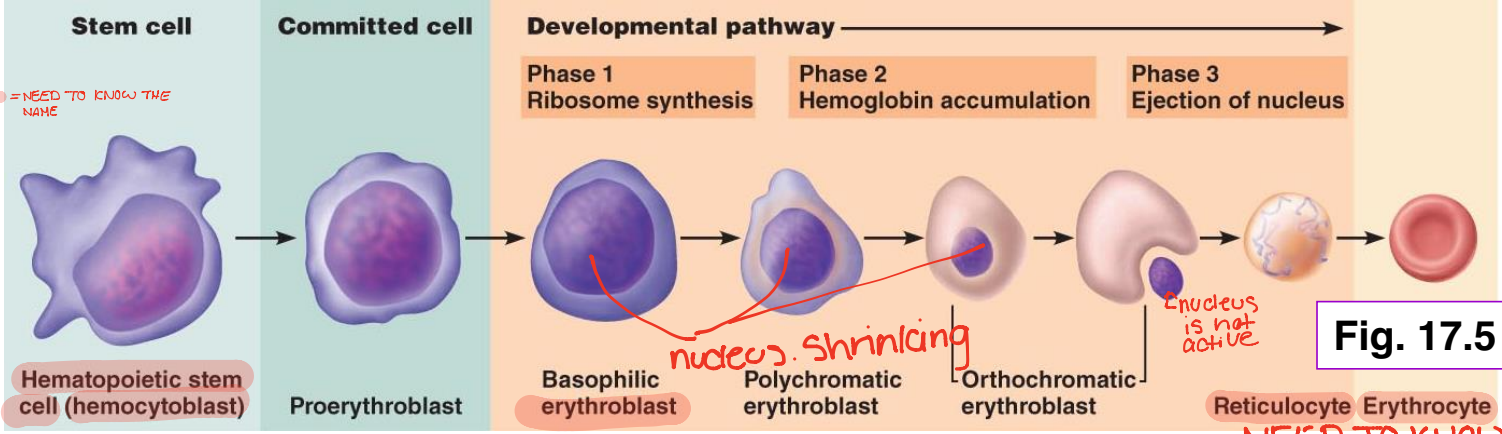


Fig. 17.5

4.1.2.2 describe the process of erythropoiesis, its regulation and the dietary requirements associated with daily production; outline the life cycle of a RBC

- hematopoiesis = production of blood cells; occurs where??
- immature RBCs here - as mature, migrate through capillary walls to blood
- hematopoietic stem cell (hemocytoblast): stem cell for all formed elements
  ➤➤ cells become committed to a particular pathway

Erythropoiesis: production of RBCs

Phase 1

Phase 2

Phase 3

What is the difference between a reticulocyte and an RBC? → no ribosome

↓

you can find some ribosome

Regulation of Erythropoiesis:

- balance between RBC production & destruction
- too few: anemia....., too many: polycythemia.....
- production rate: >2 million/sec if healthy (sufficient iron & B vitamins)

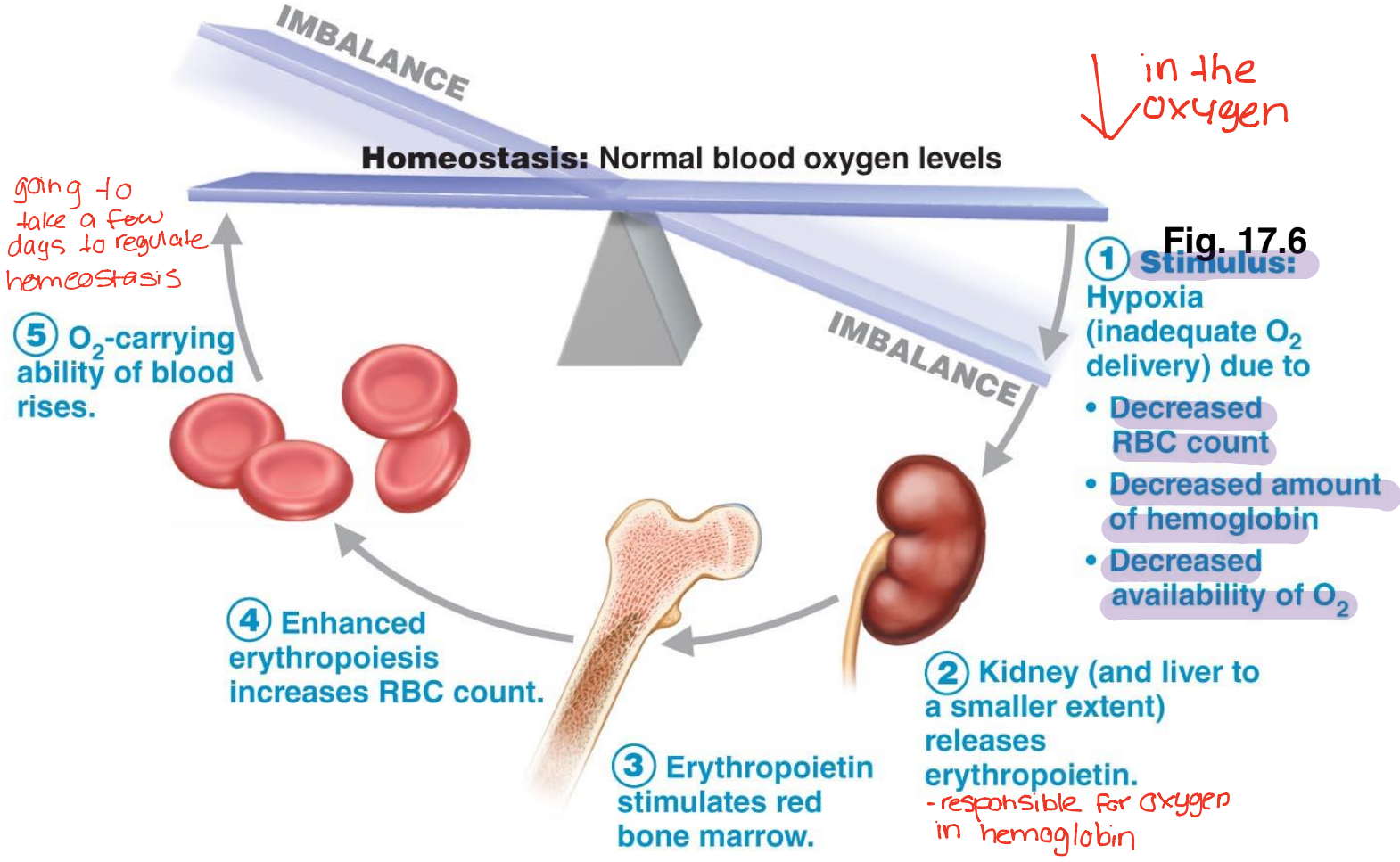


Fig. 17.6

in the oxygen

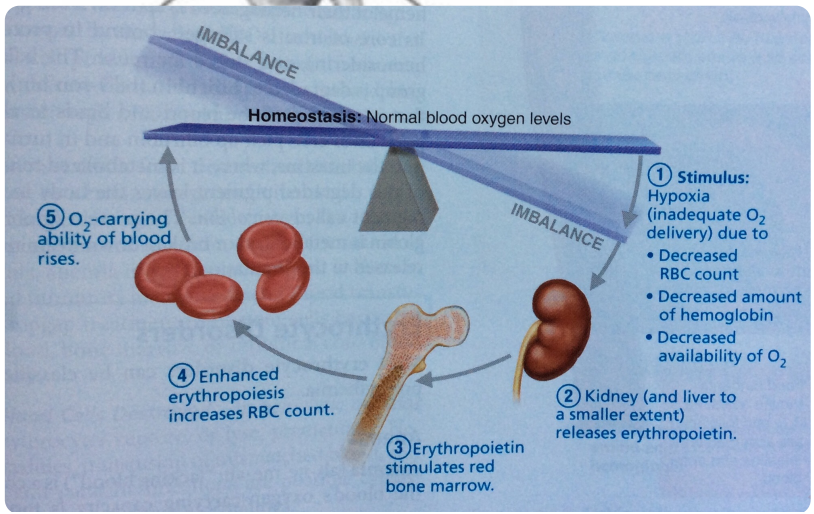
going to take a few days to regulate homeostasis

