Platelet Storage Pool Disease

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10/28/2012

Clinical History

- **Patient:** 23-year-old female
- **Clinical course:** status-post cholecystectomy, complicated by retained common bile duct stones. Following three ERCP procedures to remove stone fragments, she developed hematobilia.
- She also required transfusion of RBC's due to anemia.

Medical History

- No prior history of blood transfusions or anemia
- Lifelong “easy bruising”
- Nosebleed treated by cautery, age 10
- Irregular menses sometimes lasting a month, with clots
- Family history: Noncontributory
- Drug history: None

Physical Examination

- Grossly bloody stool
- No petechiae or ecchymosis
- No hepatosplenomegaly

Screening Coagulation Laboratory Results

- PT= 10 sec (Normal 8-14.6)
- aPTT= 35 sec (Normal 24-36.5)
- Plt= 254,000 /µL (Normal 150,000-350,000)
- Bleeding time=15 min (Normal < 9 min)

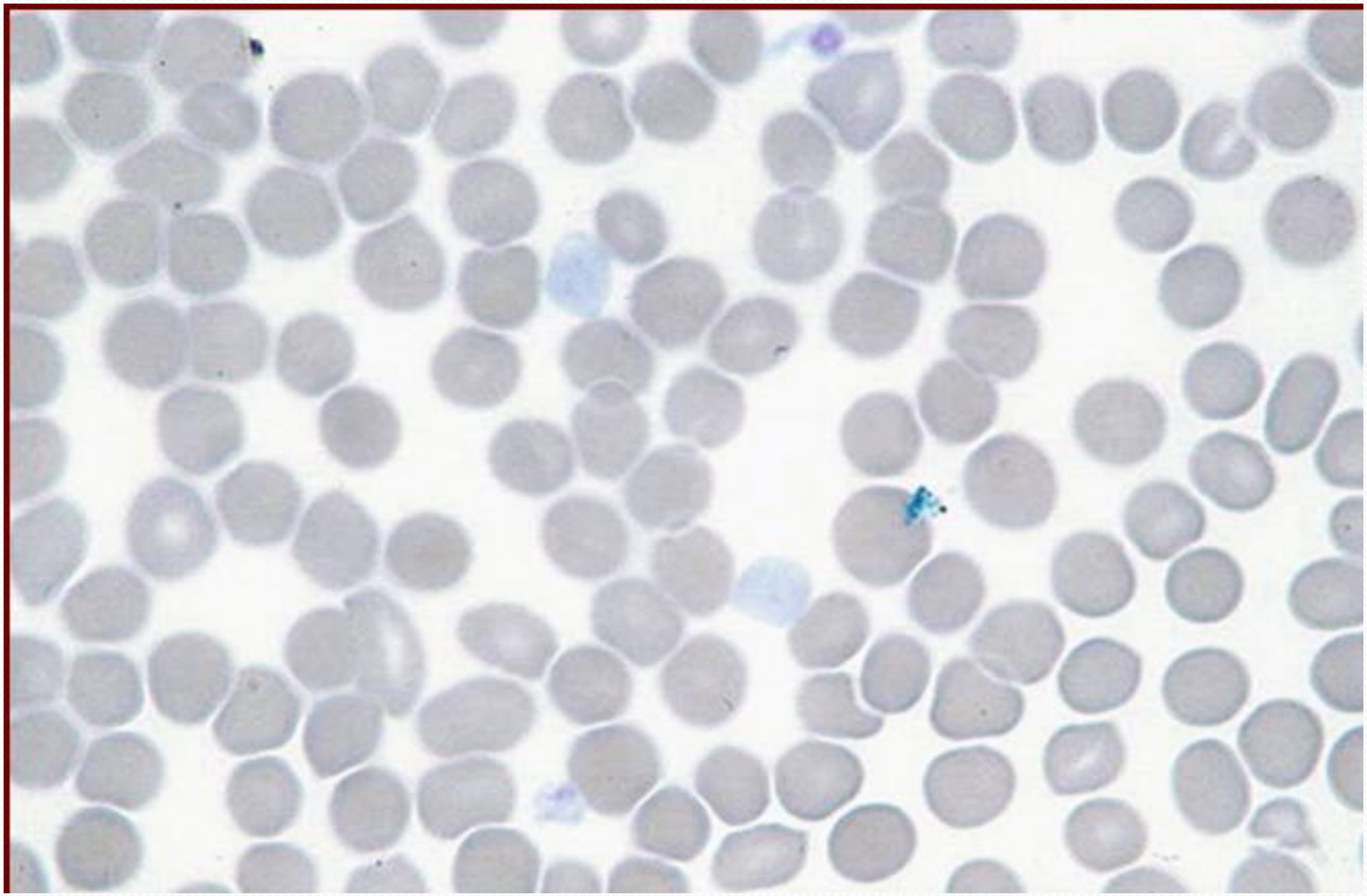
Differential Diagnosis

- Asprin and other NSAID, Plavix
- vonWillebrand disease
- Dysfunctional platelets: storage pool disease, Glanzmann thrombasthenia, Bernard Soulier syndrome, uremia

