von Willebrand's Disease

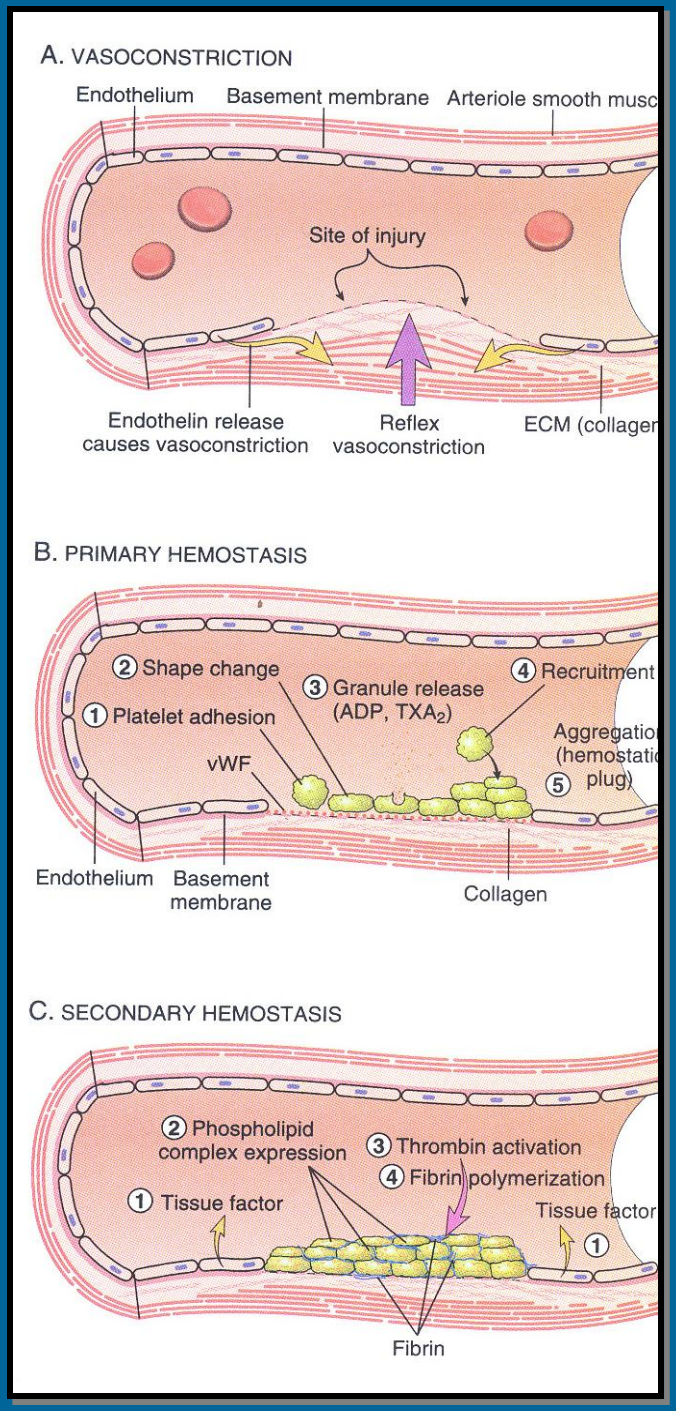
Amy Sanchez, M.D.

July 12th, 2004

Introduction

- Disorder of primary hemostasis first described in 1926 by Eric von Willebrand
- Most common inherited disorder of bleeding in humans with an estimated prevalence of 1%
- Most types are inherited in a autosomal dominant fashion – males and females equally affected
- Majority type I (70%) with 20% type II

