Coagulation Laboratory Objectives

The Coagulation Laboratory student will perform the following tasks listed under each heading as part of the 2-week rotation through the department. The objectives of the coagulation rotation will have been achieved when the equivalent of a C+ has been attained in performance and competency of the laboratory testing and a written test.

Demonstrate knowledge of the basic theory with:

1. The Coagulation Cascade by:

1. Diagramming the entire coagulation cascade.
2. State the purpose and function of Neoplastine.
3. State the contents and purpose of the activated partial thromboplastin time reagent.
4. Describe how the intrinsic and extrinsic pathways are evaluated and what factors are measured by each pathway.

2. Anticoagulant Therapy by:

1. Discussing the action of heparin and which factors are affected by it.
2. Describing how the therapeutic range of heparin is determined.
3. Stating what test is used to monitor heparin therapy.
4. Discussing the protein that accelerates the effects of heparin.
5. Stating what neutralizes the effects of heparin.
6. Explaining the action of coumadin and which factors are affected by it.
7. Stating what test is used to monitor coumadin therapy.
8. Discussing what neutralizes the effects of Coumadin.
9. Describing why coumadin is overlapped with heparin therapy.
10. Explaining how the International Normalized Ratio (INR) was developed, why it was developed, how it is used to monitor coumadin therapy and the significance of the ISI.

Demonstrate knowledge of routine procedures, including:

1. Specimen Processing and Handling by:

1. Discussing the correct procedure for processing routine specimens, including tube requirement, specimen requirement and centrifugation time.
2. Listing at least two reasons for rejecting a specimen for testing.
3. Explaining the possible effects of an increased hematocrit on results.
4. Explaining how sodium citrate functions as an anticoagulant.
5. Stating the proper blood to anticoagulant ratio.

2. Stago STAR Max by:

1. Discussing the methodology of the STAR Max for detecting clot times.
2. Demonstrating the ability to perform PTs, APTTs, and anti-Xa heparin assay on the STAR Max.
3. Demonstrating the quality control protocol for coagulation testing.

3. **Fibrinogen by:**
    1. Performing fibrinogens on the STAR Max
    2. Stating the principle of the Clauss fibrinogen and the purpose for diluting the specimens.
    3. Listing conditions which would result in an abnormal (high or low) fibrinogen.

4. **D-Dimer by:**
    1. Discussing the principle of the D-Dimer test.
    2. Listing conditions which would result in an elevated D-Dimer.
    3. Demonstrating the ability to properly perform the D-Dimer test.

5. **Fibrin Degradation Products by:**
    1. Explaining the principle of the latex test for FDP/FSP.
    2. Listing conditions which would result in elevated FSPs.
    3. Demonstrating the ability to properly perform the test for FSP.

6. **Thrombin Time by:**
    1. Discussing the principle of the thrombin time test.
    2. Naming two inhibitors that can affect the thrombin time.
    3. Listing 2 conditions that would cause an elevated thrombin time.
    4. Explaining the difference between the thrombin time and fibrinogen.

7. **PFA-Platelet Function Analyzer by:**
    1. Observing a PFA test
    2. Explaining the principle of the PFA and how the results are reported.
    3. Explaining how the results of the Epinephrine and ADP Cartridges are interpreted.

8. **Verify Now Analyzer by:**
    1. Discussing the principle of the P2Y12 and Aspirin Assay
    2. Demonstrating the ability to perform a P2Y12 and or ASA Assay

Demonstrate knowledge of special procedures, including:

1. **Factor Assays by:**
    1. Explaining how the factor assay measures specific factors
    2. Discussing the purpose of dilutions in the assay.
    3. Detecting the presence of inhibitors when evaluating assay results.
    4. Name the most common factor deficiency
    5. Performing a factor assay.

2. **Circulating Anticoagulant Screen (Mixing Study) by:**
    1. Explaining the principle of the CACS
    2. Describing the significance of the 1- and 2-hours incubation mixes.
    3. Performing at least one CACS.

3. Factor Inhibitors by:

1. Defining a factor inhibitor.
2. Naming the most commonly found factor inhibitor.
3. Discussing the mixing study pattern found with Factor VIII inhibitors.
4. Naming the unit in which Factor inhibitors are expressed and explain its application in treatment of the patient.

4. Platelet Aggregation Study by:

1. Discussing the role of platelets in coagulation.
2. Performing a platelet aggregation study if one is ordered.
3. Distinguishing aggregation pattern of von Willebrand's Disease, Bernard-Soulier syndrome, Glanzmann thrombasthenia, storage pool disease, and aspirin-like disorders.
4. Explaining aspirin's effect on platelet aggregation

5. Thromboelastography (TEG) by:

1. Explaining the principle of TEG
2. Analyzing normal and abnormal TEG patterns

6. Heparin Induced Thrombocytopenia (Heparin Antibody) by:

1. Discussing the significance of monitoring platelet counts during heparin therapy.
2. Discussing the Heparin Antibody procedure.

7. von Willebrand Factor Antigen by:

1. Describing the components of the Factor VIII molecule and discuss their roles in coagulation.
2. Performing or discussing the von Willebrand Factor Antigen test.

Demonstrate the ability to operate the computer in Coagulation by:

1. Validating all results.

2. Confirming delta checks and critical results by adhering to the guidelines established by the supervisor.

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Coagulation

Coagulation Orientation Checklist

TRAINEE:_____DATE:_____

	DATE PROFICIENT	TRAINEE	TRAINER
Policy Manger			
Review the following procedures			
1. Prothrombin Time	_____	_____	_____
2. Activated aPTT	_____	_____	_____
3. Fibrinogen	_____	_____	_____
4. Thrombin Time	_____	_____	_____
5. D-Dimer	_____	_____	_____
6. UFH	_____	_____	_____
7. LMWH	_____	_____	_____
8. FSP	_____	_____	_____
Star Max	_____	_____	_____
Verify Now Analyzer	_____	_____	_____
PFA Analyzer	_____	_____	_____
TEG	_____	_____	_____
Review procedure for saving and freezing Special Coagulation Tests	_____	_____	_____
Understanding the principle of the INR	_____	_____	_____

I,_____ determine that I have been properly trained and am proficient in performing testing in Coagulation.

Trainee Signature:_____

Trainer Signature:_____

Reviewed by Supervisor:_____Date:_____

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STAGO STAR MAX EMPLOYEE CHECKLIST

TRAINEE:_____ DATE:_____

Reagents and Supplies	DATE PROFICIENT	TRAINEE	TRAINER
1. Locate procedure and operator manual			
2. Locate the STA hotline number			
3. Reconstitute controls, calibrators and reagents			
Reading a Screen			
1. Identify each icon			
2. Access icons using touch screen and mouse			
3. Explain basic setup of screen			
Patient Icon			
1. Load racks using automatic and manual mode			
2. Explain patient analysis including:			
a. ID			
b. Rack number and position			
c. Type (stat, QC, Cal, Micro)			
d. Status Color Codes			
e. Search for a Patient			
f. Tagging samples			
g. Rediluted tests			
h. Calculated tests			
3. Explain unloading			
a. Unload racks using tag function			
b. Identify rack unloading button			
c. Identify tray reslease button and color change indicating that the tray can be removed.			
4. Explain			
a. Add a test/profile			
b. Delete a test			
c. Make a test STAT			
d. Rerun a test			
e. Reprint a test			