- responsible for oxygen in hemoglobin

Hormonal controls:

- **Erythropoietin**: EPO, glycoprotein produced in ..KIDNEYS.....
- always some EPO in blood; additional release by kidney if hypoxia due to:
  - (i) hemorrhage/excess RBC destruction ⇒ reduced # of RBC due to...
  - (ii) high altitude or pneumonia ⇒ reduced availability of O_2
  - (iii) increased demand ⇒ insufficient hemoglobin per RBC

What is monitored and acts as a signal: the number of RBCs or the level of oxygen transport?



- erythropoietin: enhances maturation rate of committed RBC precursors (1-2 days to see results)
- route of stimulation: hypoxia ➢ kidneys ➢ erythropoietin ➢ activation of bone marrow ➢ more mature RBCs

renal failure patients: additional problem is lack of EPO (RBC counts can be 50% of normal); helped by recombinant EPO

athletes & EPO abuse: can increase hematocrit from 45% to 65%; BUT increased viscosity plus dehydration during race can ➔ clotting, stroke, heart failure

What is the effect of testosterone on renal EPO production?

- Stimulatory effect

J. Carnegie, UofO

Dietary requirements (iron, B-vit)

absorption of dietary iron controlled by body's storage levels

> 65% already in Hb

> rest stored in liver, spleen, bone marrow (ferritin, hemosiderin)

iron transported in blood loosely bound to transferrin

loss of iron: feces, urine, sweat

avg daily loss=1.7 mg (♀), 0.9 mg (♂)

vitamin B_{12} & folic acid essential

RBC are unable to synthesize new proteins, grow, or divide

Fate/Destruction of Erythrocytes

lose flexability

mature erythrocytes become rigid, fragile with time (Why?); Hb begins to degenerate

useful lifespan: 100-120 days

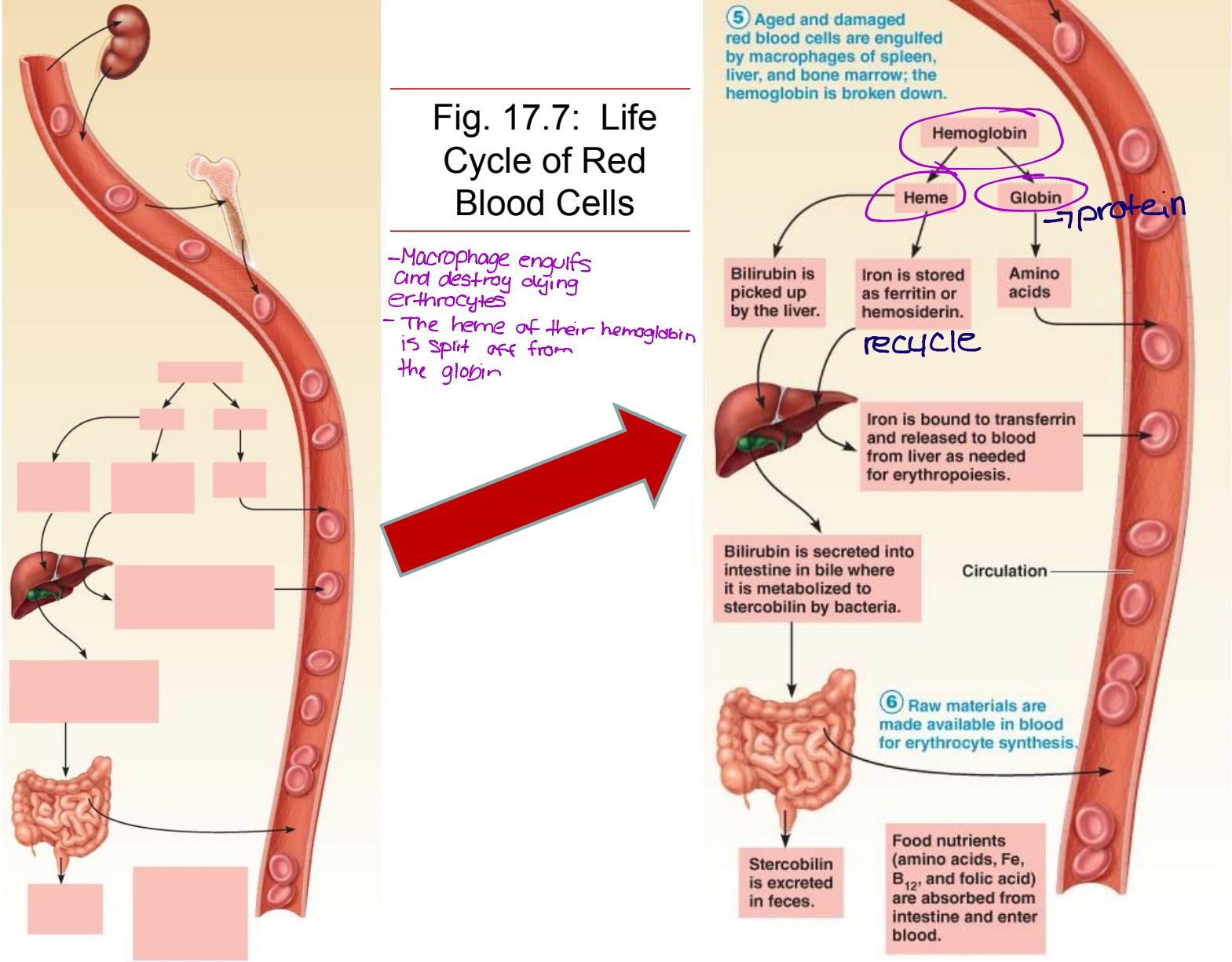
spleen = "RBC graveyard"

iron stored & reused; rest of heme degraded to bilirubin (*what happens to this?)* - eventually becomes *stercobilin* or *urobilinogen*

amino acids of globin part recycled

Fig. 17.7: Life Cycle of Red Blood Cells

- Macrophage engulfs and destroy dying erthrocytes
- The heme of their hemoglobin is split off from the globin



