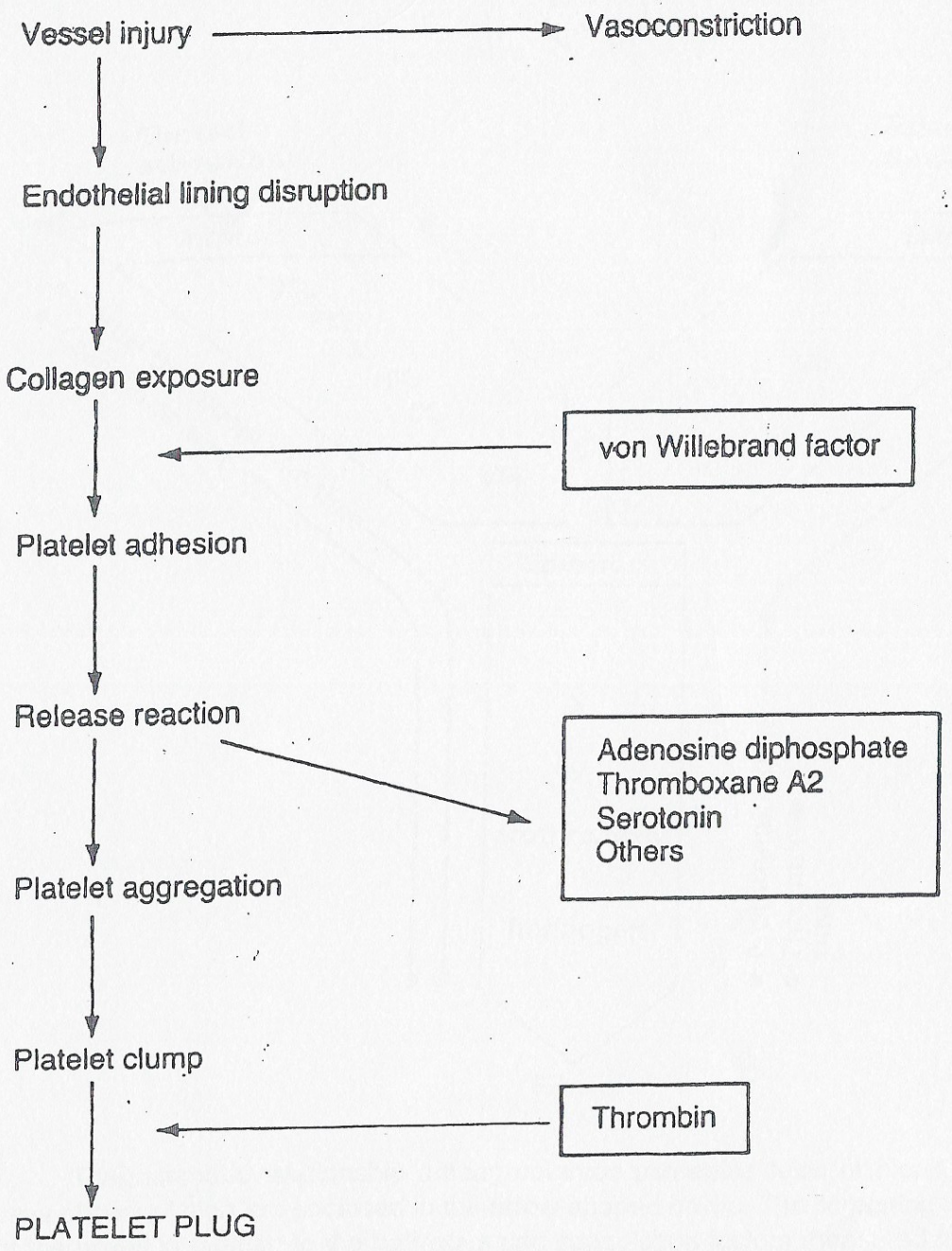