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Production

1. Identify sections of the drawer and load products with barcode
2. Explain the products on board including:

a. color codes
b. sorting by column heading
c. identify symbol for stirred reagents
d. load cuvettes and empty waste
e. load wash solution and empty waste

3. Explain drawer view using cursor to ID reagents
4. Explain product margin including:

a. symbols indicating status of test

5. Explain open drawer including:

a. changing parameters on products
b. closing drawer after loading

Calibration Icon

1. Run a new calibration
2. Select test in order to view calibration curve
3. View both calibrations on one test
4. Cancel calibration point
5. Rerun a calibration point
6. Delete an existing calibration curve
7. Modify or delete a point

Quality Control Icon

1. Explain all QC screens
2. Run Quality Control
3. Access QC results from previous runs
4. Cancel QC that is currently running
5. Daily QC screen

System

1. Explain methodologies
2. System setup including global options. System setup, and passwords
3. Archiving including search, tracking, and export

On Line Help

1. The operator is able to activate online help and access Help screens

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STAT loading

1. The operator is able to load tubes in STAT mode	_____	_____	_____

Maintenance (Weekly)

1. clean and change air filters	_____	_____	_____
2. bleach washing wells	_____	_____	_____
3. needle purge	_____	_____	_____
4. clean measurement plate, drawers, shuttles and belts	_____	_____	_____
5. clean measurement and incubation wells	_____	_____	_____
6. replace teflon tip and O ring	_____	_____	_____
7. clean suction tip	_____	_____	_____
8. change halogen lamp	_____	_____	_____
9. replace needles 1,2, and 3	_____	_____	_____
10. CAP piercing only	_____	_____	_____
a. clean sample needle daily and weekly	_____	_____	_____
11. saving menu	_____	_____	_____

Shutdown and Startup Analyzer

1. Shutdown the software and analyzer	_____	_____	_____
2. Startup the analyzer and software	_____	_____	_____

I,_____ determine that I have been properly trained and am proficient in performing testing on the Stago Star Max Analyzer.
Trainee Signature:_____

I, determine that_____ is competent and proficient in performing testing on the Stago Star Max Analyzer.
Trainer Signature:_____

Reviewed by Supervisor:_____Date:_____

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VERIFY NOW TRAINING CHECKLIST

TRAINEE:_____ DATE:_____

Assay Device	DATE PROFICIENT	TRAINEE	TRAINER
1. Device components: Finger Grip, Protective Sheath, Sample Well, Needle, Staging Well, Humidity Indicator, Mixing Chambers/ Detection Wells	_____	_____	_____
2. Storage requirements: keep in sealed foil pouch until ready to test.	_____	_____	_____
3. Spot Code on each assay device.	_____	_____	_____
4. Bar Code on assay device pouch, calibration values in bar code, expiration date of lot	_____	_____	_____
Sample Collection and Handling			
1. Tube requirement: Greiner 2.0mL tube	_____	_____	_____
2. The tubes have been validated to be sent throught the tube system.	_____	_____	_____
3. Do Not Centifuge.	_____	_____	_____
4. P2Y12 must sit for 10 mins after collection.	_____	_____	_____
5. Aspirin must sit for 30 mins after collection.	_____	_____	_____
6. Gently mix specimen 5x before sampling.	_____	_____	_____
7. Must be testing within 4 hours after collection.	_____	_____	_____
Running Quality Control			
1. Perform EQC: PASS vs FAIL.	_____	_____	_____
2. Perform WQC	_____	_____	_____
How to Run a Sample			
1. Open foil pouch immediately prior to assay	_____	_____	_____
2. Remove needle cap by pulling straight up and immediatley place in instrument. Do not twist and do not put finger in the sample well.	_____	_____	_____
3. Read in Bar Code for Calibration Information if New Lot.	_____	_____	_____
4. DO NOT remove the tube once it has been placed on the cartidge needle.	_____	_____	_____
5. DO NOT remove the cartridge and tube from the device until the assay is completed.	_____	_____	_____
6.It is important to remove the cartridge after assay is completed.	_____	_____	_____
Verify Now P2Y12 Assay			
1. Review P2Y12 Response Units	_____	_____	_____
2. Review recall results	_____	_____	_____

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Verify Now Aspirin Assay

1: Review Aspirin Reaction Units
2. Review recall results

Troubleshooting and Technical Support

1. Review Cleaning Device
2. Point out location of fan.
3. Show location of fuse.

I,_____ determine that I have been properly trained and am proficient in performing testing on the Verify Now Analyzer.

Trainee Signature: _____

I, determine that_____is competent and proficient in performing testing on the Verify Now Analyzer.

Trainer Signature:_____

Reviewed by Supervisor:_____Date:_____

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PFA ORIENTATION CHECKLIST

TRAINEE:_____ DATE:_____

SAMPLE REQUIREMENTS	DATE PROFICIENT	TRAINEE	TRAINER
1. Samples stable up to 4 hours at room temperature			
2. DO NOT CENTRIFUGE OR REFRIGERATE!!!!!			
3. The PFA-100 requires 900ul of whole blood per cartridge			
4. Specimen should "rest" 20 minutes after specimen collection			
5. Specimen should not be sent through pneumatic tube			
PFA INSTRUMENT			
1. Operator understands principle of operation			
2. Operator can identify components of PFA: carousel, printer, trigger solution compartment, LCD display, and keyboard			
3. Operator understands consumables as well as their storage			
4. Operator can load and prime a new bottle of trigger solution			
5. Operator can identify items needed to perform maintenance			
6. Operator can perform daily PM procedures			
7. Operator can change printer ribbon and paper			
8. Operator knows where cartidge storage is located			
SAMPLE TESTING			
1. Operator understands QC protocol			
2. Make sure test cartidges have reached room temp. (15min)			
3. Load cartidges on analyzer and snap into position			
4. Resuspend the sample by Gently inverting by hand 3-4 x's			
5. Pipette at least 900ul of sample			
6. Enter patient ID			
7. Single vs. Duplicate test			
8. Running Epinephrine vs. ADP cartridge			

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RESULT INTERPRETATION AND REPORTING

1. The operator can locate and define reference ranges	_____	_____	_____
2. Operator understands how to correctly enter result in LIS	_____	_____	_____

I,_____ determine that I have been properly trained and am proficient in performing testing on the PFA analyzer.

Trainee Signature:_____

I, determine that_____ is competent and proficient in performing testing on the PFA analyzer.

Trainer Signature:_____

Reviewed by Supervisor:_____Date:_____

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TEG 6s Training Checklist

TRAINEE:_____ DATE:_____

General	DATE PROFICIENT	TRAINEE	TRAINER
1. Contact information for technical support			
2. Explanation of symbols			
TEG6s Analyzer			
1. Components			
a. LCD Touch Screen			
b. Cartridge Port			
c. Lighted Strip			
d. Back Panel Components			
Assay Cartridges and Reagents			
1. Cartridge Parts			
2. Cartidge Storage			
Starting/Running the TEG 6s Analyzer			
1. Set Up			
2. Power On/Login			
3. Settings			
4. Running a Patient Sample			
Test Results			
1. Stored Tests			
2. Results Display/Printout			
3. Kaolin Heparinase Tracing			
4. Rapid TEG Tracing			
5. Functional Fibrinogen Tracing			
6. Running QC			
a. Abnormal QC			
b. Normal Donor Blood			

Troubleshooting and Maintenance

1. Errors	_____	_____	_____
2. Warnings	_____	_____	_____
3. Critical Alerts	_____	_____	_____
4. Cleaning the Analyzer	_____	_____	_____
5. Clotted Specimen	_____	_____	_____
6. Tube Requirement	_____	_____	_____

TEG Manager

1. Access the Viewer	_____	_____	_____
2. Barcode Containing Tracking #	_____	_____	_____
a. Components			
b. Toolbar	_____	_____	_____
c. Test Results	_____	_____	_____
4. Search for a Patient Diagnostic Record	_____	_____	_____
5. View Patient Diagnostic Results	_____	_____	_____
	_____	_____	_____

I,_____ determine that I have been properly trained and am proficient in performing testing for the TEG 6s Analyzer.