4.1.2.3 Define: anemia, polycythemia & give examples

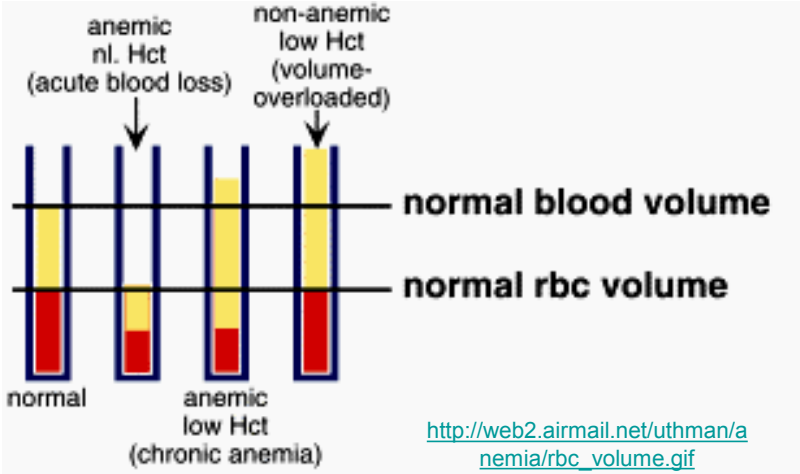
Anemia: tired, pale, short of breath, chilly - causes:

(i) Insufficient numbers of RBCs:

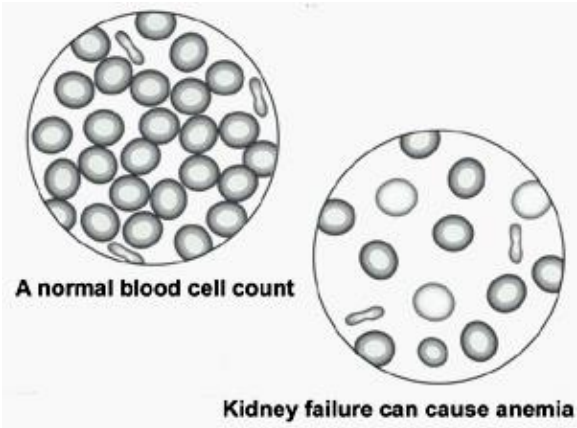
(ii) Decreases in Hb content: → not enough iron

(iii) Abnormal Hb: (e.g. sickle cell anemia)

→ not enough O_2 in cell so metabolic process cannot produce heat



http://web2.airmail.net/uthman/anemia/rbc_volume.gif



http://www.ikidney.com/iKidney/Lifestyles/LifestyleTips/PeritonealDialysis/JusttheFacts_Anemia.htmUofO

DO NOT NEED TO KNOW

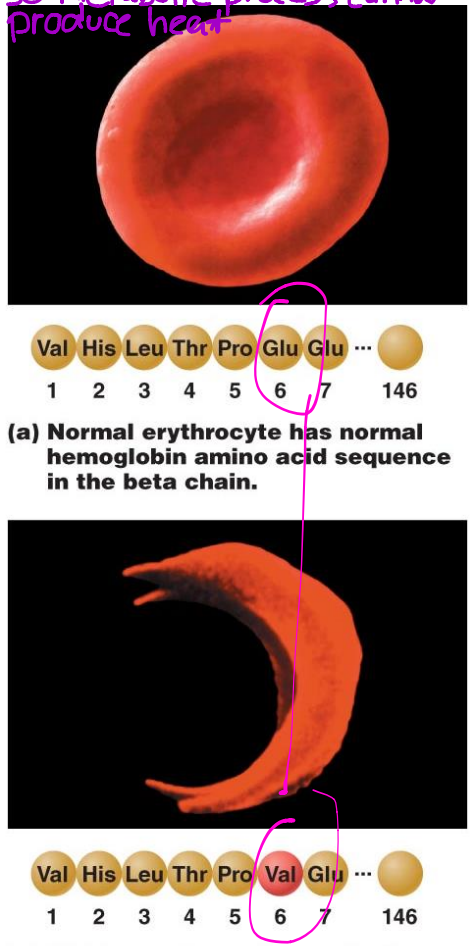


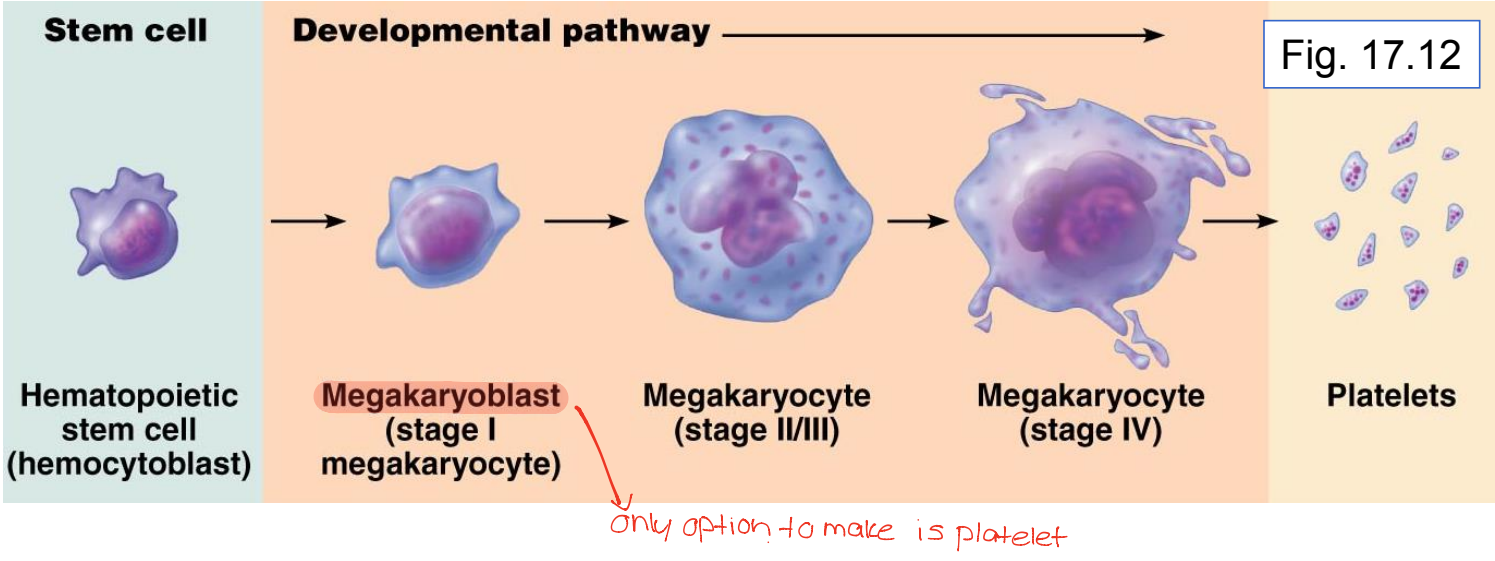
Fig. 17.8

Polycythemia: (danger is ???) clotting

(i) polycythemia vera: True / real ⇒ cancer of bone marrow

(ii) secondary polycythemia: result of something else ⇒ limits oxygen availability

(iii) artificial polycythemia: result of blood doping



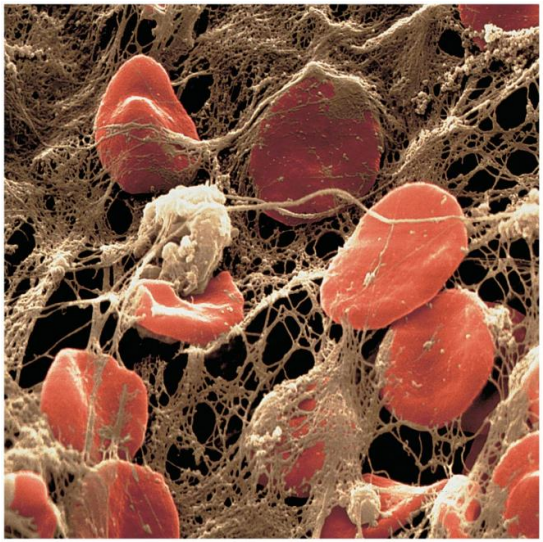
4.1.3.1 define platelet and summarize the main steps in platelet production