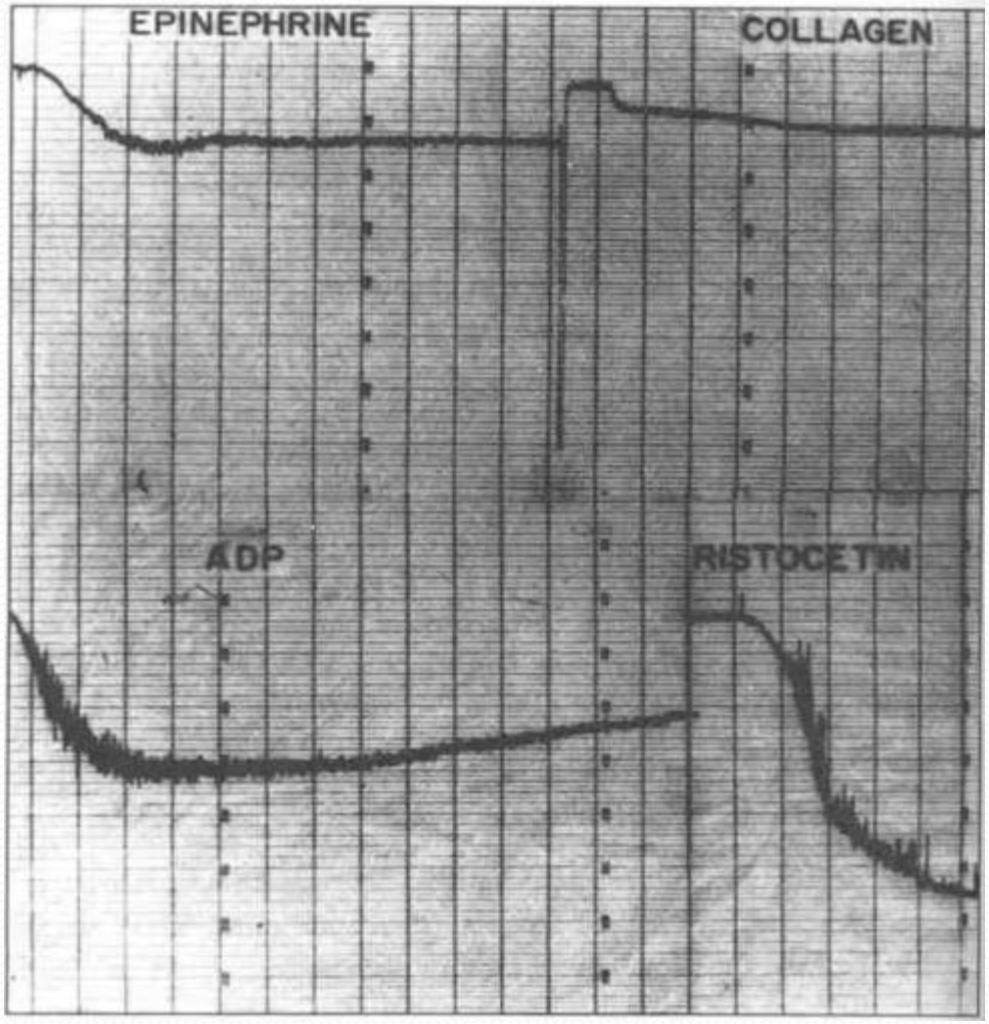
Further Findings

- Medicaion history: No asprin and other NSAID, Plavix
- vonWillebrand disease: normal vWF and F VIII levels
- Dysfunctional platelets: abnormal platelet aggregation study

Platelet Granule Defiency: Blood Smear



Platelet Aggregation Study



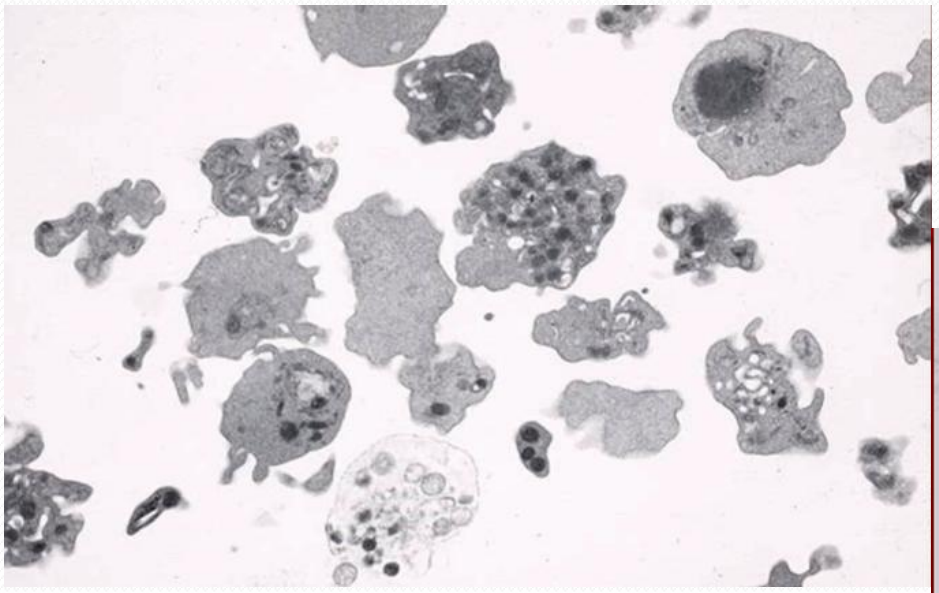
Ruled out:

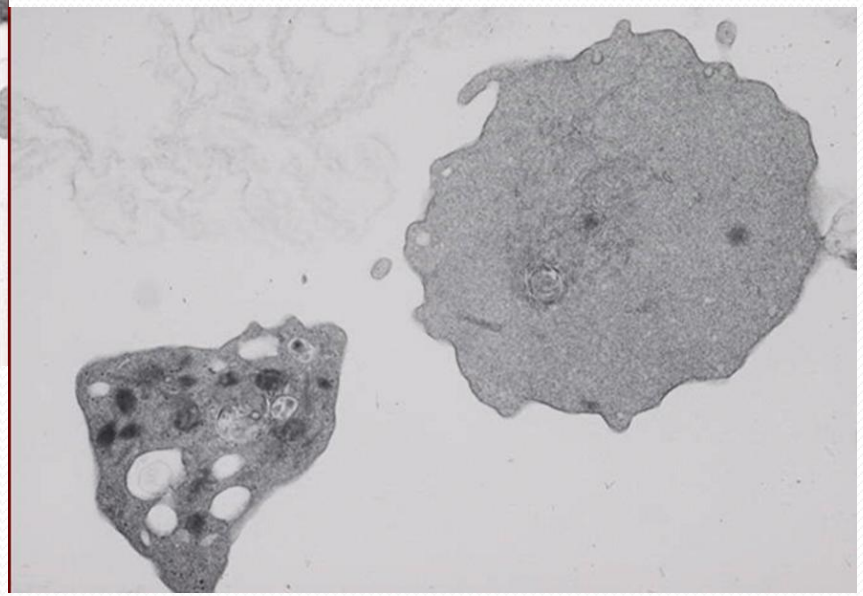
- vWD
- Bernard Soulier Syndrome
- Glanzmann Thrombasthenia
- Plavix

