Kindness is the language which the deaf can hear and the blind can see.
Early megakaryoblast.

The megakaryoblast is larger than the proerythroblast. The nucleus is often tetraploid or octaploid, with concealed nucleoli. Although mononuclear megakaryoblasts predominate, binucleate or cells containing four nuclei cells may also exist. The cytoplasm is basophilic, and may be irregular at the edges.
BLEEDING DISORDERS

THROMBOPOIESIS:
BFU-Meg
Thrombopoietin
IL-3, IL-1
Megakaryoblast → Megakaryocyte → Platelets
PLATELETS

Ultrastructure of Platelet (showing adenosine diphosphate (ADP), platelet factor (PF), and von willebrands factor (VWF)).
PLATELETS

**α granules**
PF4, β-Thromboglobulin, Fibrinogen, Factor V, Thrombospondin, Fibronectin, PDGF, PAI-1, Plasmin inhibitor

**Dense bodies**
ATP, ADP, Calcium, Serotonin, Pyrophosphate, P selectin, TGF-β, catecholamines, GDP/GTP

**Lysosomal granules**
Galactose, Fucosidoses, Glucoronidase, cathepsin
PLATELETS

Platelet Membrane:
- Phospholipids
- Cholesterol
- Glycolipids
- Glycoproteins (GP1 – GP 1X)
BLEEDING DISORDERS

Plasma membrane $\rightarrow$ Glycoprotein
Receptors (GP I – GP IX)

**Adhesion** $\rightarrow$ GP Ia - IIa $\rightarrow$ collagen
$\rightarrow$ GP Ib-IX-V $\rightarrow$ vWF $\rightarrow$ collagen

**Aggregation** $\rightarrow$ GP IIb-IIIa complex $\rightarrow$
  fibrinogen
PLATELET FUNCTIONS

Plt activation →
Adhesion
  GP Ib-IX-V complex + vWF
Shape change
  spherical with pseudopods
Aggregation
  GP IIb-IIIa + fibrinogen
Secretion
  positive feed back
ADHESION & AGGREGATION

GP IIb/IIIa

GP Ib/IX/V

GP Ia/IIa

Adhesion

Procoagulant Activity

Fibrinogen

VWF

Prothrombinase Complex

Fibrin

ADP Serotonin

PF4, βTG

Activation And Release

Collagen

Subendothelial Matrix Proteins

VWF
BLEEDING DISORDERS

Functions of platelets:
Hemostatic / platelet plug formation
→ Activation of coagulation cascade
→ Fibrin clot formation
1. Platelet adhesion
2. Platelet shape change
3. Platelet release reaction
4. Platelet aggregation
Normal Hemostasis

- Endothelium
- Platelets
- Coagulation factors
- Fibrinolysis
- Anticoagulants & inhibitors
A. VASOCONSTRICITION

- Endothelium
- Basement membrane
- Arteriole smooth muscle

Site of injury

Endothelin release causes vasoconstriction

Reflex vasoconstriction

ECM (collagen)

B. PRIMARY HEMOSTASIS

1. Platelet adhesion (ADP, TXA₂)
2. Shape change
3. Granule release
4. Recruitment
5. Aggregation (hemostatic plug)

Endothelium
Basement membrane
Collagen

vWF
C. SECONDARY HEMOSTASIS

1. Tissue factor
2. Phospholipid complex expression
3. Thrombin activation
4. Fibrin polymerization

D. THROMBUS AND ANTITHROMBOTIC EVENTS

Release of:
- t-PA (fibrinolysis)
- thrombomodulin (blocks coagulation cascade)
Formation of a Hemostatic Plug