4.1.3.2 define hemostasis; list the 3 key events involved in the process and describe the processes occurring during each of these 3 events

Platelets

- cytoplasmic fragments of megakaryocytes
- contain purple-staining granules that contain clotting factors & enzymes
- anucleate; lifespan~10 D
- platelet formation regulated by thrombopoietin
- 250,000-500,000 platelets/ul blood

Seal a blood vessel ⇒



HEMOSTASIS:

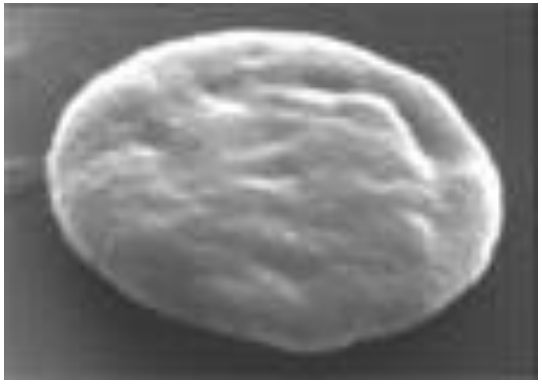
- 3 phases: A) VASCULAR SPASM
  B) PLATELET PLUG FORMATION Fig. 17.15
  C) COAGULATION

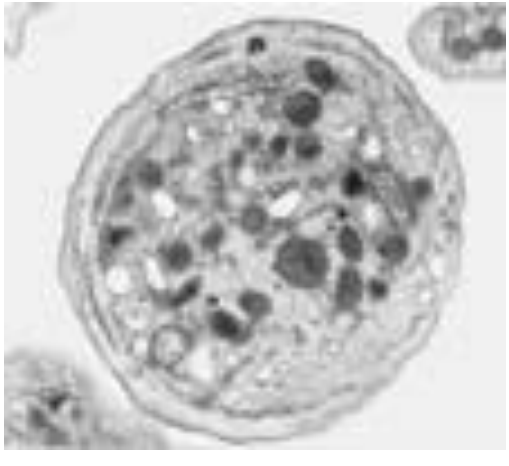
A. Vascular spasms

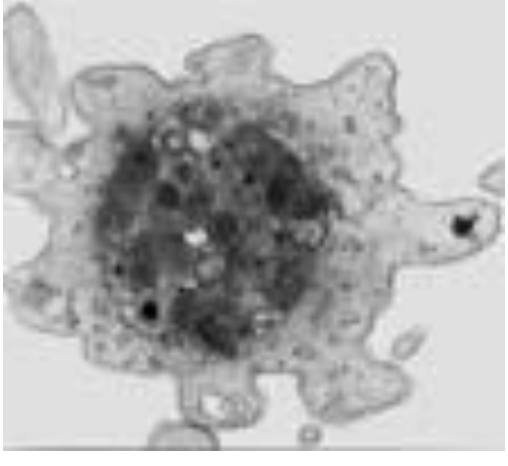
- vasoconstriction of vessel in response to damage
- triggers: damage, chemicals from endothelial cells & platelets, pain reflexes
- ***purpose?*** ⇒ slow down blood flow

B. Platelet plug formation

- usu platelets do not stick to each other or to endothelial linings
  - ↓ usually • NO & PGI_2 (prostacyclin): produced by endothelial cells; inhibits platelet aggregation *why is this important??* ⇒ (hormone)
- exposure of collagen stimulates platelets to swell, become spiky & sticky ➢ adhere to exposed collagen (von Willebrand factor) ➢ **degranulation**
  - **ADP**: enhances aggregation and degranulation
  - **serotonin** & **thromboxane A_2** – enhance vascular spasm & aggregation







Resting platelet

Activated platelet

http://www.cs.york.ac.uk/nature/tuna/useful/MeetingReports/PlateletTunaTalk.ppt#3

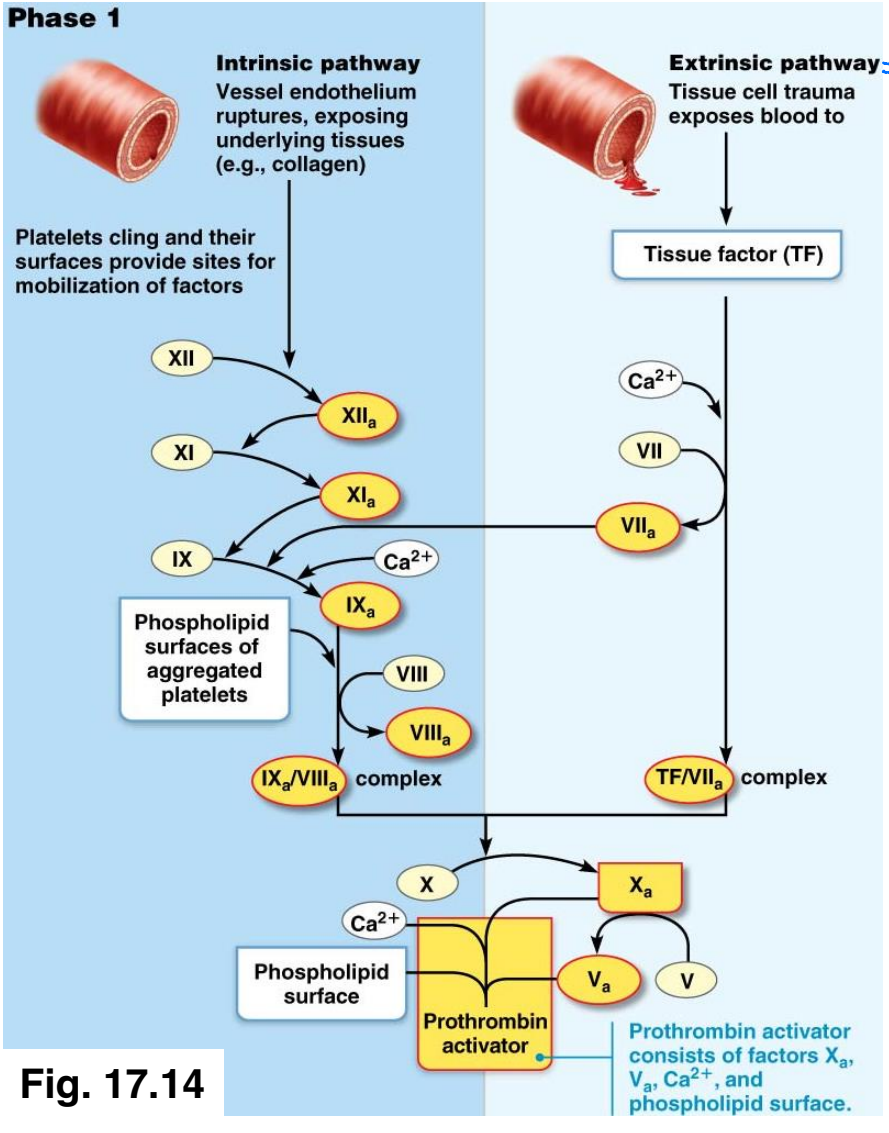
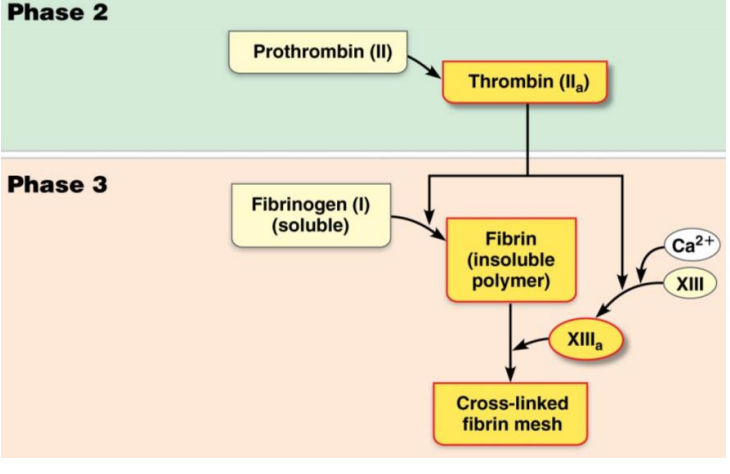