Could not rule out:

- NSAIDs
- Platelet storage pool disease

Deficiency of Alpha Granules and Delta Granules : EM





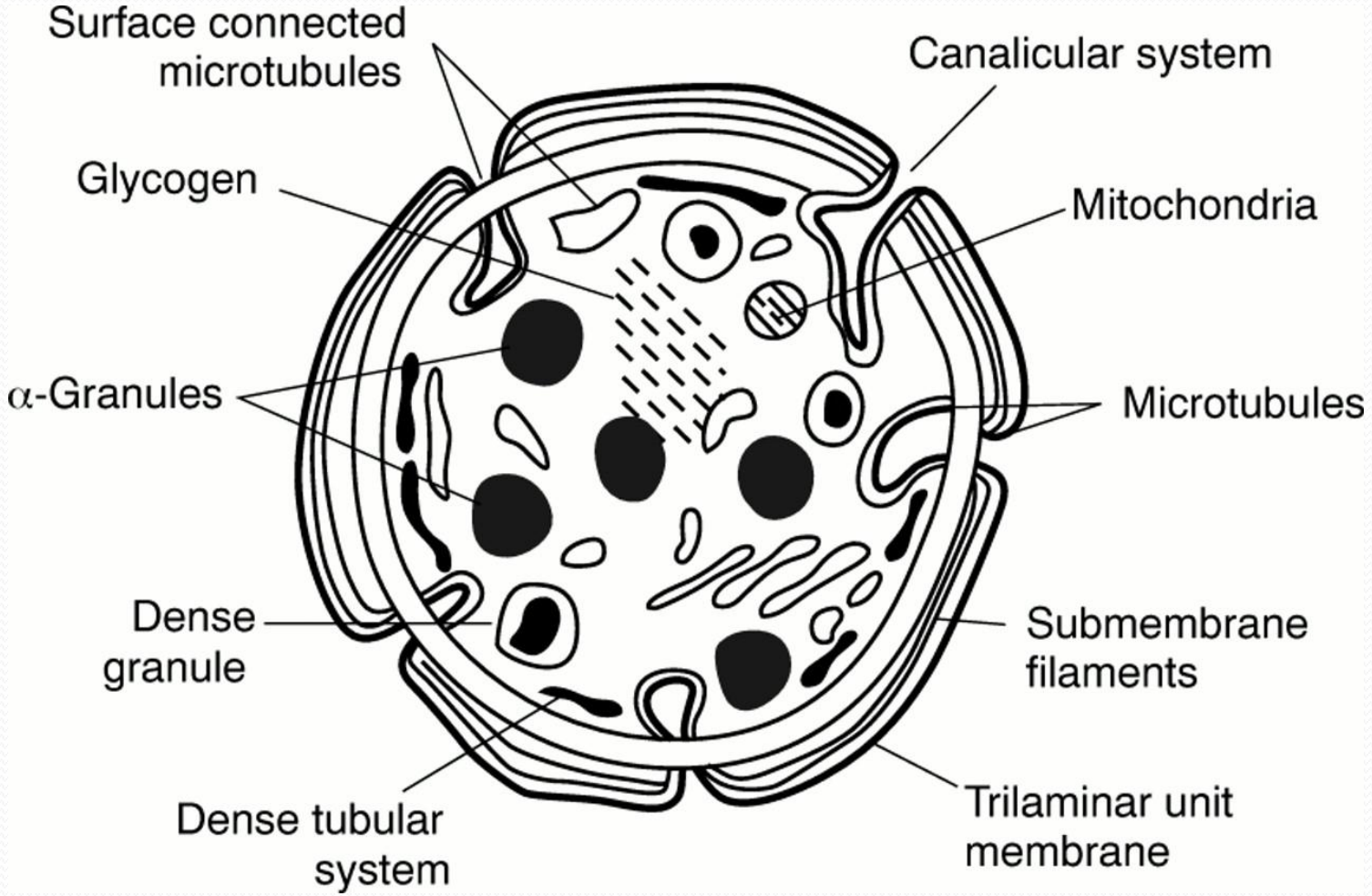
Diagnosis

- Alpha-Delta Platelet Storage Pool Disease

Review of Platelet Functional Anatomy

- **Glycocalyx**: outer surface, rich in glycoproteins
- **Microtubules**: sub-membranous band, protein tubulin, provide structural support
- **Contractile microfilaments**: actin, myosin
- **Open canalicular system:** direct communication with extracellular environment
- **Dense tubular system:** derived from smooth endoplasmic reticulum, site for arachidonic acid metabolism