Primary Hemostasis

Platelet adhesion
- Platelet glycoprotein Ib
- von Willebrand factor

Platelet aggregation
- Platelet glycoprotein IIb-IIIa
- Fibrinogen

Platelet secretion
- ADP
- Thromboxane A2

Platelet shape change

Secondary Hemostasis

Activation of the coagulation cascade
COAGULATION FACTORS

Procoagulant Pathway

Coagulation cascade

intrinsic

extrinsic

Anticoagulant Pathway

Naturally occurring inhibitors

Fibrinolytic Pathway
FIBRINOLYTIC PATHWAY

Tissue plasminogen activator (tPA)

Plasminogen activator inhibitor 1 & 2

Urokinase

Factor Xla, XIIa Kallikrein

α₂-antiplasmin

α₂-macroglobulin

FIBRIN

FIBRIN DEGRADATION PRODUCTS

THROMBIN

Thrombin-activatable fibrinolysis inhibitor
The diagram illustrates the role of t-PA and PAI-1 in the fibrinolytic system. The t-PA-PAI-1 complex inhibits t-PA. t-PA, in conjunction with u-PA, activates plasminogen. Plasmin, in turn, degrades fibrin and produces cross-linked fibrin. α2-Antiplasmin and Factor XIII regulate these processes. Thrombin activates Factor XIII.
COAGULATION FACTORS

Proteins
Synthesized in Liver, Platelets, Endothelial cells
Vitamin K dependent (II, VII, IX, X)
Tissue Factor
NATURAL INHIBITORS

Serine protease inhibitors
  AT, Heparin cofactor II, heparin like substances
  alpha 1 antitrypsin, C1 esterase inhibitor, α2-Antiplasmin, α2-Macroglobulin

Protein C pathway
  vit K dependent
  protein C, S, thrombomodulin
Bleeding disorders:

- Vessel fragility
- Platelet deficiency / functional abnormality
- Coagulation factor deficiency
- Combination of above
## BLEEDING DISORDERS

### Assessment of hemostasis:

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>150-400x10³/ul</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>2 – 7 min</td>
</tr>
<tr>
<td>PT</td>
<td>12 – 16 sec</td>
</tr>
<tr>
<td>APTT</td>
<td>30-40 sec</td>
</tr>
<tr>
<td>TT</td>
<td>15 – 19 sec</td>
</tr>
<tr>
<td>Fibrinogen levels</td>
<td>1.5 – 4 g/dl</td>
</tr>
<tr>
<td>FDPs</td>
<td></td>
</tr>
<tr>
<td>Hess test</td>
<td></td>
</tr>
<tr>
<td>Specialized tests</td>
<td></td>
</tr>
</tbody>
</table>
BLEEDING DISORDERS

PLATELET DISORDERS:
  Quantitative (Thrombocytopenia)
  Qualitative (Functional defects)

THROMBOCYTOPENIA:
Decreased production
Increased destruction / sequestration
<50,000/cmm → bleeding
BLEEDING DISORDERS

**Decreased production:**
- Aplastic anaemia
- Marrow infiltration
- Marrow suppression
- Megakaryocytic hypoplasia
- Megaloblastic anaemia
- MDS
- Fanconi’s anaemia
- TAR syndrome
BLEEDING DISORDERS

INCREASED DESTRUCTION:

IMMUNE:

ITP
Other autoimmune states (SLE, CLL)
Drugs (quinine, gold, penicillin)
Infection (viruses, malaria, HIV, EBV)
Post transfusion purpura
Neonatal alloimmune thrombocytopenia
BLEEDING DISORDERS

NON IMMUNE:
DIC
TTP / HUS
Congenital/acquired heart disease
Cardiopulmonary bypass

SEQUESTRATION:
Hypersplenism
BLEEDING DISORDERS

DILUTIONAL LOSS:
Massive Tx
Exchange Tx

HEREDITARY THROMBOCYTOPENIA:
Wiskott-Aldrich syndrome
May-Hegglin anomaly
Bernard-Soulier syndrome
BLEEDING DISORDERS

22 yrs female
Throat infection one week
Took some medicine by a GP
Easy bruising 3 days
Epistaxis 3 days
O/E pallor +
Peticheal haemorrhages on limbs
BLEEDING DISORDERS

