Mechanisms of Human Disease
Small Group Sessions

Case Studies on Bleeding and Thrombotic Disorders

Study Aids

September/October 2019

COMPLETE BLOOD COUNT ON THE CELL DYN

LOYOLA UNIVERSITY MEDICAL CENTER
HEMATOLOGY
(708) 216-8570

CD30254 CELLDYN#2

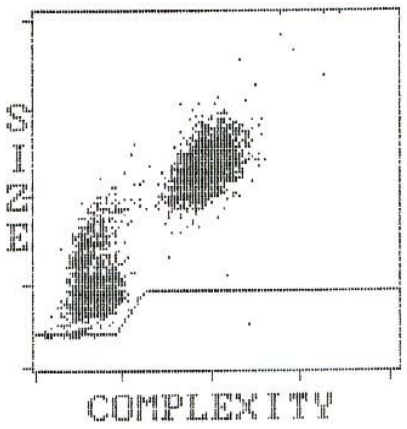
Specimen ID 6167
ResRBC
Sex DOB
Dr
Param: 1 Limits: 1

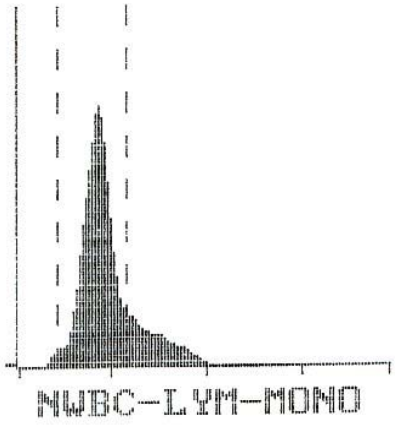
Aug 01 2001 17:57
Operator ID 010
Sequence # 8641
Open Sampler

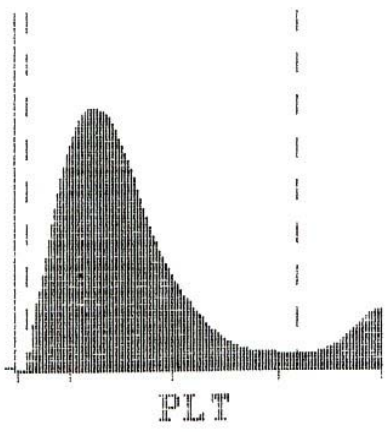
WBC	5.71	K/uL	
NEU	3.04	53.4	%N
LYM	2.01	35.2	%L
MONO	.481	8.43	%M
EOS	.161	2.82	%E
BASO	.010	.177	%B

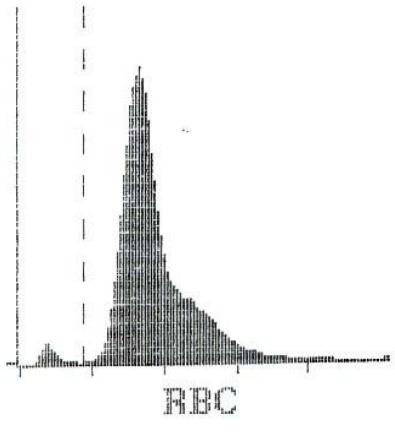
F	5.40	M/uL
	13.4	g/dL
HCT	41.2	%
MCV	76.4	fL
MCH	24.9	pg
MCHC	32.6	g/dL
RDW	14.2	%

PLT	281.	K/uL
MPV	9.82	fL
PCT	.275	%
PDW	16.9	10(GSD)