Hemostasis Review



vasoconstriction

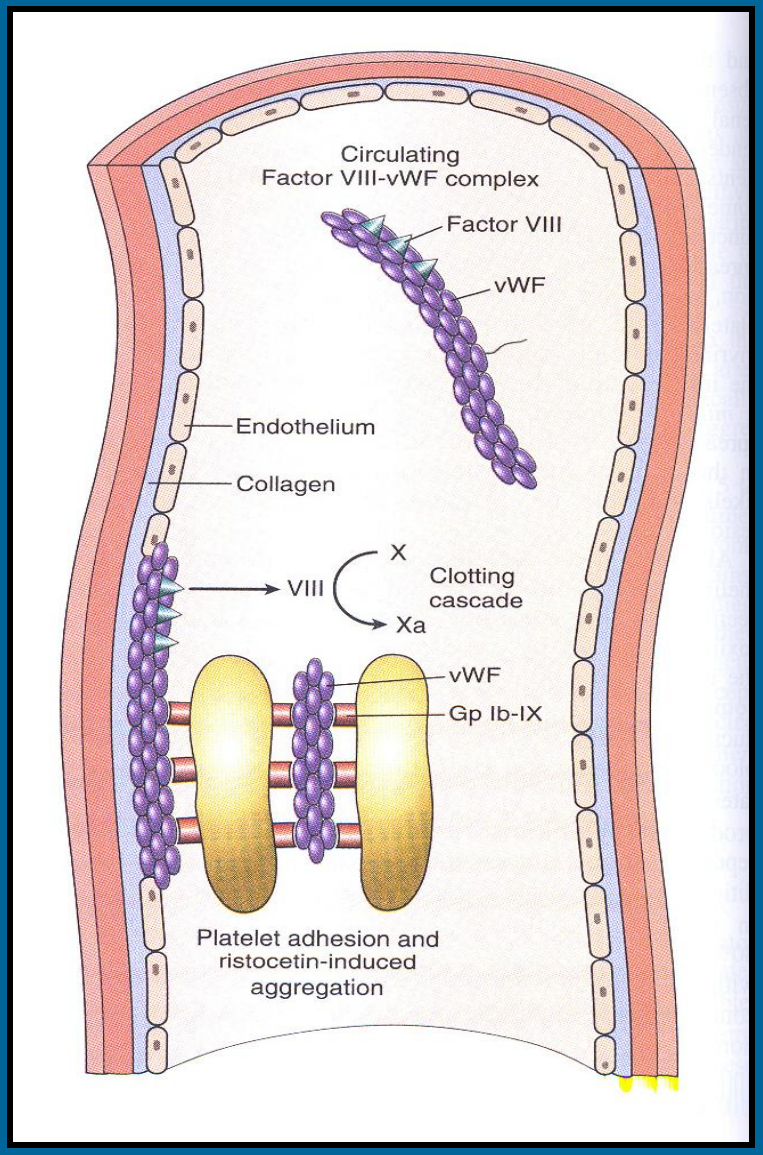
1. exposed ECM
2. platelet adhesion
3. granule release
4. aggregation

1. coagulation cascade
2. fibrin polymerization

Symptoms

- Spectrum of clinical severity- many are subclinical
- Recurrent mucocutaneous bleeding, often spontaneous
- Excessive bleeding from wounds
- Menorrhagia
- Do not have intramuscular or deep subcutaneous bleeding or hemarthroses
- All in the setting of prolonged bleeding time with normal platelet count

von Willebrand Factor



Type I

- Most common, 70% are Type I
- Reduced quantity of circulating vWF
- AD with reduced penetrance and variable expressivity, heterozygous
- Clinical symptoms usually mild
- Factor VIII activity (VIII:C), vWF antigen (vWF:Ag), and the ristocetin cofactor activity (vWF:RCoF) decreased
- Normal spectrum of multimers
- Responds to DDAVP

Type II –General

- Autosomal dominant, heterozygous
- Much less common with several variants
- Characterized by normal levels of dysfunctional protein
- Lack of larger multimers in plasma while retaining smaller multimers

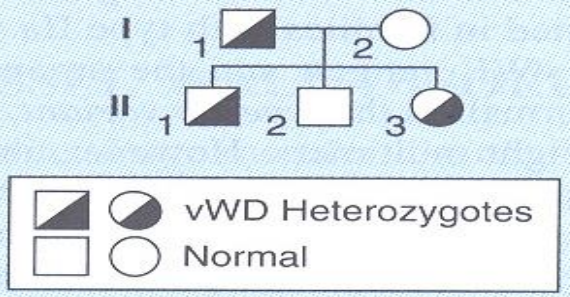
Type IIA

- Absence of **large** and **medium-sized** multimers in plasma and platelets
- Small multimers cannot bind to the GPIb receptor on platelets in the presence of ristocetin
- VIII:C ↓, vWF:Ag ↓, vWF:RCoF ↓, bleeding time ↑↑
- Clinical symptoms usually moderate to severe
- DDAVP ineffective

Type IIB

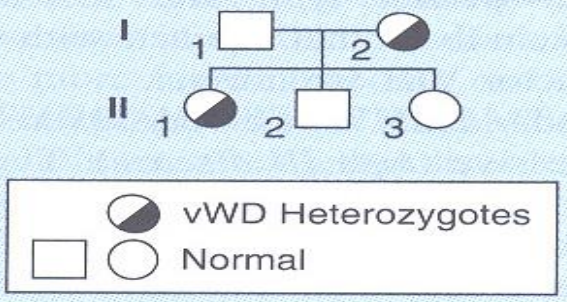
- Much less common than Type IIA
- Autosomal dominant
- Absence of **large** multimers in plasma but not in platelets due to abnormal affinity for platelet adhesion – creates secondary thrombocytopenia
- Adverse response to DDAVP