Trainee Signature:_____

I, determine that_____ is competent and proficient in performing testing on the TEG 6s Analyzer.

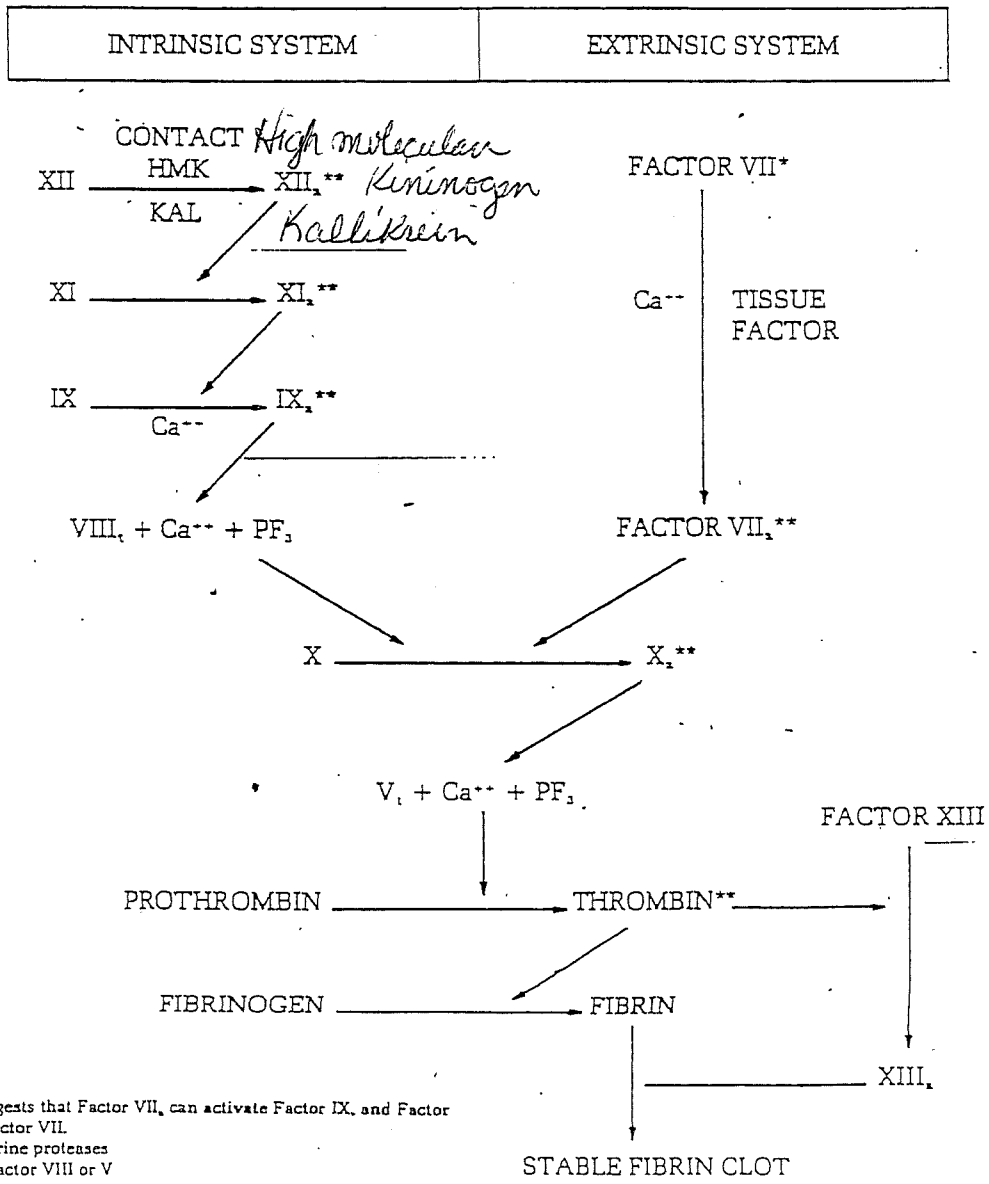
Trainer Signature:_____

Reviewed by Supervisor:_____Date:_____

by no clinical evidence of bleeding although the laboratory evaluation of hemostasis will be markedly abnormal (prolonged activated partial thromboplastin time and normal prothrombin time). Ironically, patients with deficiencies of Hageman factor and Fletcher factor appear to be predisposed to thrombotic episodes. This group of factors characteristically is not adsorbed by barium sulfate nor are they consumed during the process of coagulation. They tend to be stable in banked blood and they do not require Vitamin K for their synthesis.

Cascade System of Coagulation

In the past 20 years, a number of schemes of coagulation have been proposed. The "cascade" or "waterfall" hypothesis of prothrombin activation states that all clotting factors are distinct entities in plasma, synthesized independently and present in the circulation as inactive precursors. It was initially proposed that each factor was converted to its enzymatically active form by the preceding factor in the sequence in a series of reactions best described as a chain reaction. The various enzymatic series ultimately result in the formation of thrombin which then acts upon fibrinogen to form fibrin. (Figure 2) Fibrin subsequently polymerizes and is stabilized to form a fibrin clot. Recent studies have emphasized that all coagulation factors are necessary for formation of the fibrin clot, however, their mode of action is not necessarily as originally hypothesized in the "cascade" sequence. Two exceptions are Factors V and VIII. Both



*Evidence now suggests that Factor VII$_a$ can activate Factor IX, and Factor IX$_a$ can activate Factor VII.
**Indicates active serine proteases
t = transformed Factor VIII or V