TLC  11500/cmm
Hb  11.0 g/dl
Plt  35,000/cmm
Neutrophilia & giant platelets
Normocytic, normochromic
BLEEDING DISORDERS

Bone marrow examination
(not required for acute ITP)
Anti-platelet antibodies
BLEEDING DISORDERS

IMMUNE THROMBOCYTOPENIA:
Primary/Idiopathic
Secondary
Autoantibodies IgG, IgM $\rightarrow$ GP IIb-IIIa
GP Ib-IX
$ightarrow$ Complement activation $\rightarrow$
phagocytosis RE cells
Antibodies \( \rightarrow \) impaired production
Compensatory \( \uparrow \) megakaryopoiesis

**ITP:**
Purpura, epistaxis, menorrhagia, gum bleeding

\( < 5,000-100,000/\text{cmm} \)

Giant platelets \( \uparrow \) MPV
BM \( \uparrow \) megakaryopoiesis
BLEEDING DISORDERS

Spleen:
Normal in acute ITP
↑ chronic ITP
Congested sinusoids
Enlarged follicles
BLEEDING DISORDERS

PLATELET FUNCTION DEFECTS:
Inherited:
Defects of adhesion
  Bernard Soulier syndrome
Defects of aggregation
  Glanzmann’s thrombasthenia
Defects of release reaction
Storage Pool disorders
Platelet function studies:
  platelet rich plasma
  aggregants
  analyzer
results → interpretation
BLEEDING DISORDERS

Acquired:
NSAIDs
Aspirin
Uremia
Cell Membrane Phospholipids

- HETEs
- HPETEs
- Other Lipoxygenases
- Phospholipases
- Steroids Inhibit
- Arachidonic Acid
- 5-Lipoxygenase
- 5-HPETE
- 12-Lipoxygenase
- Leukotriene A₄ (LTA₄)
- COX-1 and COX-2 inhibitors, aspirin, indomethacin inhibit
- Prostaglandin G₂ (PGG₂)
- Prostaglandin H₂ (PGH₂)
When one door of happiness closes, another opens, but often we look so long at the closed door that we do not see the one that has been opened for us.
BLEEDING DISORDERS

COAGULATION FACTOR DEFICIENCY:
Factor VIII → Hemophilia A
Factor IX → Hemophilia B
vWF → vWD
01 yr old boy
Painful swelling of knees off & on since started crawling
Prolonged bleeding at circumcision
Similar complaints in one of his maternal cousins
O/E pallor +
## BLEEDING DISORDERS

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>7500/cmm</td>
</tr>
<tr>
<td>Hb</td>
<td>8.0 g/dl</td>
</tr>
<tr>
<td>Plts</td>
<td>335,000/cmm</td>
</tr>
<tr>
<td>DLC normal</td>
<td></td>
</tr>
<tr>
<td>Mild microcytic, hypochromic picture</td>
<td></td>
</tr>
<tr>
<td>Retics</td>
<td>3.5 %</td>
</tr>
<tr>
<td>Test</td>
<td>Value</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>BT</td>
<td>3.0 min</td>
</tr>
<tr>
<td>PT</td>
<td>14/13 sec</td>
</tr>
<tr>
<td>APTT</td>
<td>90/34</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2.0 g/dl</td>
</tr>
<tr>
<td>FDPs</td>
<td>normal</td>
</tr>
</tbody>
</table>

Advice: Coagulation Profile with mixing studies
# BLEEDING DISORDERS

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>90 sec</td>
</tr>
<tr>
<td>Control</td>
<td>34 sec</td>
</tr>
<tr>
<td>Test + Control</td>
<td>40 sec</td>
</tr>
<tr>
<td>Test + aged serum</td>
<td>96 sec</td>
</tr>
<tr>
<td>Test + adsorbed plasma</td>
<td>38 sec</td>
</tr>
</tbody>
</table>
BLEEDING DISORDERS