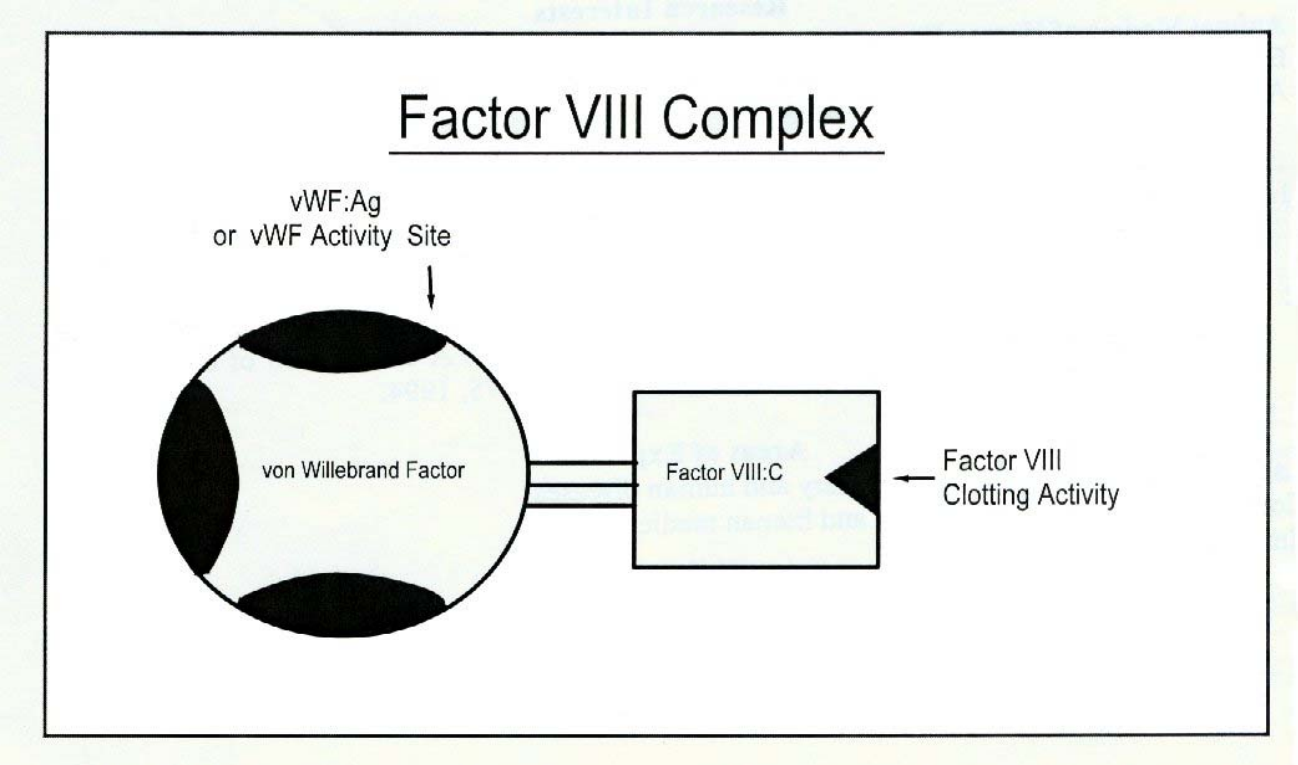






Coagulation Testing to Screen Hemostatic Defects	
Test	**Defect or Therapeutic Anticoagulant Effect**
Bleeding Time	Platelet function, anti-platelet drugs
Prothrombin Time (PT)	Defects of extrinsic system, monitoring of oral anticoagulant drugs
Partial Thromboplastin Time (APTT)	Defects of intrinsic system, monitoring of heparin
Thrombin Time (TT)	Final pathway defect. Monitoring of thrombolytic therapy
Factor Assays	Individual clotting factor defects

Differentiation of Hemophilia A and von Willebrand's Disease by Laboratory Testing			
Test	**Hemophilia A**	**vWD**	**Normal Range**
Prothrombin time	Normal	Normal	10-12 seconds
APTT	Abnormal	Normal or abnormal	34-42 seconds
Platelet count	Normal	Normal	130,000-400,000/µl
Bleeding time	Normal	Normal or abnormal	2-8 minutes
Mixing APTT	Normal	Normal	34-42 seconds
Factor VIII:c	5% to 25% mild <1% severe	Normal or abnormal	50% to 150%
vWF:ag	Normal	Abnormal	50% to 150%
vWF:activity	Normal	Abnormal	50% to 150%