Figure 2

THE FIBRINOLYTIC SYSTEM

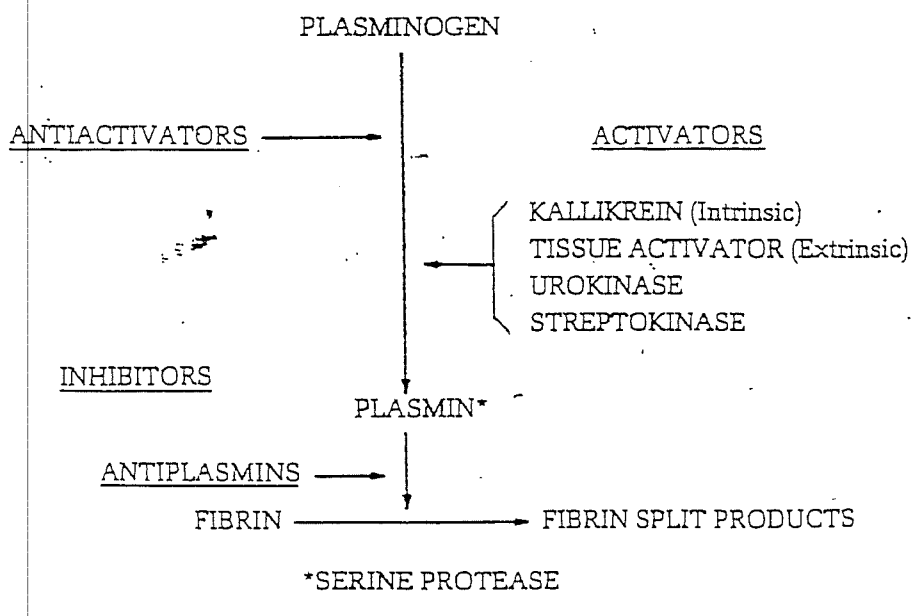


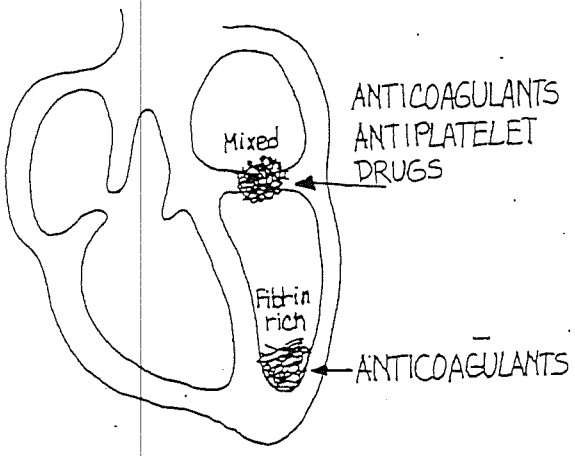
Figure 5

Interpretation of Laboratory Studies

TESTS	CONCLUSION	
Prolonged Bleeding Time and Normal Platelet Count	Vascular or Platelet Function Disorder or von Willebrand's disease	
Prolonged Bleeding Time and Platelets ↓	Thrombocytopenia +/- platelet function defect	
Prolonged Bleeding Time and Abnormal PTT	von Willebrand's disease	
Prolonged PTT (Normal PT)	Bleeding	Factor VIII ↓ (Hemophilia A or von Willebrand's) Factor IX ↓ (Christmas) Factor XI ↓ Heparin*
	No Bleeding	"Lupus-like" inhibitor* Factor XII ↓ Prekallikrein ↓ Kininogen ↓
*PT sometimes slightly prolonged		
Prolonged PT (Normal PTT)	Factor VII ↓ (unusual)	
Prolonged PTT & PT	Factor II ↓ (prothrombin) Factor V ↓ Factor X ↓ Factor I ↓ (fibrinogen) Vitamin K deficiency Warfarin Therapy DIC Therapeutic Fibrinolysis Liver disease	
Prolonged TT	Fibrinogen ↓ DIC Therapeutic fibrinolysis Liver disease Heparin	} usually in combination with coagulation defects
No Abnormalities on routine screening tests	Bleeding	Factor XIII ↓ Mild coagulation defects which do not give abnormal screening tests. α_2 Antiplasmin deficiency

A prolonged bleeding time is indicative of either a vascular or a platelet abnormality. An isolated long bleeding time may be due to a low platelet count or a platelet functional defect. With a normal platelet count a long bleeding time suggests the possibility of a

Intracardiac Thrombi



Most intracardiac thrombi are fibrin-rich and can either be prevented from forming or prevented from growing by the use of anticoagulant drugs. Thrombi that form on diseased or prosthetic valves are usually of mixed platelet - fibrin composition and can be prevented by a combination of anticoagulants and drugs which suppress platelet function.

Anticoagulant Drugs

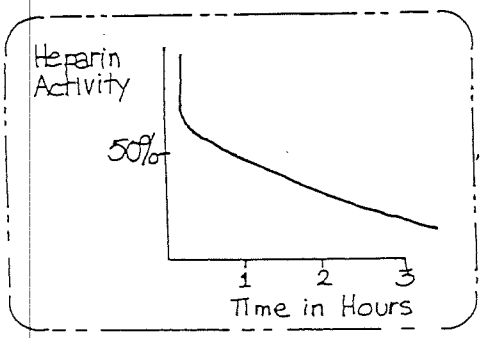
- Heparin
- Vitamin K Antagonists

The anticoagulant drugs in clinical use are heparin and the vitamin K antagonists.

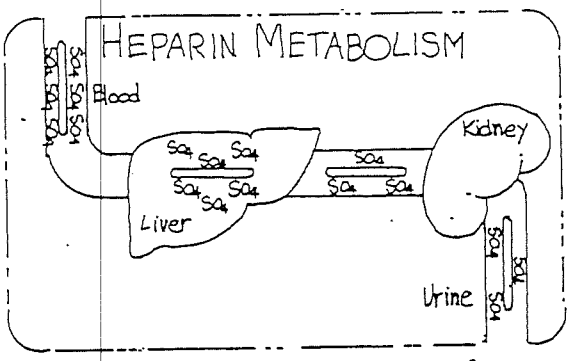
Heparin

- M.W. 6,000 – 25,000
- Immediate Effect
- Must be given by Injection
- Effective in experimental + clinical venous thrombosis
- ½ Life = One Hour

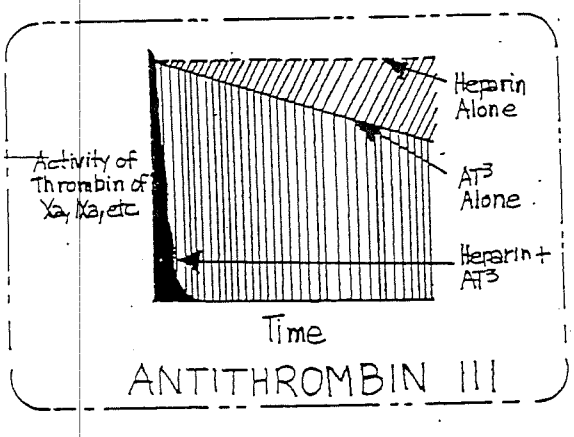
Heparin is a negatively charged, highly sulfated mucopolysaccharide with a molecular weight which ranges between 6,000 and 25,000 Daltons. It is not absorbed from the gastrointestinal tract and must, therefore, be given by injection. It has an immediate anticoagulant effect. Heparin is highly effective in both the prevention and treatment of venous thrombosis and pulmonary embolism.



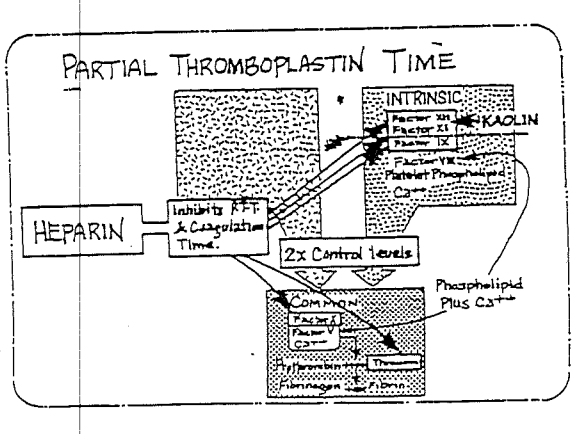
A single intravenous injection is cleared from the blood with a half-life of approximately 60 minutes in normal individuals. There is an initial rapid clearance of approximately 40% of the injected heparin in 5 minutes followed by a more gradual clearance.