Ultrastructure Of Platelets Indicating Storage Granules



Saif M W , Hamilton J M Postgrad Med J 2001;77:e6-e6

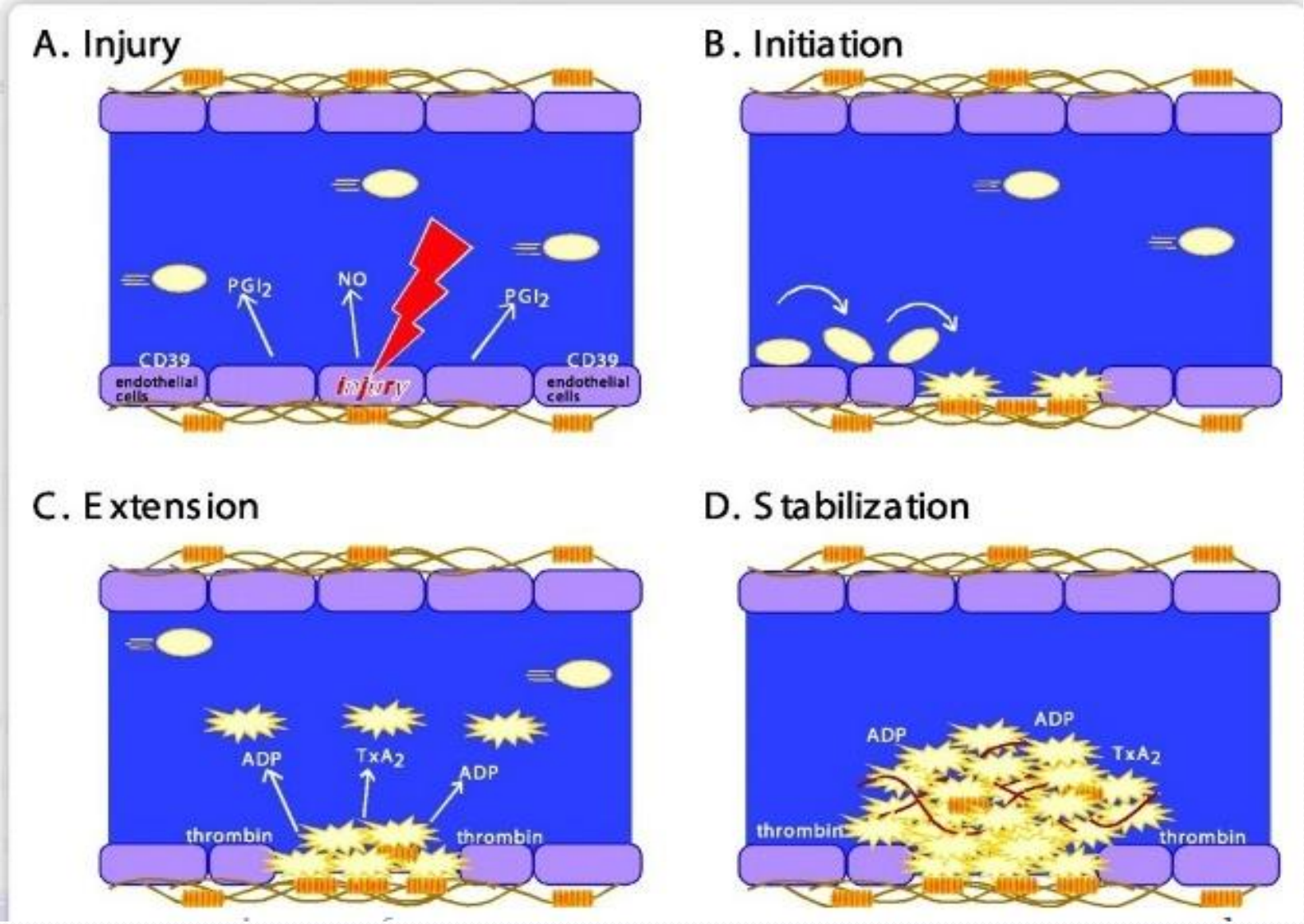
3 Types Of Platelet Granules

- **α-granules**: >300 proteins synthesized in megakaryocytes or endocytosed from plasma, involved in platelet adhesion:
  - VWF, P-selectin, fibronectin, fibrinogen, coagulation factors (factors V and XIII), growth factors (PDGF, TGF-β), and platelet factor-4.
- **δ-granules (dense bodies):** primarily small molecules:
  - calcium, ATP, ADP, serotonin, histamine, and epinephrine.
- **Lysosomes:** mostly enzymes:
  - proteases, glycosidases