Clinical Aspects of Bleeding Disorders			
Type of Disorder	**Platelet**	**Coagulation**	**Fibrinolysis**
Timing of Bleeding	Immediate	Immediate	Delayed
Sites of Bleeding	Mucosal, post-operative	Soft Tissue joints	Mucosal Genitourinary
Examples	von Willebrand's disease Glanzmann's Thrombasthenia Aspirin and NSAIDS	Factor VIII deficiency Factor IX deficiency Coumadin or Heparin	Liver dysfunction Factor XIII deficiency Thrombolytic therapy

Prothrombotic Risk Factors for Venous Thrombosis		
Acquired	**Genetic**	**Precipitating Events**
Antiphospholipid Antibodies	APC-R/Factor V Leiden	Prolonged Immobility
Lupus Anticoagulant	Prothrombin 20210	Surgery
Myeloproliferative Disorders	Elevated Factor VIII	Trauma
Malignancy	Hyperhomocysteinemia	Pregnancy
Previous Thrombosis	MTHFR C677T and A1298C	Oral Contraceptives/Hormone Replacement Therapy
Age >50 Years	Protein C Deficiency (Autosomal Dominant)	Severe Infection
Smoking	Protein S Deficiency (Autosomal Dominant)	Severe Dehydration
Obesity	AT III Deficiency (Autosomal Dominant)	
Renal Disease	Dysfibrinogenemia (Autosomal Dominant)	
Congestive Heart Failure		

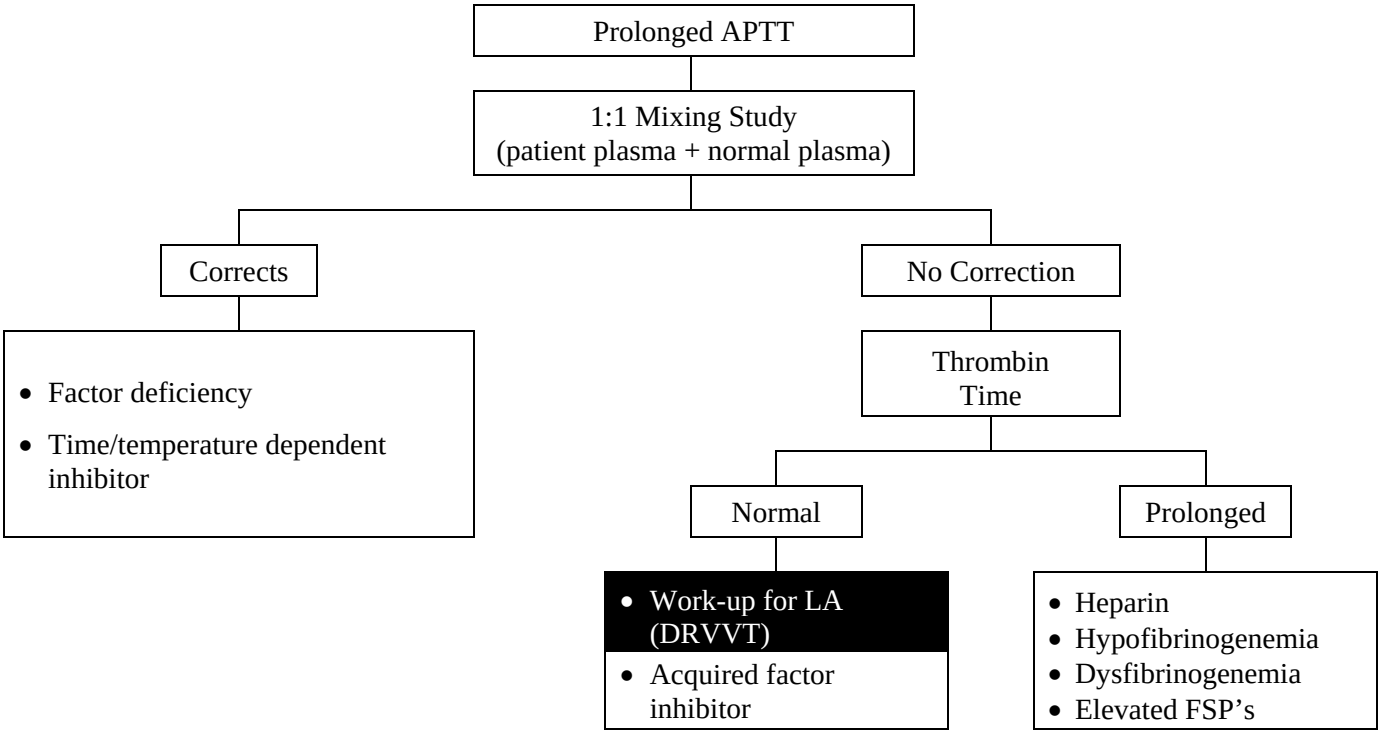
Congenital Platelet Related Bleeding Disorders		
Disease	**Defect**	**Laboratory Findings**
von Willebrand's Disease	Adhesion Autosomal Dominant	von Willebrand's factor defect; BT prolonged; ristocetin aggregation absent
Bernard-Soulier Syndrome	Adhesion Autosomal Recessive	GP Ib/IX/V receptor decreased or dysfunctional; BT prolonged; large platelets; thrombocytopenia; ristocetin aggregation absent
Storage Pool Disease	Secretion Autosomal Dominant Autosomal Recessive	Deficiency of granules; BT normal to prolonged; poorly stained platelets; thrombocytopenia; ADP, collagen, aggregation decreased
Glanzmann's Thrombasthenia	Activation/Aggregation Autosomal Recessive	GP IIb/IIIa receptor decreased or dysfunctional; BT prolonged; ADP, collagen, arachidonic acid, aggregation absent