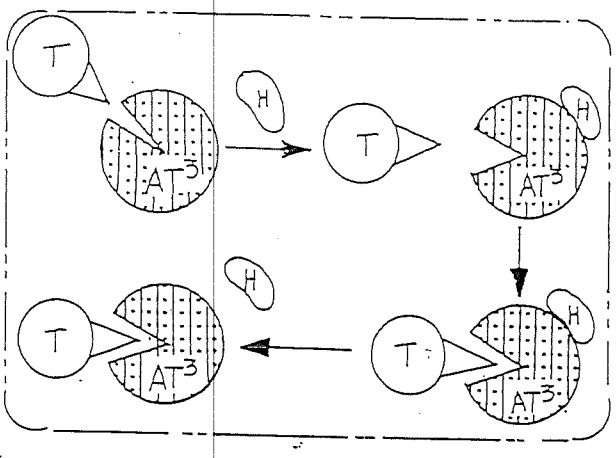
Heparin is cleared by the reticuloendothelial system, particularly the liver, where it is partly inactivated by the process of desulphation and subsequently excreted in the urine in a less active form.



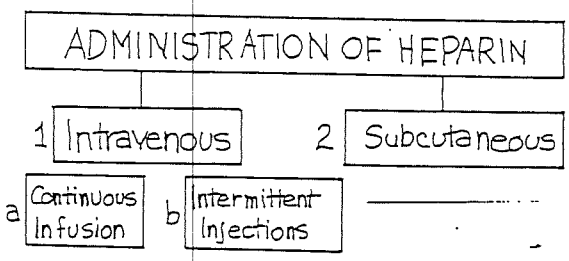
Heparin does not directly inhibit the action of thrombin on purified fibrinogen but it requires the presence of antithrombin III for its anticoagulant effect. Heparin is ineffective in the absence of antithrombin III. Antithrombin by itself irreversibly combines with a number of activated clotting factors and slowly and progressively inactivates them. Heparin and antithrombin III together result in an almost immediate inactivation.



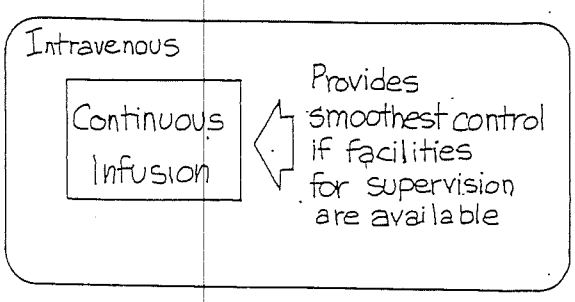
This is a diagram of the intrinsic clotting system, the integrity of which is measured by the partial thromboplastin time. Heparin acts as an anticoagulant in conjunction with antithrombin III to accelerate the inactivation of Factors XII, XI, IX, X and thrombin.



As we saw in Chapter 10, heparin acts by binding to antithrombin III, instituting a conformational change, which markedly accelerates the rate of inactivation of a number of activated coagulation factors by antithrombin III. Heparin is released once the coagulation enzyme-antithrombin III complex is formed, and can, therefore, be reutilized to inactivate other activated coagulation factors. Only about 1/3 of the heparin used clinically binds to antithrombin III and it is this high affinity heparin fraction which is responsible for the anticoagulant activity of heparin. This fraction has a unique saccharide sequence which is responsible for its binding to antithrombin III and therefore for its anticoagulant and antithrombotic properties.

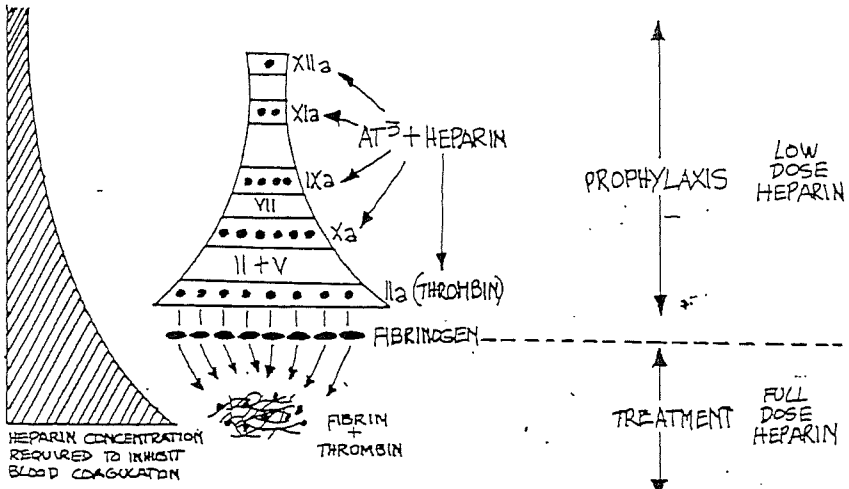


When used to treat venous thrombosis or pulmonary embolism, heparin can be administered by intravenous injection either as a continuous infusion or as intermittent injection or by the subcutaneous route. It should not be given by intramuscular injection because of the danger of local hemorrhage.



All three methods of administration are acceptable but there is evidence that hemorrhagic complications are less when the continuous intravenous route is used rather than the intermittent intravenous route.

Heparin Prophylaxis — Inhibition of Blood Coagulation by Heparin

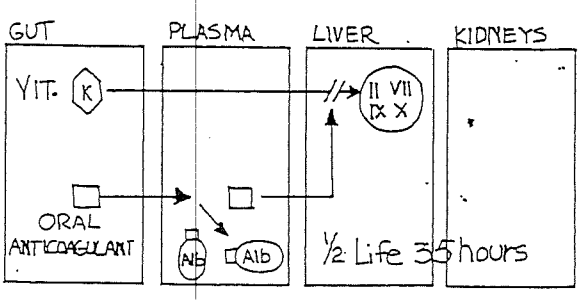


Low doses of heparin which are ineffective in the treatment of established venous thrombosis are very effective in preventing venous thrombosis. When used prophylactically, heparin is usually given subcutaneously in a dose of 5,000 units 8 hourly or 12 hourly. The prophylactic effect of low doses of heparin is related to the well-recognized phenomenon that the blood coagulation sequence is amplified with each successive step in the activation process.

Therefore, much less heparin is required to inhibit the early stages of activation of blood coagulation than is required to inhibit thrombin once it has formed. In addition, when a thrombus is formed, thrombin is adsorbed onto the fibrin and requires higher concentrations of heparin to inhibit it than it would in a fluid phase. For these reasons, higher concentrations of heparin are required to arrest the growth of an established thrombus than are required to prevent its formation.

Vitamin K Antagonists

(ORAL ANTICOAGULANTS)
- Coumarin Derivatives
- Indanedione Derivatives

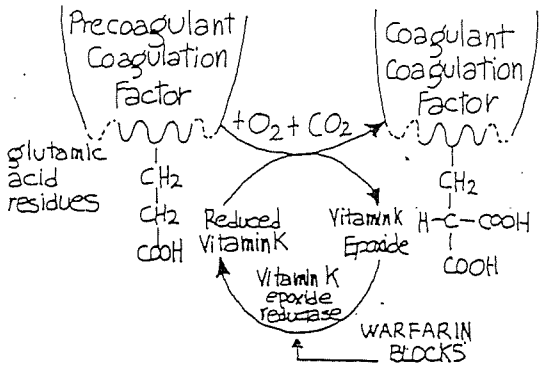


FACTOR	½ LIFE (HRS.)
VII	4-5
V, VIII	15
IX	25
X, XI, XII	40
II Prothrombin	60
I Fibrinogen, XIII	90
Platelets	100-120

The vitamin K antagonists in clinical use are derived from coumarin.