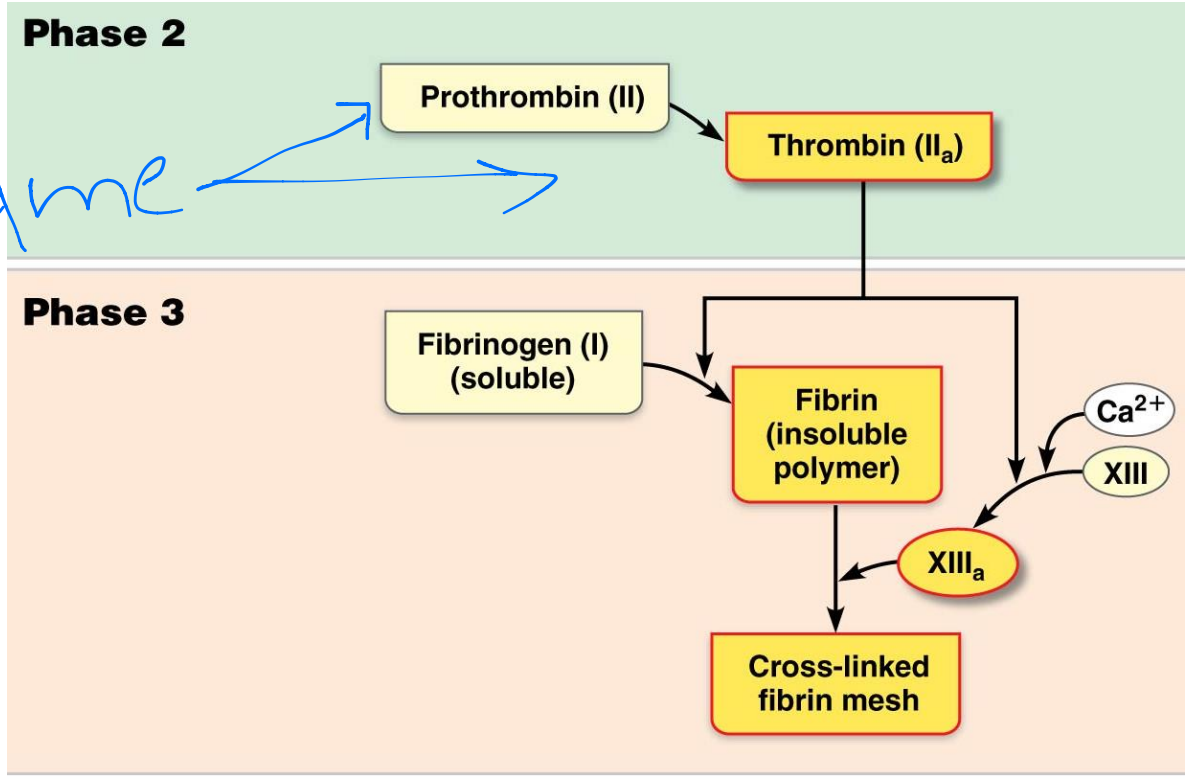
Fig. 17.14

=> short cut, damage to cell wall

4.1.3.3 differentiate between the intrinsic and extrinsic pathways for the formation of prothrombin activator (conditions and relative speed of each pathway)

* not too important for midterm II





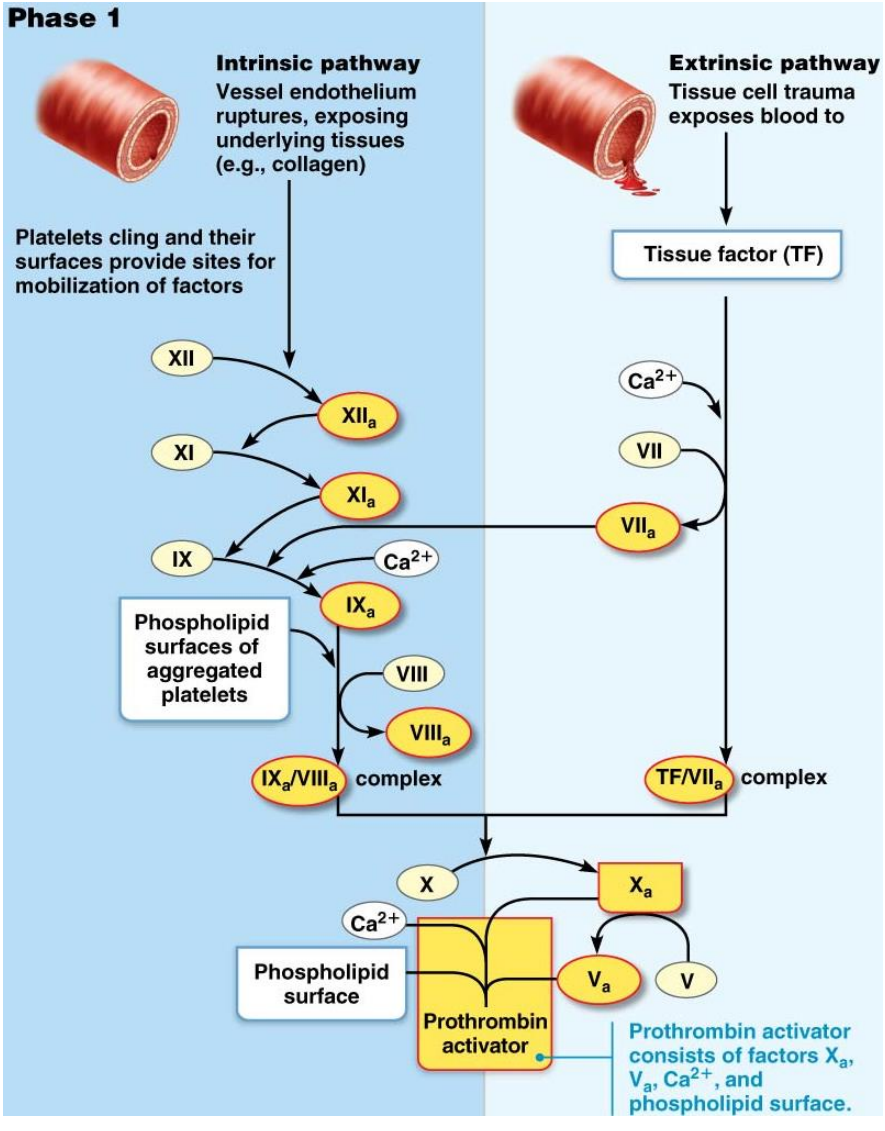
enzyme

3.