Prothrombotic Risk Factors for Venous Thrombosis		
Defect	**% of Patients with Thrombosis**	**Mechanism**
Unknown	20-30%	—
Elevated Factor VIII or Elevated Fibrinogen	25%	More substrate for continued activation of the coagulation system
Activated Protein C-Resistance/Factor V Leiden	20%	FV resistant to inhibition by activated protein C thus clotting continues
Anticardiolipin/Antiphosphatidlyserine Antibodies	15%	Increased localization of prothrombotic proteins; block natural inhibitors; activate cell membrane signaling (platelets)
Lupus Anticoagulant	15%	Increased localization of prothrombotic proteins; block natural inhibitors; activate cell membrane signaling (platelets)
MTHFR C677T and A1298C	10%	Results in elevated level of homocyteine affecting normal endothelial cell function
Prothrombin 20210 Gene Mutation	6%	Causes elevated levels of prothrombin; more substrate for continued activation of the coagulation system
Protein C Deficiency	3%	Loss of natural coagulation inhibitor
Protein S Deficiency	1-2%	Loss of natural coagulation inhibitor
Antithrombin III Deficiency	1%	Loss of natural coagulation inhibitor
Dysfibrinogenemia	<1%	Fibrin formed is resistant to lysis by plasmin; abnormal fibrin polymerization; abnormal binding of thrombin leads to increased circulating thrombin