Unlike heparin, they are well absorbed from the gastrointestinal tract and are usually administered orally. These oral anticoagulants are low molecular weight, organic compounds which have similar structure to vitamin K. They are bound in the circulation to albumin and only the small unbound fraction (1-10%) of these drugs is pharmacologically active. Of the various vitamin K antagonists available for clinical use, warfarin is the most useful because of its predictable clinical effects including onset of action and duration of effect. The mean half-life of a single dose is 35 hours.

The anticoagulant effects of warfarin is delayed until the normal clotting factors are cleared from the circulation, approximately 48 hours.



The function of vitamin K is to promote carboxylation of glutamic acid residues on the coagulation proteins Factors II, VII, IX and X. The carboxylation of these coagulation proteins increases their affinity for calcium and, hence, facilitates their binding to platelet phospholipid. The normal activation of these vitamin K related clotting proteins involves the participation of platelet phospholipid, calcium ions, an accessory protein and a proteolytic enzyme. The fundamental abnormality produced by treatment with oral anticoagulants is an inability of the vitamin K dependent clotting factors to bind to phospholipid through ionic calcium bridges due to an absence of gamma carboxylated glutamic acid residues. The interaction between vitamin K and the vitamin K antagonists is complex. Coumarin anticoagulants function by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide. This metabolic block interferes with the vitamin K dependent gamma carboxylation of glutamic acid residues on the precursor protein.

USE OF ORAL ANTICOAGULANTS

- Treatment (after heparin)
- Prophylaxis

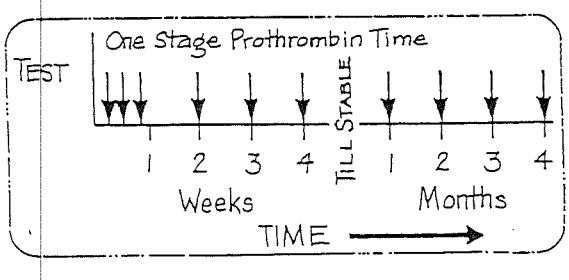
Oral anticoagulants can be used in either the prevention or treatment of venous thromboembolism. Their use in prophylaxis has been largely superceded by low doses of heparin, by intermittent pneumatic compression, and by dextran. Oral anticoagulants are often used subsequent to heparin therapy for the treatment of acute venous thromboembolism.

Treatment with oral anticoagulants is usually commenced after the patient has received heparin for 5 or 6 days. The two drugs are given in combination for 4 - 5 days before heparin therapy is stopped and oral anticoagulants continued for a variable period of time.

MONITORING

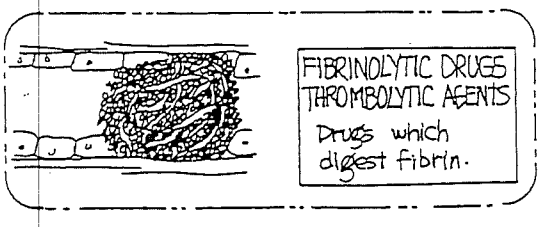
Aim to keep one-stage Prothrombin time at 2x normal

The test most commonly used to measure the effects of oral anticoagulants on blood coagulation is the one-stage prothrombin time (PT) (also known as the Quick prothrombin time). The prothrombin time is sensitive to reduced activity of Factors II, VII and X but is insensitive to reduced activity of Factor IX.

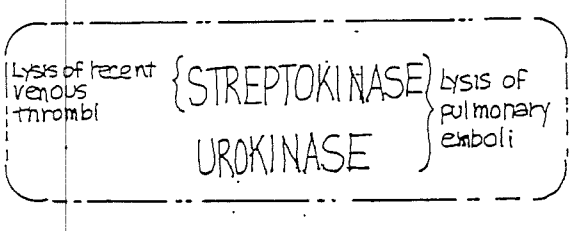


This test is performed three times in the first week after commencing the oral anticoagulants, and then weekly until the maintenance dose is stable. Thereafter it is performed at biweekly or monthly intervals.

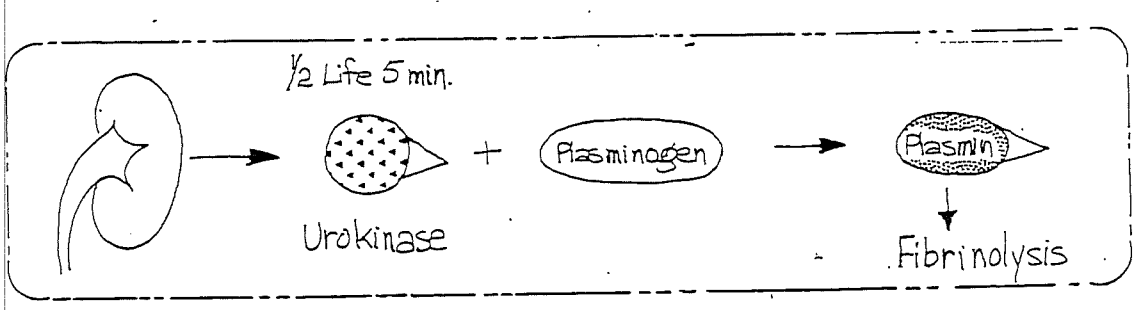
Fibrinolytic Agents



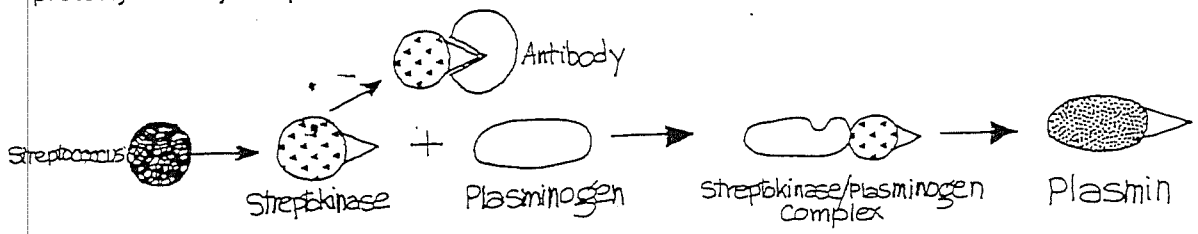
The objective of thrombolytic therapy is to induce dissolution of thrombi by digesting their fibrin framework.



The thrombolytic agents in clincial use are the plasminogen activators urokinase and streptokinase. Both are administered by intravenous injection.

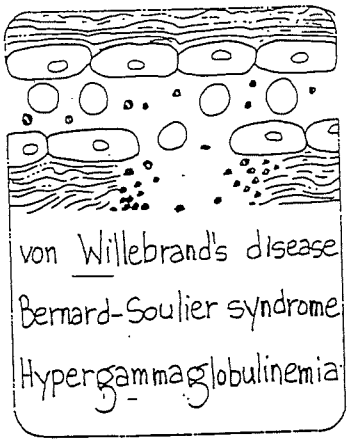


Urokinase is present in human urine and is produced by renal cells. It is not antigenic in man and, therefore, does not stimulate the formation of neutralizing antibodies. It cleaves plasminogen converting it into the proteolytic enzyme plasmin. It is cleared rapidly with more than half of the injected dose disappearing within 5 minutes and the remainder disappearing more gradually with an in vivo half-life of the plasminogen activator of approximately 10-15 minutes.