Coagulation

- blood transformed from a liquid to a gel
- 3 phases: (i) prothrombin activator formed
  (ii) prothrombin to thrombin
  (iii) fibrinogen molecules ➢ fibrin mesh

Also there are many procoagulants & anticoagulants; the latter predominate in an intact vessel



2 pathways to prothrombin activator:

(i) intrinsic pathway: clotting of blood outside body (eg: in a tube) or in slightly damaged vessel - slower pathway to factor X and PA

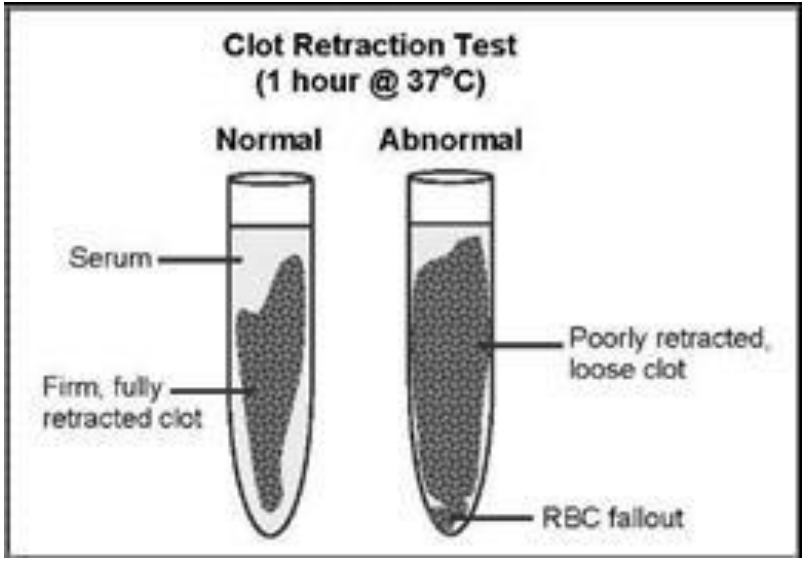
(ii) extrinsic pathway: clotting of blood assoc with body & blood vessel damage ➢ release of tissue factor ➢ bypass many steps of intrinsic pathway - faster pathway to factor X and PA

prothrombin activator is the rate-limiting step; once achieved, clot formation in 10-15 sec via phase 2 & 3 common pathways

4.1.4 describe briefly the processes of clot retraction and fibrinolysis

Clot Retraction & Repair

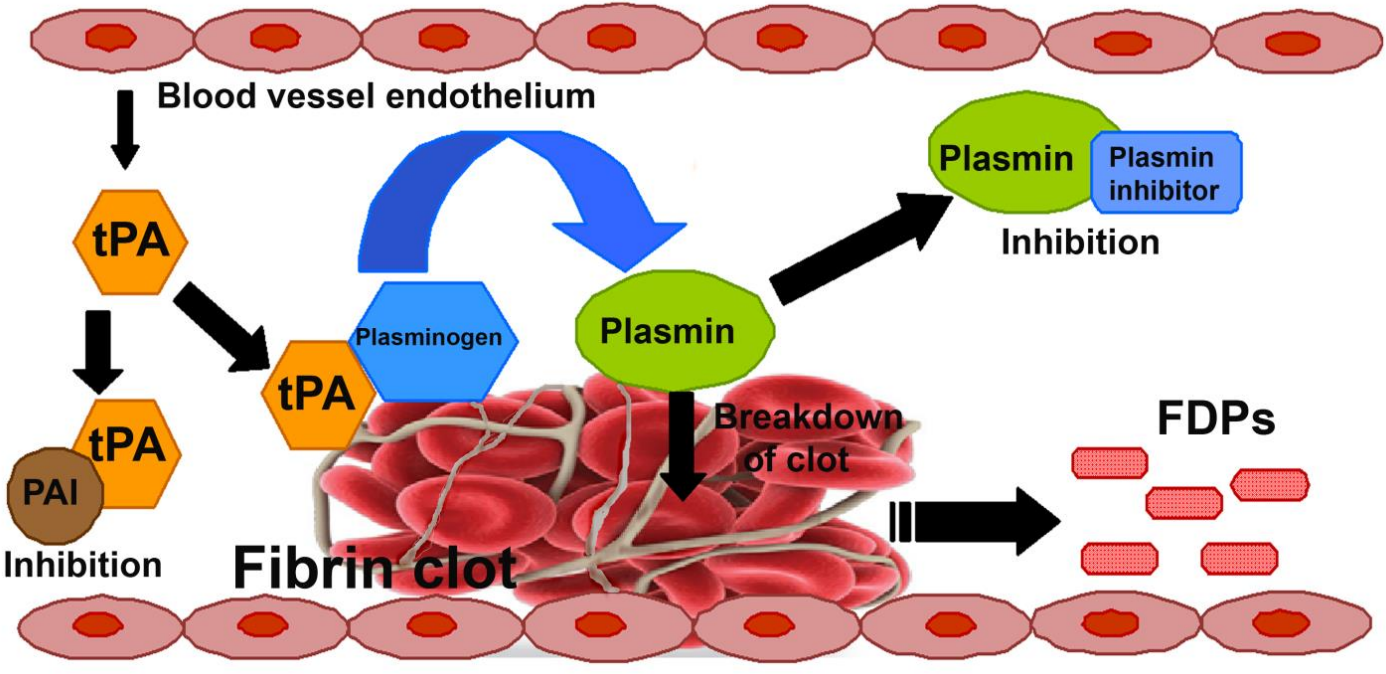
- occurs within 30-60 min; platelets contract (contain actin & myosin), exerting pull on surrounding fibrin strands
- serum squeezed from clot & ruptured edges of blood vessels pulled closer
- PDGF released during degranulation stimulates smooth muscle cells & fibroblasts to divide & rebuild wall; endothelial cells multiply to fill gap in lining (VEGF = vascular endothelial growth factor)



http://webmedia.unmc.edu/alliedhealth/honeycutt/CLS416/SL06D12Coag/SL06D12Coag_slide0046_image031.jpg

Fibrinolysis

- removal of clot when no longer needed
- key enzyme is plasmin [precursor = plasminogen] - plasminogen is activated by tPA (tissue plasminogen activator) released by endothelial cells
- begins within 2 days & continues until clot is dissolved



http://www.intechopen.com/source/html/46041/media/image4.png

Factors Limiting Clot Growth/Formation

- 2 homeostatic mechanisms:
  - (i) swift removal of coagulation factors
  - (ii) inhibition of activated clotting factors

- clot formation requires [procoagulation factors] > [anticoagulation factors]

(i) normally flowing blood washes away procoagulants

(ii) as thrombin forms, adsorbed onto fibrin threads (limits clot size)

(iii) antithrombin III (in plasma) inactivates any escaping thrombin

(iv) antithrombin III & protein C (liver) inactivate many intrinsic pathway procoagulants