Hereditary Coagulation Factor Deficiencies That Cause Bleeding

Defect	Mode of Inheritance	Incidence	Laboratory Defect	Clinical Defect
FXII	Autosomal Recessive	Very Rare	Abnormal APTT	None
FXI	Autosomal Recessive	Rare	Abnormal APTT	Disproportionately Mild
FIX Christmas Disease Hemophilia B	Sex-linked Recessive	Uncommon	Abnormal APTT	Proportionately Severe
FVIII Hemophilia A	Sex-linked Recessive	Uncommon	Abnormal APTT	Proportionately Severe
FVIII von Willebrand's Disease	Autosomal Dominant	Uncommon	Abnormal APTT	Proportionately Severe
FVII	Autosomal Recessive	Very Rare	Abnormal PT	Disproportionately Moderate
FX	Autosomal Recessive	Very Rare	Abnormal APTT & PT	Proportionately Severe
FV	Autosomal Recessive	Very Rare	Abnormal APTT & PT	Proportionately Severe
FII (Prothrombin)	Autosomal Recessive	Very Rare	Abnormal APTT & PT	Proportionately Severe
FI (Fibrinogen)	Autosomal Recessive	Very Rare	Abnormal APTT & PT	Proportionately Severe
FXIII	Autosomal Recessive	Very Rare	Normal APTT & PT	Disproportionately Severe

Laboratory Diagnosis of Coagulation Inhibitors Associated with Bleeding



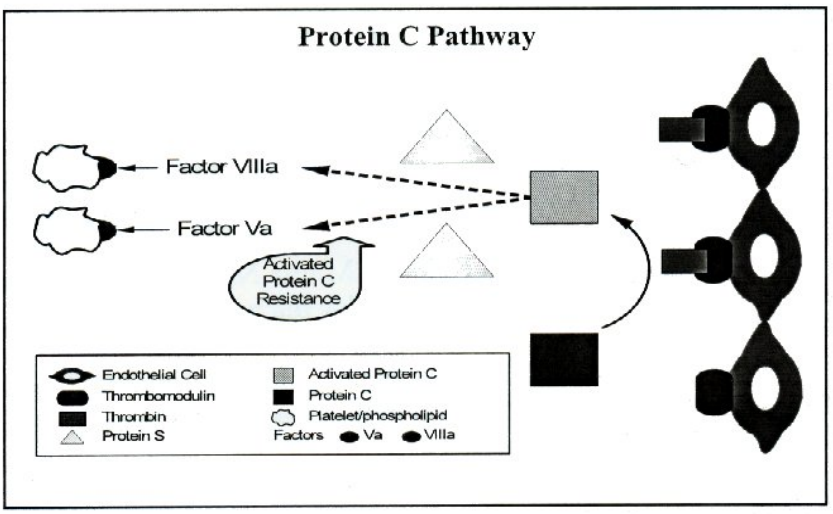
= LA associated with thrombosis

DRVVT: Sensitive to LA not to heparin

COAGULATION INHIBITORS: There are many inhibitors to blood clotting, which are associated with bleeding, that are detected by the APTT. These include acquired inhibitors (e.g., FVIII inhibitor), drugs (e.g., heparin), and elevated fibrin/fibrinogen split products.

The lupus anticoagulant (LA) is a special case. LA is an antiphospholipid antibody that interferes with the APTT reagent causing a prolongation. Although the lab result appears as a potential bleeding problem, the LA is associated with thrombosis.

Variants of Antithrombin III Deficiency			
Type	**Antigen Concentration**	**Heparin-Cofactor Activities**	**Effect of Mutation**
I (Classic)	Decreased	Decreased	Reduced synthesis
II	Normal	Decreased	Defect in AT III binding to heparin; defect in serine protease inhibition
More than 80 genetic point mutations have been identified which alter the AT III molecular structure and function.			



Factor V Leiden is a mutation of coagulation FV at the site where activated protein C cleaves activated FV. Thus, high levels of FVa are maintained, thrombin generation persists and blood clotting occurs.