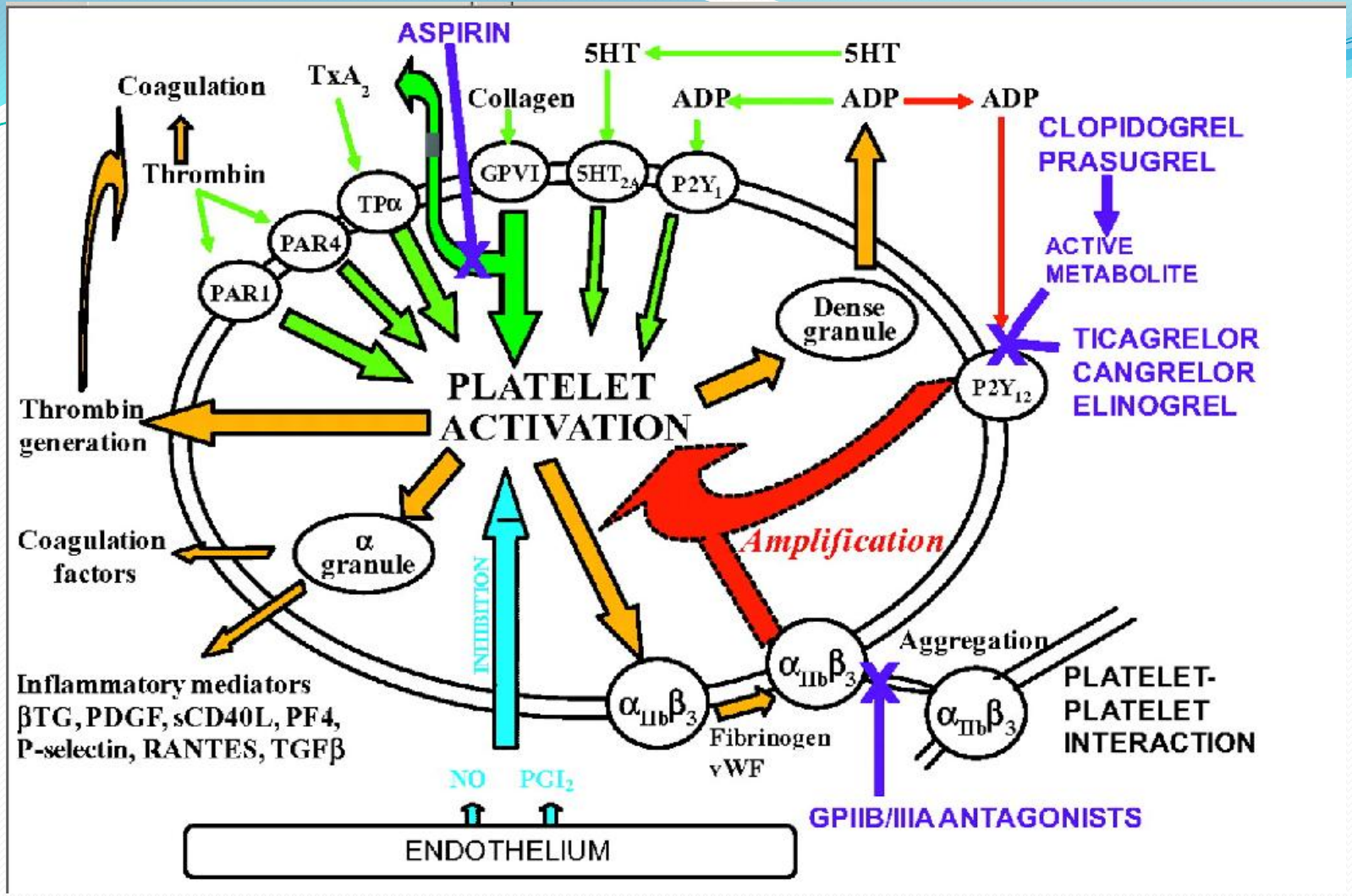
Platelet Membrane Glycoprotein

- Identified by
  - radio-active labeling of surface glycoproteins
  - solubilization of the membranes
  - electrophoresis on polyacrylamide gels
- Clinically important: GP Ib, V, IX, IIb, IIIa

Platelet Plug Formation



Atrial Fibrillation - Basic Research and Clinical Applications. Edited by Jong-Il Choi, ISBN 978-953-307-399-6, Published: January 11, 2012 . Cardiology and Cardiovascular Medicine



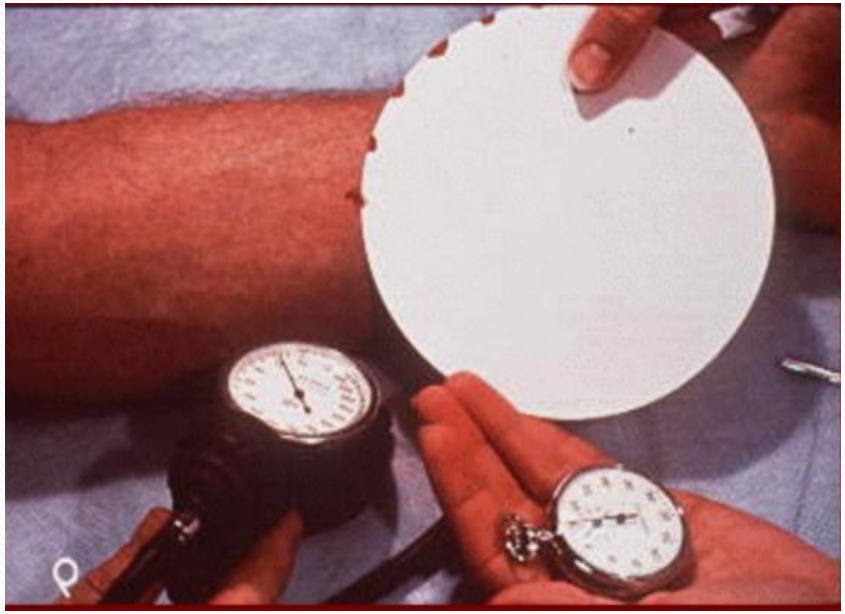
Mechanisms of platelet activation and site of action of platelet inhibitors. Numerous platelet surface receptors initiate platelet activation leading to platelet aggregation, release of alpha and dense granule contents, and conversion of the platelet surface membrane to a catalytic surface for thrombin generation ('platelet procoagulant activity').

Screening Tests of Platelet Function

- Platelet count & morphology
- Bleeding Time
- PFA-100 analysis
  - An automated screening test available 24/7, replacing Bleeding Time test.

Platelet Function Testing

- Platelet count:
  - 130,000-350,000 x10^9 /L
- Bleeding time:
  - a crude test of hemostasis
  - normal range: < 9 min.
  - poor reproducibility
  - no longer a recommended test