Type I



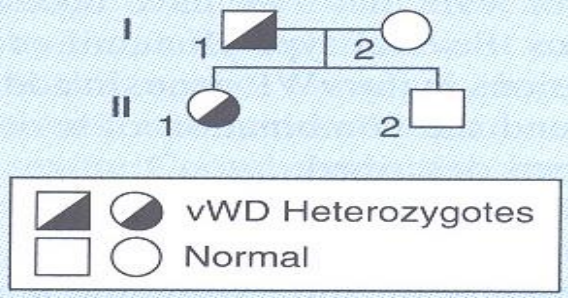
	II-1 vWD	II-2 Normal
VIII	↓	N
vWF:Ag	↓	N
vWF:RCoF	↓	N
RIPA	↓ or N	N
Multimer pattern	▬ ≡	▬ ≡

Type IIA



	II-1 vWD	II-2 Normal
VIII	↓	N
vWF:Ag	↓	N
vWF:RCoF	↓ ↓	N
RIPA	↓ ↓	N
Multimer pattern	≡	▬ ≡

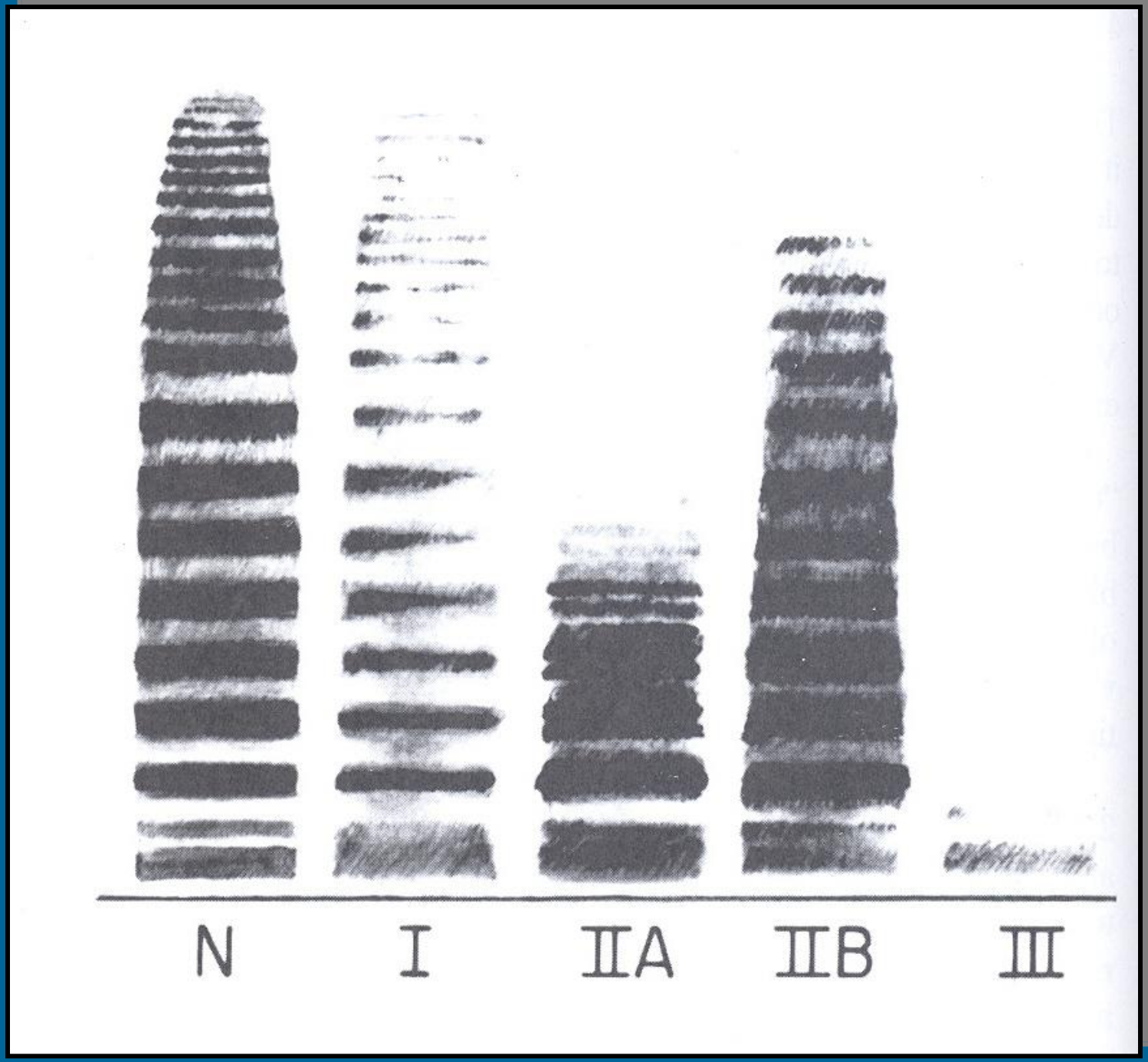
Type IIB



	II-1 vWD	II-2 Normal
VIII	↓	N
vWF:Ag	↓	N
vWF:RCoF	↓ ↓	N
RIPA	↑	N
Multimer pattern	≡	▬ ≡

Type III

- Rare, very severe, autosomal recessive form, 1:1,000,000
- Usually offspring of two parents with mild type I disease
- May be compound heterozygous or homozygous for one defect
- No detectable vWF activity