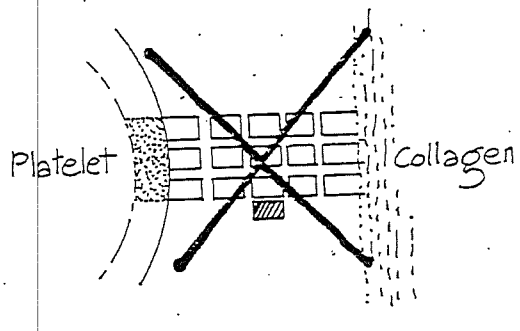
Streptokinase is a product of beta hemolytic streptococci. In contrast to urokinase, streptokinase activates plasminogen indirectly. The drug first forms an equimolar stoichiometric complex with plasminogen. This produces a conformational change in the complexed plasminogen molecule which in turn converts non-complexed plasminogen to plasmin. Streptokinase is antigenic in man and stimulates the production of neutralizing antibodies. Antibodies to streptokinase, the result of prior streptococcal infections, are present in most persons in titres which vary considerably between individuals. These antibodies combine with streptokinase and form inactive antigen/antibody complexes. The infusion of streptokinase may stimulate a rapid rise of antistreptokinase antibody levels over a period of 4 - 10 days which limits the length of time that a thrombolytic state can be sustained with streptokinase.

Failure of Platelets to Adhere



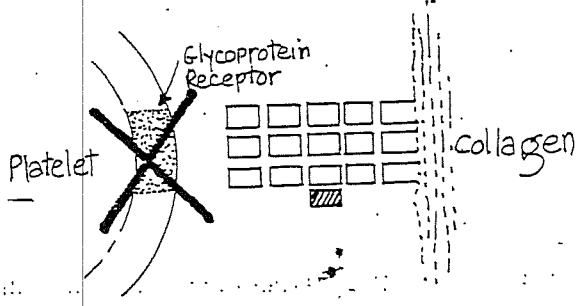
Failure of platelets to adhere to subendothelial connective tissue is seen in von Willebrand's disease, the Bernard-Soulier syndrome, and when there is hypergammaglobulinemia.

von Willebrand's disease



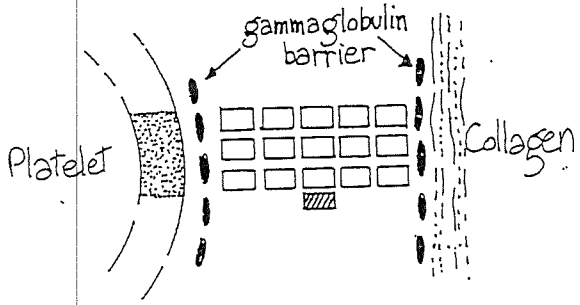
In von Willebrand's disease, there is either a quantitative or qualitative abnormality of the von Willebrand portion of the Factor VIII molecule such that effective bridging between the platelets and subendothelial collagen is not achieved. Strictly this is not a disorder of the platelets themselves, but abnormality of the von Willebrand factor prevents platelets from fulfilling their role in the hemostatic process.

Bernard-Soulier syndrome



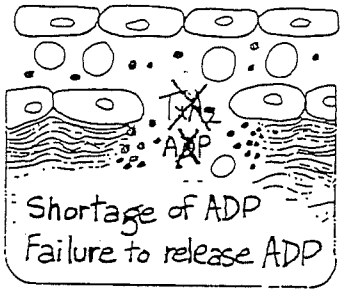
In the Bernard-Soulier syndrome on the other hand there is an intrinsic platelet membrane abnormality associated with the lack of one of the membrane glycoproteins which is a receptor for the von Willebrand portion of the Factor VIII molecule, and for this reason platelets do not adhere to subendothelium. Patients with Bernard-Soulier syndrome have giant platelets which are also relatively ineffective in supporting blood coagulation.

Hypergammaglobulinemia

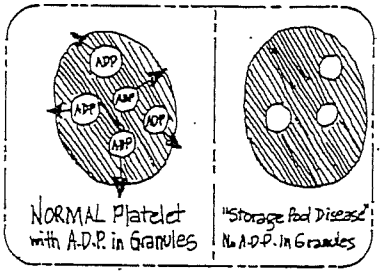


Abnormalities of platelet adhesion to subendothelium have also been described in hypergammaglobulinemia, possibly because the gammaglobulin coats the platelets and interferes with their adhesion to subendothelial structures.

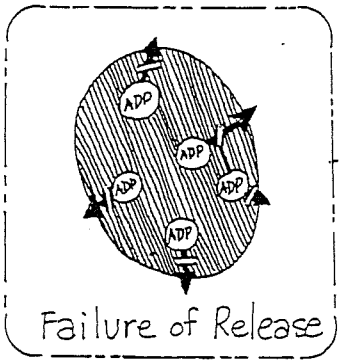
Failure to Release ADP and TxA2



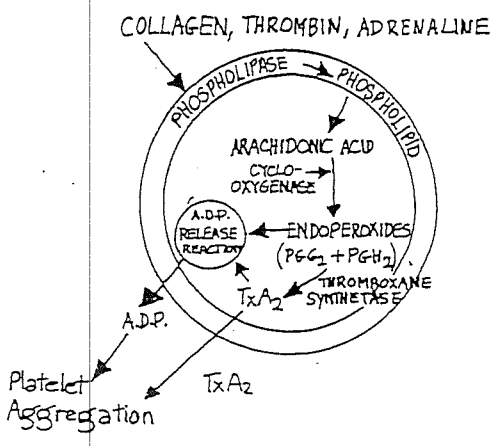
There are two types of release defects. One is associated with reduced levels of adenosine diphosphate in the platelet dense granules and is called storage pool disease. The other is associated with an abnormality of the platelet release mechanism.



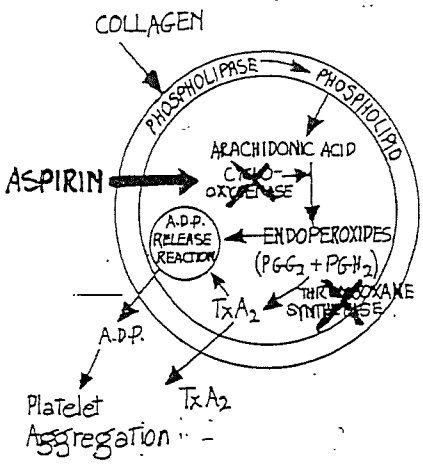
Patients with storage pool disease have a demonstrable decrease in the number of ADP storage granules (dense granules) and show abnormal aggregation with collagen, thrombin and adrenaline. There is a family history of the defect, the bleeding time is prolonged, and the bleeding manifestations vary from mild to severe.



The defect in the release mechanism is less well-defined. These patients have normal amounts of ADP in their granules but do not release the ADP in normal amounts in response to collagen or adrenaline. In many instances this is caused by an abnormality of the prostaglandin synthetic pathway, which leads to defective production of TxA_2, which is a mediator of the platelet release reaction. Platelet prostaglandins are important mediators of platelet function.



When platelets are exposed to various stimuli including collagen, thrombin and adrenaline, the platelet surface enzyme phospholipase A_2 is activated and this in turn cleaves arachidonic acid from membrane phospholipid. The arachidonic acid is then oxidized by cyclo-oxygenase to the endoperoxides PGG_2 and PGH_2. PGH_2 is converted by thromboxane synthetase to thromboxane A_2, which stimulates platelets to release adenosine diphosphate and also causes platelet aggregation independently of ADP release.