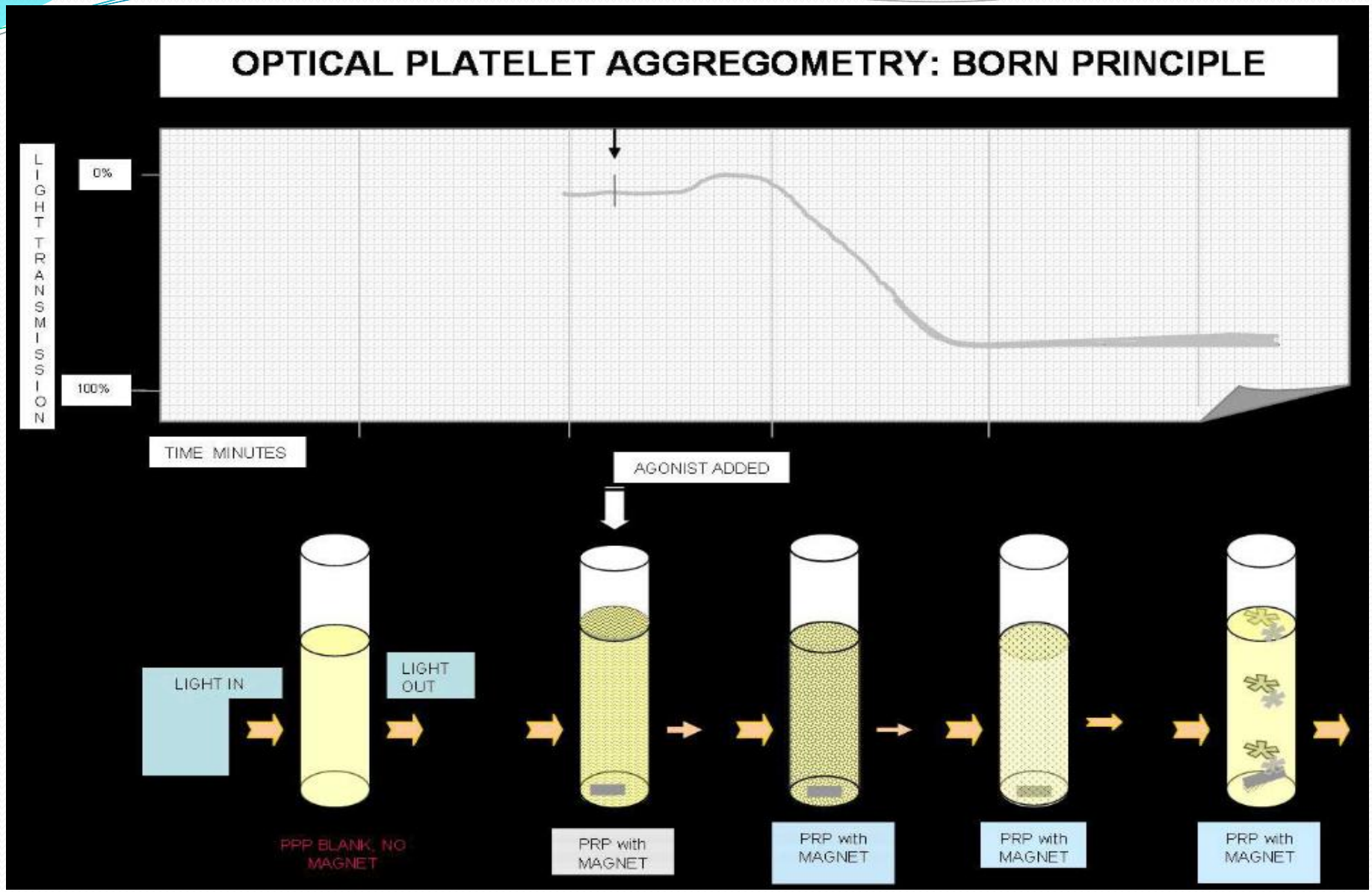
Platelet Function Testing

- **PFA-100**
  - screen to detect problems with primary haemostasis
  - replace the bleeding time
  - citrated whole blood is aspirated at high shear rates through disposable cartridges containing an aperture within a membrane coated with either collagen and epinephrine (CEPI) or collagen and ADP (CADP).
  - these agonists induce platelet adhesion, activation and aggregation leading to rapid occlusion of the aperture and cessation of blood flow termed the closure time (CT).

Platelet Aggregation Study

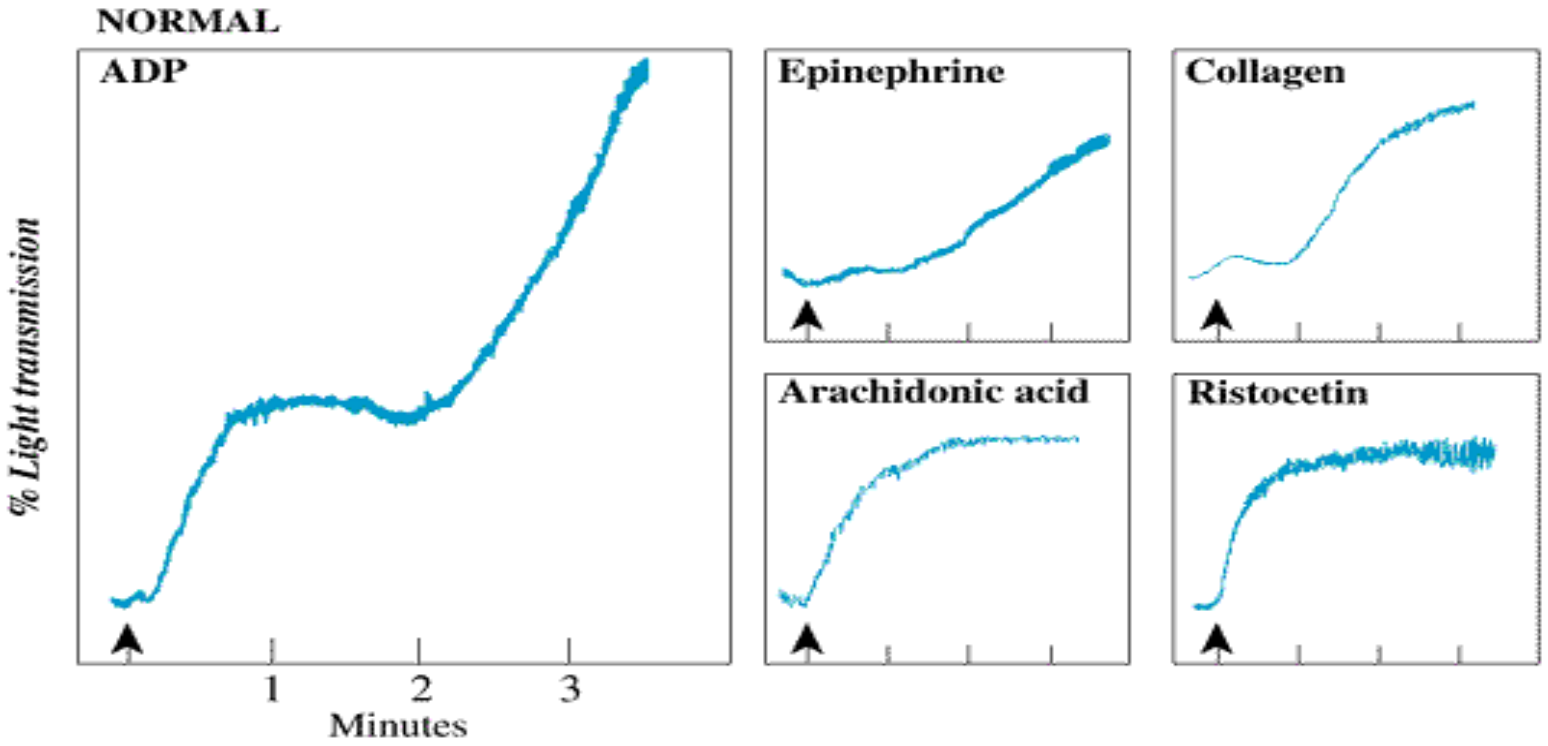
- Principle:
  - Aggregation in response to an added chemical stimulus can be monitored by change in transmittance
  - Stimulating agent:
    - Arachidonic acid, ADP, collagen, epinephrine, and ristocetin
    - Platelet functional disorders have typical aggregation patterns