- Severe mucosal bleeding with occasional hemarthroses
- No response to DDAVP


N
I
IIA
IIB
III

Acquired vWD

- Sporadic form
- Associated with immunologic disorders (lymphoma, SLE, MM, myeloproliferative d/o, benign monoclonal gammopathy)
- IgG autoantibodies to the VIII:vWF complex or absorption by malignant cells
- Treat the underlying disorder i.e. corticosteroid therapy or radiation

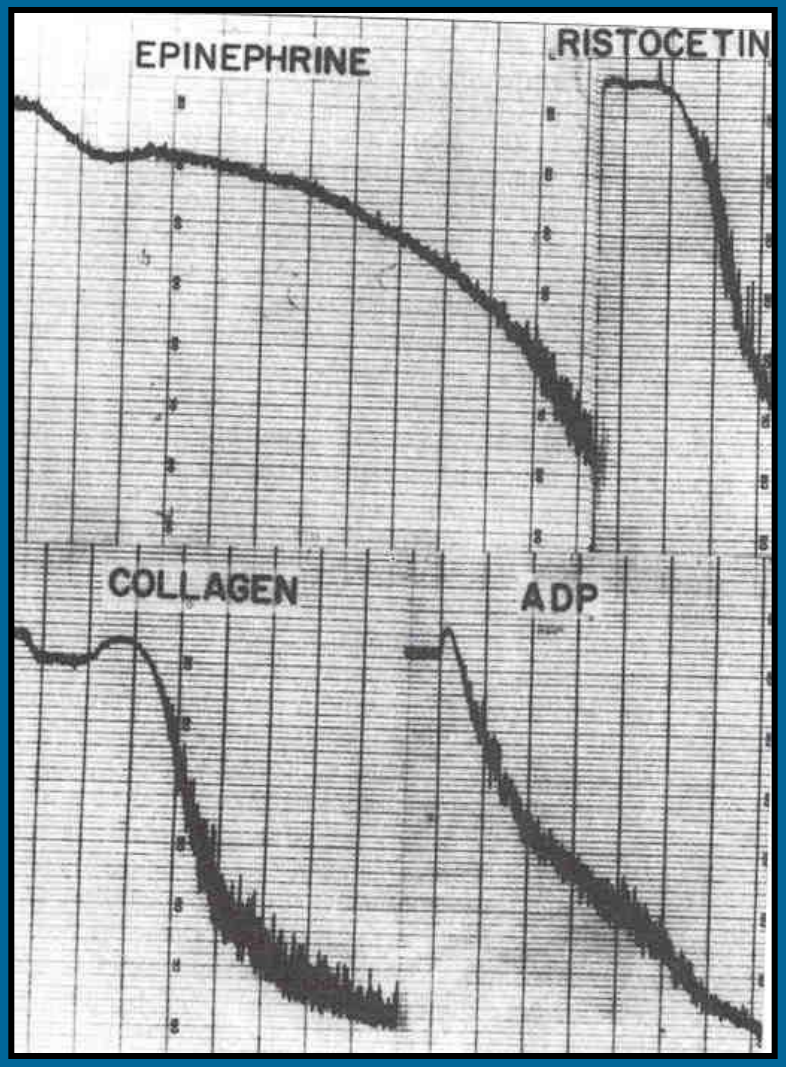
Platelet Type (Pseudo) vWD

- Similar picture to that of Type IIB
- Mutation in the GPIb gene that produces increased affinity of platelets to vWF
- Lack of large multimers secondary to clearance by platelet binding