(v) heparin (basophils & mast cells) - enhances activity of antithrombin III

(vi) smooth endothelial lining of undamaged blood vessels (also endothelial-derived heparin & prostacyclin)

One action of Hirudin is to inhibit the action of thrombin;

http://www.bloodservices.ca/CentreApps/Internet/UW_V502_MainEngine.nsf/page/Blood+Suckers?OpenDocument

4.1.4.2 define: thrombus, embolus, thrombocytopenia, hemophilia

Thromboembolytic conditions: (undesirable intravascular clotting)

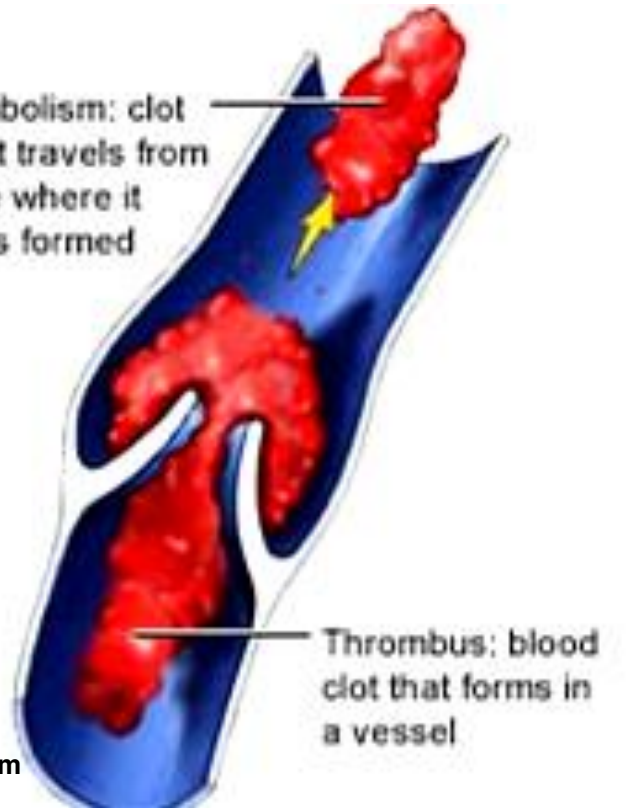
thrombus: clot that develops & persists in an unbroken blood vessel - can block critical blood circulation to those tissues

embolus: a thrombus which has broken free ➢ can get stuck in a vessel of small diameter (eg: pulmonary or cerebral emboli)

- drugs such as tPA, streptokinase to dissolve clots

What might promote thrombus formation in an unbroken blood vessel?

Why is aspirin a good preventative therapy in heart attack risk patients??



http://www.nlm.nih.gov/medlineplus/ency/article/001124.htm

Bleeding Disorders:

interference with normal clotting: thrombocytopenia, liver disorders,hemophilias

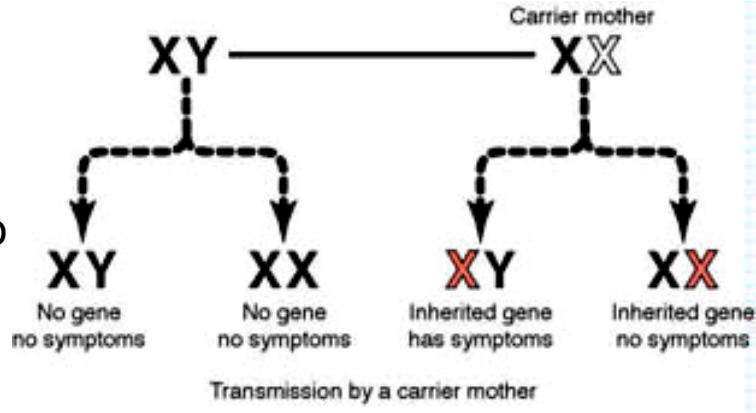
(i) Thrombocytopenia: any condition harmful to bone marrow (malignancy, radiation, drugs) ➢ any movement leads to bruising (internal hemorrhage)

> platelet count < 50,000/µl

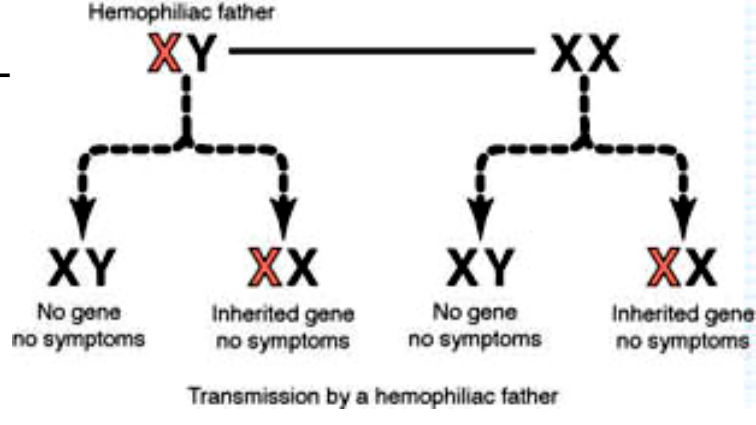
> whole blood transfusions provide **temporary** (why?) relief

(ii) Impaired liver function: eg: hepatitis, cirrhosis (liver is source of procoagulants) - liver disease also associated with reduced bile production; bile needed to absorb vitamin K (why?)

(iii) Hemophilias: hereditary bleeding disorders; hemophilia A (83% of cases) - deficiency in factor VIII; hemophilia B - deficiency in factor IX - both sex-linked conditions - require transfusions/injections of purified clotting factors



Transmission by a carrier mother

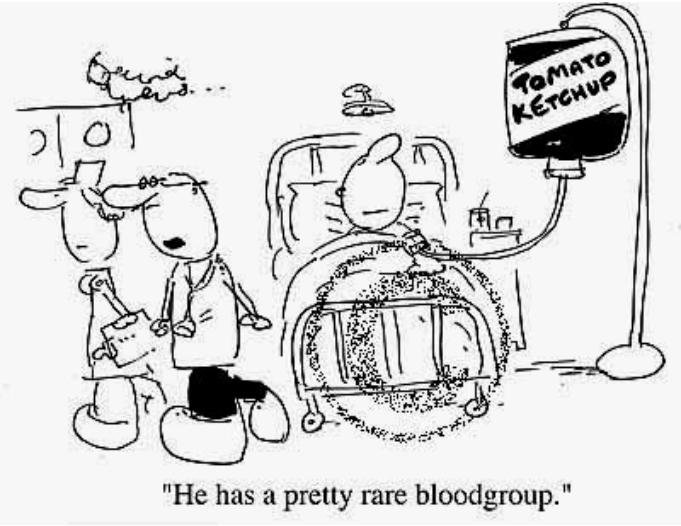


Transmission by a hemophiliac father

http://www.healthatoz.com/healthatoz/atoz/images/ency/00042741.jpg

4.1.5.1 define the components of the ABO and Rh blood group systems; describe a transfusion reaction using the terms agglutination & hemolysis

- body compensates for some blood loss by:
  (i) vasoconstriction to decrease blood vessel volume
  (ii) increased rate of erythropoiesis
- loss of 15-30% ➔ weakness, pallor; loss > 30% can induce shock
- whole blood transfusion: substantial blood loss or thrombocytopenia; packed red cells for anemia
- donor blood mixed with heparin (Ca^{++} chelator, anticoagulant) - can be stored several weeks @ 4^0C



"He has a pretty rare bloodgroup."