Platelet Aggregation Study



http://www.practical-haemostasis.com/Platelets/platelet_function_testing_lta.html

Platelet Aggregation Patterns



	ADP	EPI	COLL	ARACH	RISTO
von Willebrand disease	NORMAL				ABNORMAL
Storage pool disease	ABNORMAL			NORMAL	
Glanzmann thrombasthenia	ABNORMAL				NORMAL
Bernard-Soulier syndrome	NORMAL		+/-	NORMAL	ABNORMAL

Inherited Disorders of Platelet Function: Surface Membrane Defects

- Glanzmann thrombasthenia: autosomal recessive, defective GP IIb/IIIa
- Bernard Soulier syndrome: autosomal recessive, thrombocytopenia, large platelets, defective GP Ib,V,IX
- Collagen receptor defect: defective thrombospondin
- Platelet-type vWD: autosomal dominant, high affinity for vWF, borderline thrombocytopenia, addition of cryo-> aggregation

Platelet Storage Pool Disease

- The clinical syndrome is called α-SPD, δ-SPD, or combined αδ-SPD.
- These disorders, affecting the extension phase of clot formation
  - a/w impaired platelet function as indicated by decreased aggregation responses.

Platelet Storage Pool Defects

- a/w a variety of other inherited diseases
  - Hermansky-Pudlak syndrome
  - Chediak-Higashi syndrome
  - Wiskott-Aldrich syndrome
  - Thrombocytopenia-absent radius (TAR) syndrome

Acquired Platelet Storage Pool Defects

- a/w Systemic lupus erythematosus (SLE)
- cardiovascular bypass
- hairy-cell leukemia
- other disorders with chronic platelet activation.

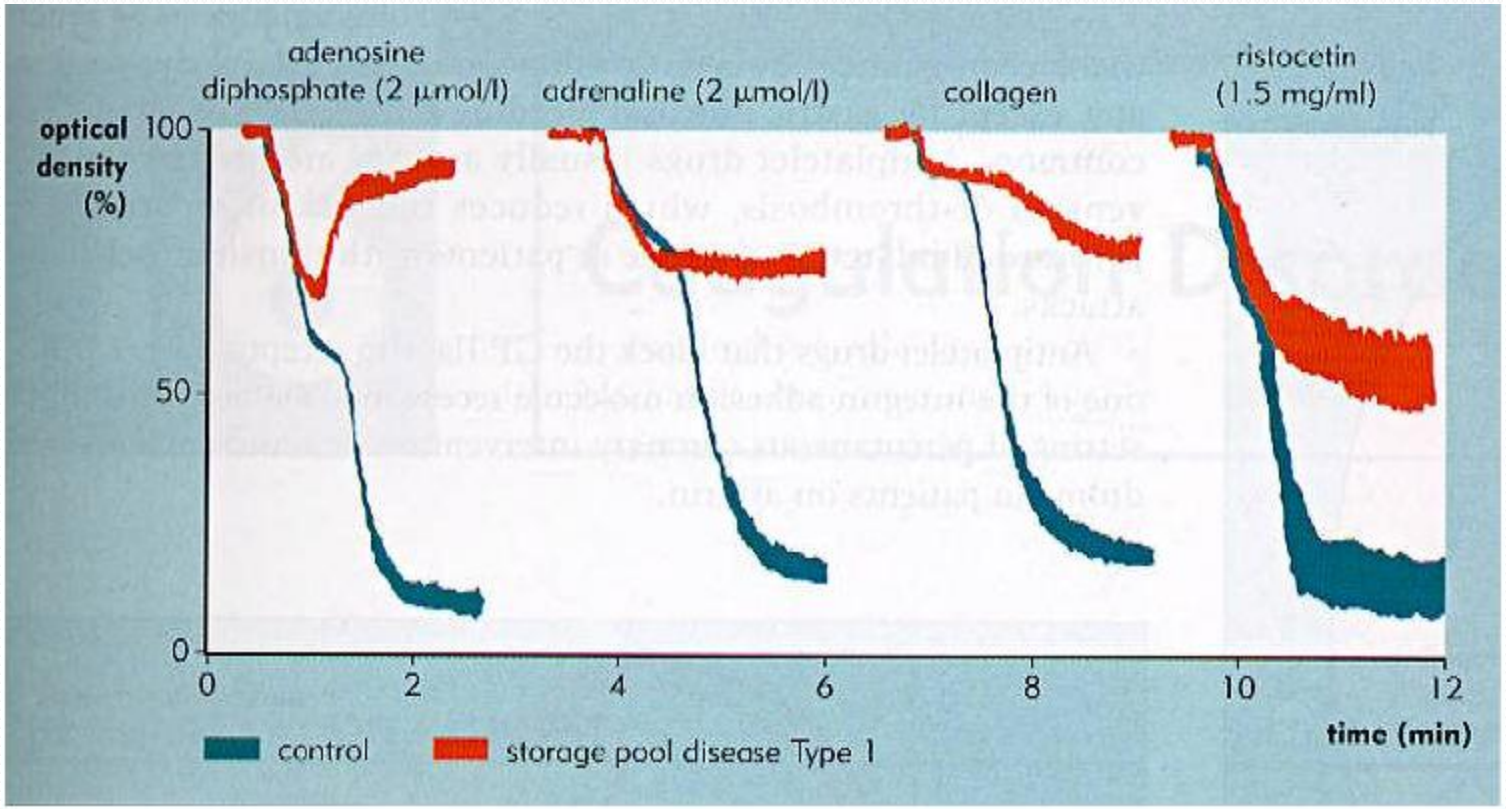
Four Major Types Of Congenital Platelet Storage Pool Disease