FACTOR ASSAY
Factor VIII deficiency

↓

DIAGNOSIS:

↓

Hemophilia A
BLEEDING DISORDERS

Half life of coagulation factors
Correction of APTT
Aged serum $\rightarrow$ V, VIII
Adsorbed plasma $\rightarrow$ II, VII, IX, X
BLEEDING DISORDERS

Intrinsic

Extrinsic

APTT

PT

Common
# BLEEDING DISORDERS

<table>
<thead>
<tr>
<th>Test result</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ PT only</td>
<td>Factor VII</td>
</tr>
<tr>
<td>↑ APTT only</td>
<td>XII, XI, IX, VIII</td>
</tr>
<tr>
<td>↑ PT &amp; APTT</td>
<td>II, VII, IX, X</td>
</tr>
</tbody>
</table>
Time is like river. You can’t touch the same water twice, because the flow that has passed will never pass again. Enjoy every moment of life...
BLEEDING DISORDERS

HEMOPHILIA:
X linked recessive
Females → carriers
Factor VIII → Hemophilia A
Factor IX → Hemophilia B
Queen Victoria
Inheritance of Hemophilia

“Carrier” Mother and Father Without Hemophilia

Parents

Father (without hemophilia)
XY

Mother (carrier for hemophilia gene)
XX

Children

Son (without hemophilia)
XY

Daughter (carrier for hemophilia gene)
XX

Son (has hemophilia)
XY

Daughter (does not carry hemophilia gene)
XX
Presentation:
Bleeding manifestations:

**Hemarthrosis**
Into muscles (compartment syndromes)
Hematuria
CNS bleed
Retroperitoneal bleed
Bubbling
Tingling
Heat

Swelling
Pain
Heat

Boggy
Swollen
Muscle Wasting
Morning Stiffness
Chronic Pain
Limited Movement
<table>
<thead>
<tr>
<th>SEVERITY OF HEMOPHILIA</th>
<th>1\textsuperscript{st} YEAR OF LIFE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEVERE HEMOPHILIA</td>
<td></td>
</tr>
<tr>
<td>FACTOR LEVELS $&lt;$1%</td>
<td>EASY BRUIISING</td>
</tr>
<tr>
<td></td>
<td>OUT OF PROPORTION BLEEDING</td>
</tr>
<tr>
<td>MODERATE HEMOPHILIA</td>
<td>INTERMEDIATE &amp; VARIABLE SEVERITY</td>
</tr>
<tr>
<td>1 - 5% FACTOR LEVEL</td>
<td></td>
</tr>
<tr>
<td>MILD HEMOPHILIA</td>
<td>TRAUMA INDUCED BLEED</td>
</tr>
<tr>
<td>$&gt;$5% FACTOR LEVEL</td>
<td>SURGERY</td>
</tr>
<tr>
<td></td>
<td>LATER IN LIFE</td>
</tr>
</tbody>
</table>
BLEEDING DISORDERS

**Diagnosis:**
History
Examination
Baseline tests
Factor levels
Radiology
BLEEDING DISORDERS

Complications:
Chronic Arthropathy
Factor VIII inhibitors
HCV
HIV
HBV
BLEEDING DISORDERS

Management:
Factor VIII concentrates
Tranexamic acid
DDAVP
Cryoprecipitate
Surgical repair
Antenatal diagnosis
Physiotherapy
17 years female
C/O menorrhagia since menarche
Epistaxis off and on
Prolonged bleeding after
Appendicectomy 3 years back
O/E few peticheal hemorrhages on legs
Pallor +
Blood CP:
Hb: 7.8 g/dl
TLC: 8.2
PLT: 180,000/cmm