Human Blood Groups

- transfusion of incompatible blood can be fatal
- RBC antigens promote agglutination
- only the ABO and Rh antigens cause serious agglutination problems during transfusion

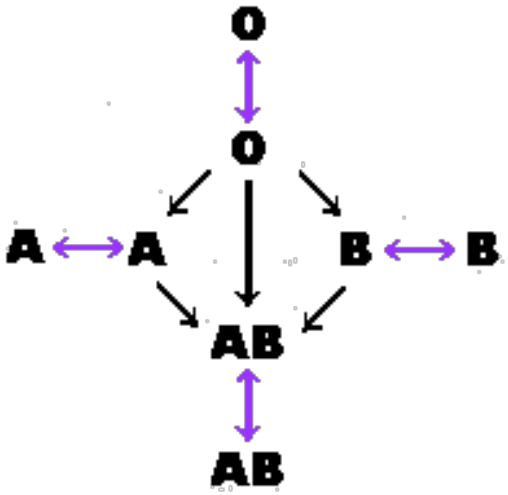
preformed antibodies called agglutinins; newborn blood has no agglutinins (begin to appear within ___ months; peak @ _____yrs, slowly decline with age

ABO Blood Groups:

Why is type O the universal donor? Why is type AB the universal recipient?

Which blood type is most common? Least common?

J. Carnegie, UofO



Blood type	Antigens	Antibodies
A	A	Ant-B
B	B	Anti-A
AB	A & B	None
O	None	Anti-A/B

Rh Blood Groups:

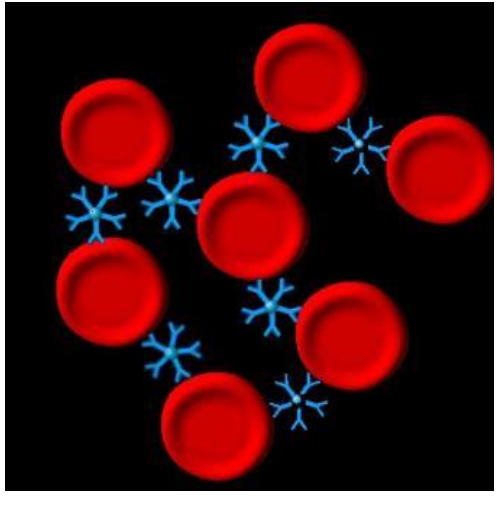
- at least 8 different types of Rh factors (only C, D & E are fairly common)
- *Rh D* first identified in Rhesus monkeys, then in humans (~85% North Americans Rh+ (meaning??? ……..)
- Rh antibodies NOT spontaneously formed in blood of Rh- individuals - individuals become sensitized upon first exposure to Rh antigens (transfusion, Rh+ fetus) ➢ antibodies will attack donor RBCs in response to second & subsequent exposures
- Rh- mothers carrying second Rh+ fetus treated with *RhoGAM (anti-Rh serum)* to prevent erythroblastosis fetalis

Transfusion Reactions: Agglutination & Hemolysis

- problem is recipient's agglutinins (antibodies), not donors - *Why?*
  (i) agglutination: clogs small blood vessels
  (ii) clumped RBCs rupture or are destroyed by phagocytes & Hb released
- overall result:
  (i) blocked flow to tissues
  (ii) reduced O_2-carrying ability of blood
  (iii) Hb precipitates/clogs kidney tubules ➢ possible kidney failure

also: fever, chills, nausea, vomiting, general toxicity - critical to prevent kidney failure by administering alkaline fluids to dilute & dissolve Hb; also diuretics

- autologous transfusion (eg: 1 unit/4 days up to 3 days before surgery)

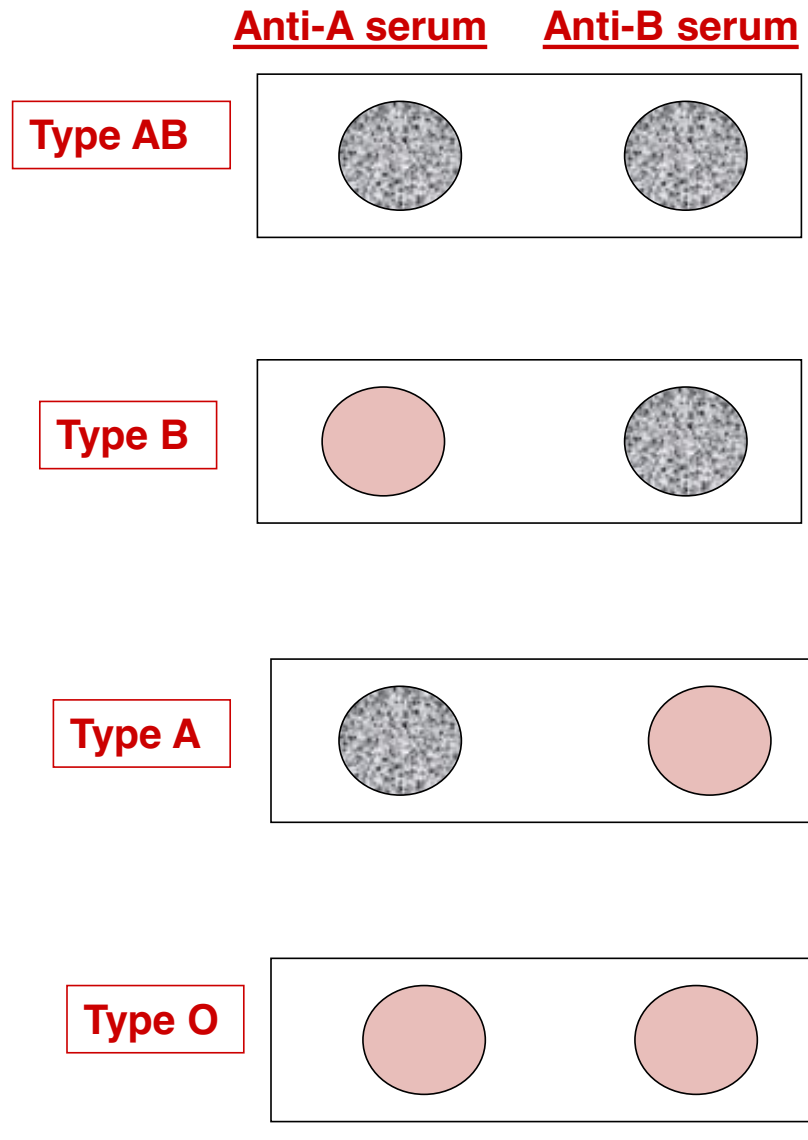


http://www.chxa.com/a/what-is-blood-agglutination/

4.1.5.2 demonstrate an understanding of the process of blood typing

Blood Typing

- use serum containing anti-A or Anti-B agglutinins
- similar procedure for Rh factor typing



1. Fibrinolysis is increased by:
   a) activation of thrombin
   b) activation of plasminogen
   c) release of tPA
   d) heparin
   e) b) & c)

2. Which of the following would NOT be a serious concern during a transfusion reaction?
   a) donor antibodies attacking recipient RBCs
   b) clogging of small vessels by agglutinated clumps of RBCs
   c) lysis of donated RBCs
   d) blockage of kidney tubules