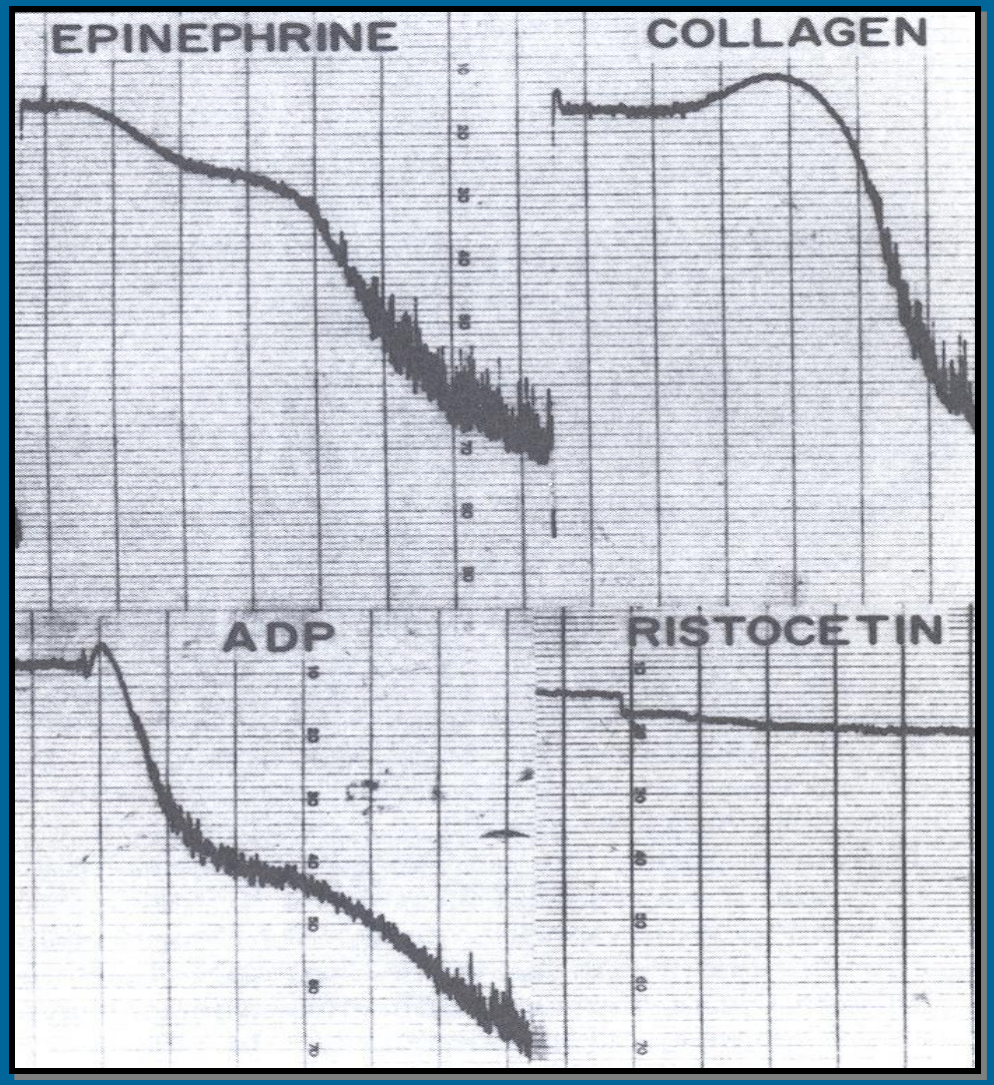
Testing

Parameter	Type 1	Type 2A	Type 2B	Type 3
Bleeding time	↑ or N	↑	↑	↑
Platelet count	N	N	↓ or N	N
vWF:Ag	↓	↓ or N	↓ or N	↓↓
vWF:RCoF	↓	↓	↓, N or ↑	↓↓
Multimers	N	Abn	Abn	ND
VIII	↓	↓ or N	↓ or N	↓↓
RIPA	↓ or N	↓	↑	↓↓

Ristocetin Induced Aggregation



Ristocetin Induced Aggregation



Treatment

- Type I – DDAVP usually sufficient for transient control of bleeding for minor surgical procedures
- Type 2A – cryopercipitate or purified factor VIII
- Type 2B – cryoprecipitate or purified factor VIII, DDAVP contraindicated
- Type 3 – cryopercipitate or purified factor VIII

References

- McClatchey, Kenneth D., Clinical Laboratory Medicine. Second edition, 1013-1016.
- Kjeldsberg, Carl. Practical Diagnosis of Hematologic Disorders. Third Edition, 751-773.
- Jandl, James H. Blood: Textbook of Hematology. Second Edition, 1382-1391
- Fauci et al. Harrison's Principals of Internal Medicine. 14th Edition, 732-734.