DLC normal
Microcytic hypochromic morphology
<table>
<thead>
<tr>
<th>Test</th>
<th>Control (C)</th>
<th>Patient (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time</td>
<td>&gt; 15 min</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>C: 12 sec</td>
<td>P: 13 sec</td>
</tr>
<tr>
<td>APTT</td>
<td>C: 30 sec</td>
<td>P: 85 sec</td>
</tr>
</tbody>
</table>
Mixing studies (APTT based):
P + C: 36 sec
P + aged serum: 78 sec
P + abs plasma: 42 sec

F VIII levels: 2 u/dl
VWF antigen: reduced
RiCoF analysis: < 30u/dl
VWF multimer analysis by Electrophoresis: absent multimers

VWD → Type 3
BLEEDING DISORDERS

VON WILLEBRAND DISEASE:
vWF → endothelial cells
→ platelets
Functions → carrier for F VIII
→ adhesion of platelets
vWD → autosomal inheritance
(recessive/dominant)
Both sexes
BLEEDING DISORDERS

Types of vWD:
Type 1 → quantitative deficiency
  dominant, 70%
Type 2 → qualitative deficiency
  2A, 2B, 2M, 2N
  dominant/recessive, 15-20%
Type 3 → complete deficiency
  recessive
BLEEDING DISORDERS

Presentation:
Mucocutaneous bleeds
Menorrhagia
Prolonged bleeding cuts, dental extractions, trauma, surgery
Variable degree
BLEEDING DISORDERS

Diagnosis:
History, examination
↑ APTT
↑ BT
Thrombocytopenia (type 2B)
F VIII levels
vWF antigen, RiCoF, RIPA
Multimer analysis
BLEEDING DISORDERS

Treatment:
DDAVP (contraindicated in 2B)
rVWF concentrates
Cryoprecipitate, FFPs
Tranexamic acid
Too often we underestimate the power of a touch, a smile, a kind word, a listening ear, an honest compliment, or the smallest act of caring, all of which have the potential to turn a life around.
BLEEDING DISORDERS

DISSEMINATED INTRAVASCULAR COAGULATION

Consumptive Coagulopathy
Activation of coagulation sequence →
Microthrombi formation microcirculation →
Platelet & coagulation factor consumption →
bleeding →
Fibrinolysis → > bleeding
Homeostasis

(Balance of)

Coagulation + Fibrinolysis

Vascular Injury

Coagulation Cascade

Prothrombin

Thrombin

Fibrinogen

Fibrin... Stable Clot Formation

Tissue Injury

FDPs Excreted

Fibrin Degradation Products (FDPs)

Fibrinogen + Fibrin Clot Breakdown

Plasmin

Plasminogen
Failure of normal compensation

- Release of Thromboplastin (Ph-L) into Blood → activation of coagulation (tissue trauma)
- Direct activation of F X or Prothrombin (snake venom)
- Vascular endothelial injury (septicaemia, burns, acidosis) → TF
Direct platelet activation (endoth damage, septicaemia)

- Thrombin generation
- Fibrinogen → fibrin
- Activation of fibrinolysis
- Activation of inhibitors of coagulation
BLEEDING DISORDERS

CAUSES OF DIC:

1. Obstetric complications
   - Abruptio placentae
   - RPOCs
   - septic abortion
   - Amniotic fluid embolism
   - Toxaemia
Bleeding Disorders

2. Infections

- Gram negative sepsis
- Meningococcaemia
- Rocky mountain spotted fever
- Histoplasmosis
- Aspergillosis
- Malaria
BLEEDING DISORDERS

3. Neoplasms
   CA pancreas, prostate, lung & stomach
   Acute promyelocytic leukaemia

4. Massive tissue injury
   Traumatic
   Burns
   Extensive surgery
5. Miscellaneous
   acute intravascular hemolysis
   snake bite
   giant hemangioma
   shock, heat stroke
   vasculitis
   aortic aneurysm
   liver disease
Diagnosis:
Blood CP → thrombocytopenia
→ neutrophilia
→ schistocytes
Prolonged PT, APTT, TT
Low plasma Fibrinogen
Raised FDPs, D-Dimers