Disorder	Etiology
Dense body deficiency	Decreased dense bodies with decreased secretion of ADP and serotonin
Gray platelet syndrome	Decreased α-granules and contents
Factor V Quebec	Severe multimerin deficiency, protease degradation of α-granules
Mixed α-granule/dense body deficiency	Decreased α-granules and dense bodies

Platelet Storage Pool Deficiency

- Platelet aggregation due to deficiencies in either dense granules/ alpha granule contents or both.
- Normal morphology, no granules in EM
- Platelet aggregation studies:
  - **NO 2nd wave-ADP, epinephrine**
  - ↓collagen +AA, normal ristocetin
  - ↑ ATP:ADP ratio

Platelet Storage Pool Deficiency



Storage Pool Deficiencies

- **Gray platelet syndrome**
  No α granules,
  Large gray plts, no granules
  From cardio pulmonary bypass
  Plt agg blunted with all agents except ADP/epi
- **Quebec plt disorder**
  No α granules
- **Wiscott Aldrich syndrome**
  x-linked
  No δ granules EM
  Small granulated plts, like FeDa
  Thrombocytopenia, infection, eczema
  ↑ malignancy
- **Chediak Higashi**
  No δ granules EM
- **Hermansky-Pudlak Syndrome**
  No δ granules EM
  ↑ pigment reticuloendothelial cell
- Swiss cheese platelets
- ↑AK, nevi, tumors, pulmonary fibrosis
- Puerto Rican/Swiss, ↑vW
- **Thrombocytopenia w absent radii**

Transfus Med Hemother 2010;37:248–258

Table 1. Inherited storage pool diseases (SPD): genetic mutations and associated phenotypes

Syndrome	Bleeding symptoms	Platelet count $\times 10^9$/l	Platelet ultrastructure	Inheritance (gene)	Platelet function abnormality	Associations
α-Storage pool disease (α-SPD)						
GPS	mild to moderate	30–100	↓ / empty α-granules, ↑ platelet size	autosomal recessive (most) or dominant (gene(s) unknown)	normal or ↓ aggregation with thrombin, collagen	myelofibrosis
QPD	mild to moderate	normal or ↓	↓ α-granule content	autosomal dominant (*PLAU*)	↓ aggregation with epinephrine	
ARC syndrome	mild	normal	lack of α-granules, ↑ platelet size	autosomal recessive (*VPS33B*, *VIPAR*)	↓ aggregation with ADP, arachidonate	arthrogryposis multiplex congenita, renal dysfunction, cholestasis, ichthyosis, recurrent infections
δ-Storage pool disease (δ-SPD)						
HPS (subtype 1–8)	moderate to severe	normal	↓ dense granules	autosomal recessive (*HPS1–HPS8*)	↓ second wave of aggregation	oculocutaneous albinism, ceroidlipo-fuscinosis, nystagmus, ↓ visual acuity, (HPS2: immunodeficiency, HLH; HPS1,4: granulomatous colitis, pulmonary fibrosis)
CHS	moderate to severe	normal	↓ dense granules, giant inclusion bodies	autosomal recessive (*LYST*)	↓ second wave of aggregation, ↑ ATP/ADP ratio	partial albinism, immunodeficiency, HLH, neurological defects, hepatosplenomegaly
GS (subtype 1–3)	mild to absent	normal or ↓	n.d.	autosomal recessive (*MYO5A*, *RAB27A*, *MLPH*)	n.d.	partial albinism, silver hair, (GS1: neurological defects; GS2: immunodeficiency)
αδ-Storage pool disease (αδ-SPD)						
X-linked dyserythropoietic anemia with thrombocytopenia/ X-linked macrothrombo-cytopenia	moderate	mostly ↓	↓ dense granules, variable α-granules, ↑ platelet size	X-linked dominant, (*GATA1*)	↓ aggregation	β-thalassemia, congenital erythropoietic porphyria
WAS	moderate to severe	10–100	↓ granules, ↓ platelet size	X-linked recessive (*WAS*)	↓ aggregation	eczema, immunodeficiency, risk for autoimmune disorders

n.d. = Not detected.