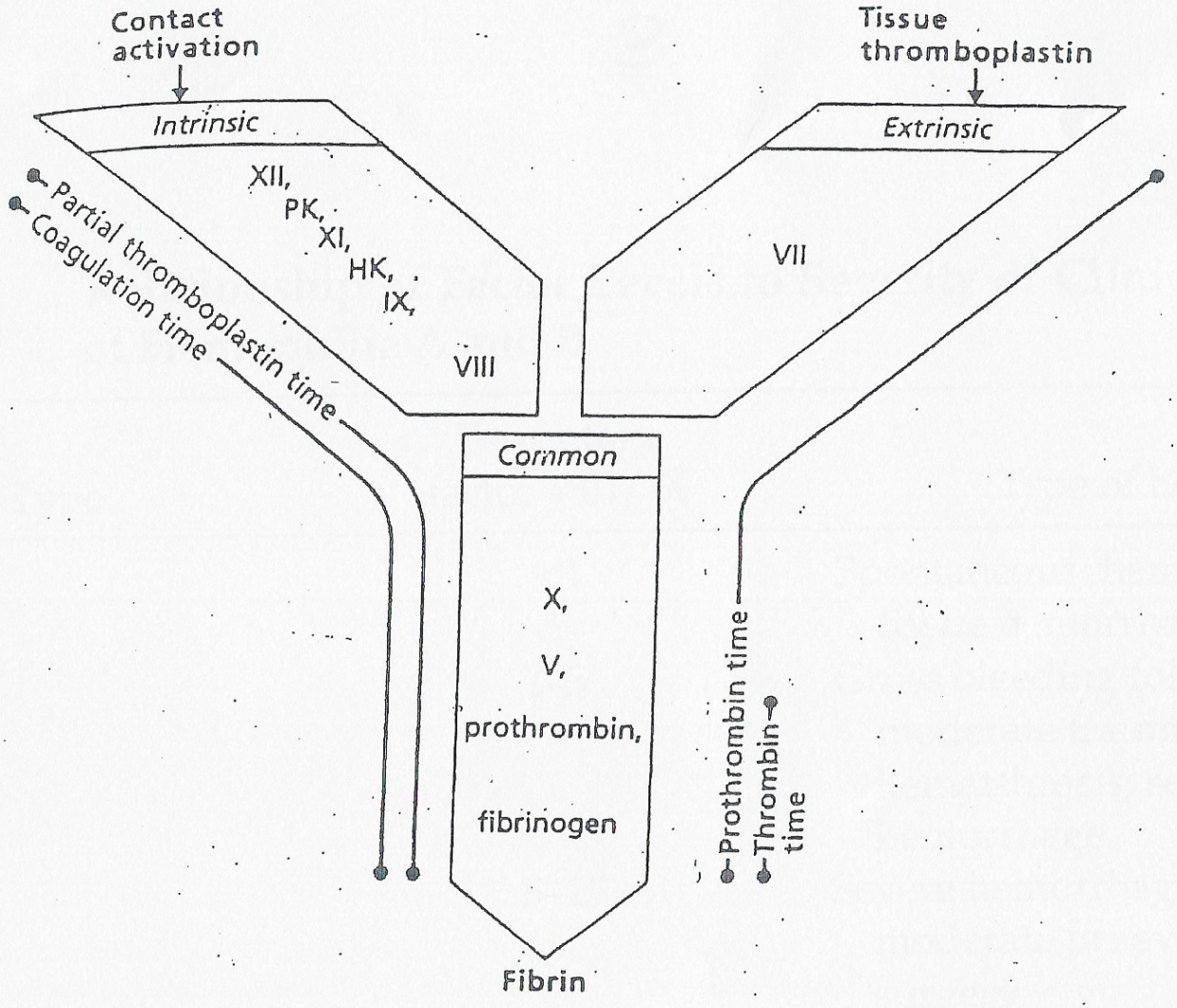