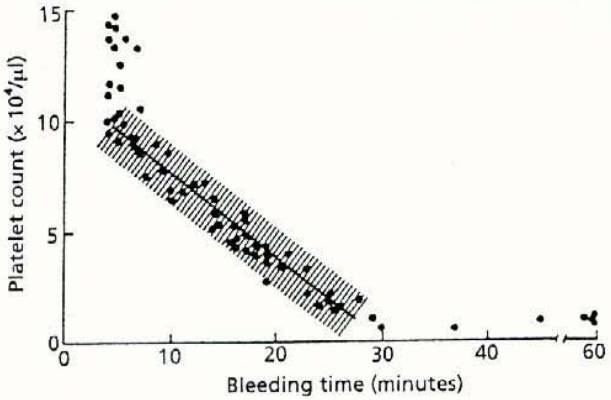


FIGURE 23.3. Relationship between the bleeding time and the platelet count, as determined in 70 individuals with marrow failure and platelet counts of less than 150,000/mm^3. In individuals with platelet counts between 10,000 and 100,000/mm^3, there was a direct, inverse relationship between bleeding time and platelet count. At platelet counts less than 10,000/mm^3, bleeding time was greater than 30 minutes. (Adapted with permission from Harker LA, Slichter SJ. The bleeding time as a screening test for evaluation of platelet function. N Engl J Med 1972;287:155–159.)

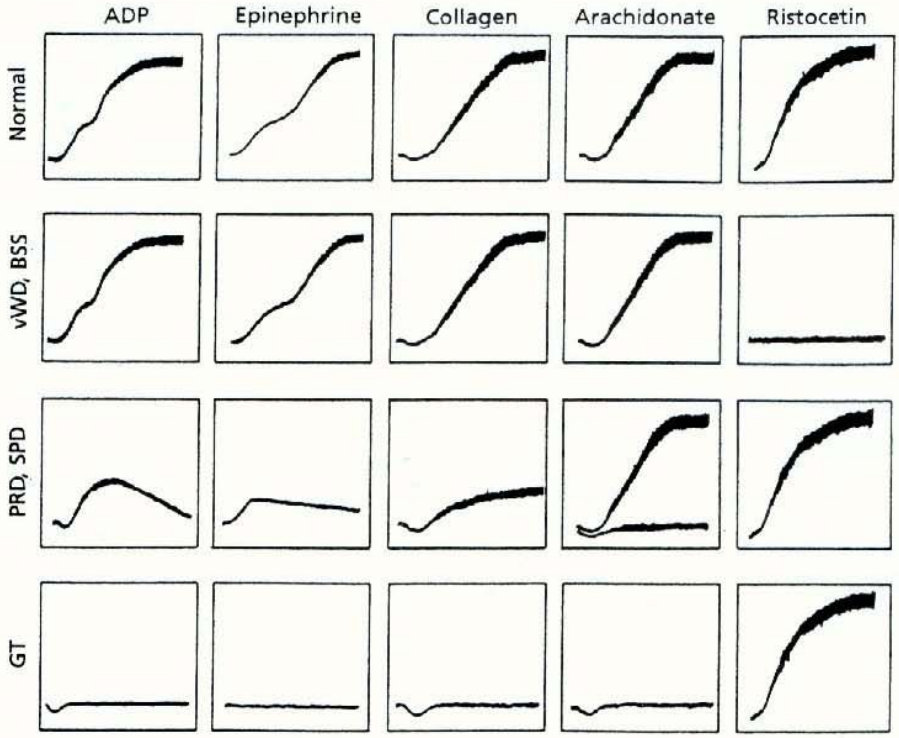


FIGURE 23.10. Normal and abnormal patterns of platelet aggregation in response to adenosine diphosphate (ADP), epinephrine, collagen, arachidonate, and ristocetin. In classic (type I) von Willebrand disease (vWd) and Bernard–Soulier syndrome (BSS), platelet aggregation is normal with all agents except ristocetin. In platelet release defects (PRD) and storage pool disease (SPD), only first-wave aggregation occurs in response to ADP and epinephrine, and collagen-induced aggregation is markedly blunted; arachidonate-induced aggregation may or may not be abnormal, but is always lost following aspirin ingestion. In Glanzmann's thrombasthenia (GT), the initial shape-change remains normal, but aggregation is completely inhibited in response to all agents except ristocetin. (Adapted with permission from Schafer AI. Thrombocytopenia and disorders of platelet function. In: Stein JH, ed. Internal medicine. 3rd ed. Boston: Little, Brown, 1990; pp. 1041–1048.)