Vessel injury
Vasoconstriction
Endothelial lining disruption
Collagen exposure
von Willebrand factor
Platelet adhesion
Release reaction
Adenosine diphosphate
Thromboxane A2
Serotonin
Others
Platelet aggregation
Platelet clump
Thrombin
PLATELET PLUG

Page 1



Diagrammatic relationship among common screening tests of blood coagulation. The major pathways of coagulation are enclosed in the arrow-shaped boxes. The screening tests are indicated at the side of the boxes in relation to the pathways and coagulation factors measured by each.

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Relationship of Factor Levels to Severity of Clinical Manifestations of Hemophilia A and B

Type	Percentage factor VIII/IX	Type of hemorrhage
Severe	<1	Spontaneous; hemarthroses and deep-tissue hemorrhages
Moderate	1–5	Gross bleeding following mild to moderate trauma; some hemarthrosis; seldom spontaneous hemorrhage
Mild	5–25	Severe hemorrhage only following moderate to severe trauma or surgery
High-risk carrier females	30–50	Gynecologic and obstetric hemorrhage

Differences Between von Willebrand Disease and Hemophilia A

	von Willebrand Disease	Hemophilia A
Symptoms	Bruising and epistaxis	Joint bleeding
	Menorrhagia or mucosal bleeding	Muscle bleeding
Sexual distribution	Males = females	Males
Frequency	1:200 to 1:500	1:6000 males
Abnormal protein	vWF	Factor VIII
Molecular weight	0.6-20 X 10^6 Da	280 kDa
Function	Platelet adhesion	Clotting cofactor
Site of synthesis	Endothelial cell or megakaryocytes	??
Chromosome	Chromosome 12	X chromosome
Inhibitor frequency	Rare	14-25% of patients
History	Abnormal	Abnormal
aPTT	Normal or prolonged	Prolonged
Factor VIII activity	Borderline or decreased	Decreased or absent
vWF Ag	Decreased or absent	Normal or increased

From: Montgomery RR, Gill JC, Scott JP. Hemophilia and von Willebrand disease. In: Nathan D, Orkin S, editors. Nathan and Oski's Hematology of Infancy and Childhood, 5th ed. Philadelphia: Saunders.

Testing for Thrombotic Predisposition

Hereditary predisposition to thrombosis is associated with a reduction of anticoagulant function (protein C, protein S, AT-III); the presence of a factor V molecule that is resistant to inactivation by protein C (factor V Leiden); elevated levels of procoagulants (a mutation of the prothrombin gene); or a deficiency of fibrinolysis (plasminogen deficiency). When patients are being screened for prothrombotic tendencies, specific tests of the natural anticoagulants are warranted. Although both immunologic and functional tests are usually available, functional assays of protein C, protein S, and AT-III are clinically more useful.

Factor V Leiden is a common mutation in factor V that is associated with an increased risk of thrombosis. A point mutation in the factor V molecule prevents the inactivation of factor Va by activated protein C and, thereby, the persistence of factor Va. This defect, also known as *activated protein C resistance*, is easily diagnosed with DNA testing.

The prothrombin gene mutation (G20210A) is a mutation in the noncoding portion of the prothrombin gene, with a glycine (G) at position 20210 being replaced by an alanine (A). This mutation increases the amount of prothrombin messenger RNA, is associated with elevations of prothrombin, and causes a predisposition to thrombosis. This abnormality is easily identified with molecular diagnostic (DNA) testing.

Elevated Homocysteine

Levels of homocysteine may be increased as a result of genetic mutations, causing homocystinuria. Patients with homocysteine elevation are predisposed to arterial and venous thrombosis as well as to an increase in arteriosclerosis.

POTENTIAL PROTHROMBOTIC STATES

CONGENITAL
Deficiency of anticoagulants
AT-III, protein C or protein S, plasminogen
Resistance to cofactor proteolysis
Factor V Leiden
High levels of procoagulants
Prothrombin 20210 mutation
Elevated factor VIII levels
Damage to endothelium
Homocystinemia
ACQUIRED
Obstruction to flow
Indwelling lines
Pregnancy
Polycythemia/dehydration
Immobilization
Injury
Trauma, surgery, exercise
Inflammation
IBD, vasculitis, infection, Behçet syndrome
Hypercoagulability
Pregnancy
Malignancy
Antiphospholipid syndrome
Nephrotic syndrome
Oral contraceptives
L-Asparaginase
Elevated factor VIII levels
RARE OTHER ENTITIES
Congenital
Dysfibrinogenemia
Acquired
Paroxysmal nocturnal hemoglobinuria
Thrombocythemia
Vascular grafts

AT-III, antithrombin III; IBD, inflammatory bowel disease.