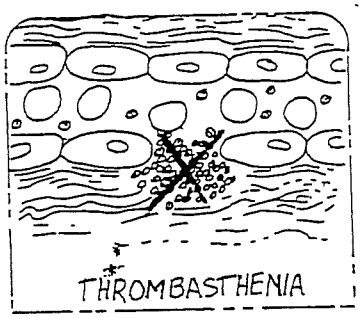
Abnormalities of the prostaglandin synthetic pathway can either be at the level of the enzyme cyclo-oxygenase which converts arachidonic acid into the endoperoxides PGG_2 and PGH_2, or at the level of the enzyme thromboxane synthetase which converts PGH_2 to thromboxane A_2. Since this is one of the mediators of ADP release failure of synthesis results in defective ADP release. This type of abnormality is most commonly seen in patients who have ingested aspirin but is also seen in patients with myeloproliferative disorders, following cardiac bypass surgery in which a pump oxygenator has been used, and as an inherited primary platelet function defect.

Aspirin causes:

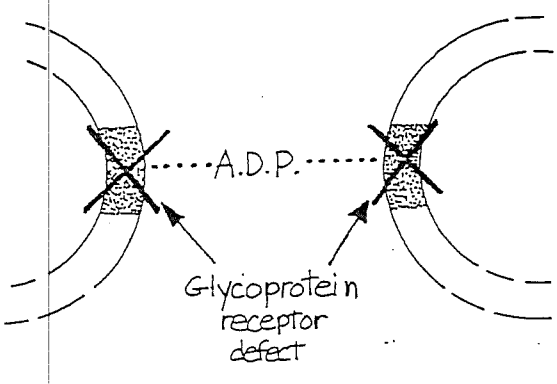
Irreversible acetylation of enzyme Cyclo-oxygenase

The effect of aspirin on platelets is of considerable interest because of its possible therapeutic applications. Although aspirin is cleared from the blood stream rapidly (within 30 minutes of ingestion), the platelet function defect produced by aspirin lasts for up to 4 - 7 days. This is because aspirin irreversibly acetylates the enzyme cyclo-oxygenase and so inhibits platelet function for the life-span of the circulating platelets.

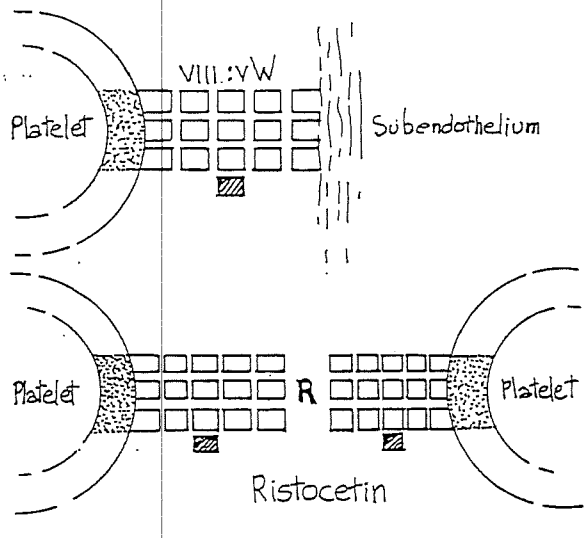
Failure to Aggregate



Failure of platelets to aggregate with ADP is seen in one well-defined but rare primary disorder known as thrombasthenia.



Thrombasthenia is associated with the lack of a specific glycoprotein receptor on the platelet surface which is believed to be responsible for the interaction of ADP with platelets. Patients with thrombasthenia may have a severe bleeding abnormality with bruising, petechiae and purpura.



The missing plasma factor responsible for the platelet function defect is the Factor VIII von Willebrand polymer which is required for the adhesion of platelets to subendothelium, and for the aggregation of platelets with ristocetin.

- Variable.

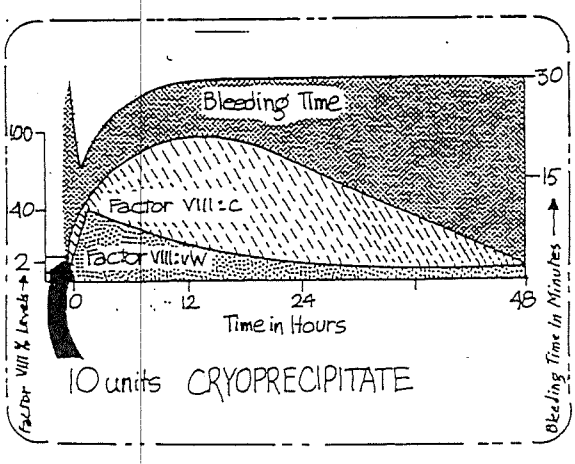
MILD ↓ SEVERE.

The severity of the disorder varies considerably even within a given family and usually bears a close relationship both to the Factor VIII level and the bleeding time. Bleeding is usually mild and of the skin and mucous membrane variety, but occasionally catastrophic and even fatal.

Treatment

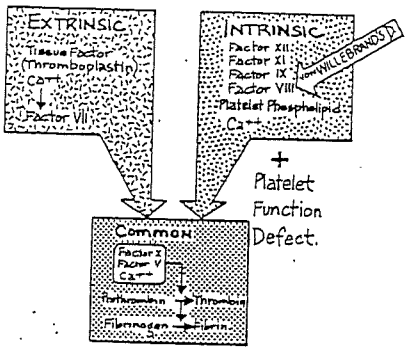
- Controlled with fresh Plasma. or cryoprecipitate

Fresh plasma or cryoprecipitate is often effective in controlling bleeding. It produces a rise in Factor VIII:vW which is short-lived and a more sustained rise in Factor VIII:c, possibly because the Factor VIII:vW induces synthesis of Factor VIII:c in patients with von Willebrand's disease.

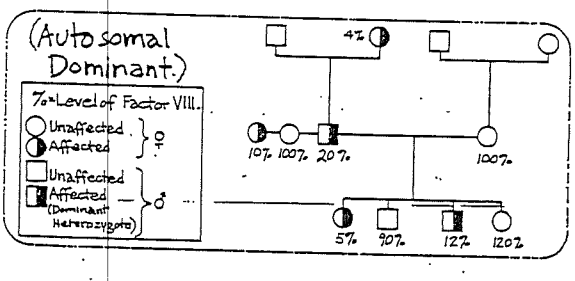


Following transfusion there is an immediate rise in Factor VIII (both :vW and :c) equivalent to the amount infused. This is followed by a slow rise in Factor VIII:c which reaches a maximum in 6 - 12 hours, and falls to pre-treatment levels in 48 hours. The bleeding time is also sometimes shortened following transfusion of fresh plasma, but the effect only lasts for up to 3 hours after infusion and reflects the level of Factor VIII:vW.

von Willebrand's Disease



von Willebrand's Disease is a hereditary disorder, which is due to a deficiency of Factor VIII and an associated platelet function defect.



It is transmitted as an autosomal dominant trait. Thus, the disorder is transmitted from parent to child irrespective of their sex, as shown in the diagram.

Prolonged Bleeding Time.

Low Factor VIII.

Defective Platelet Function.

It is characterized by a prolonged bleeding time, a low Factor VIII:c level and defective platelet function which is caused either by a lack of, or an abnormality of, the von Willebrand portion of the Factor VIII molecule. This platelet function defect can be demonstrated by measuring platelet aggregation induced by the antibiotic ristocetin. The platelet aggregating effect of ristocetin was a side effect which precluded its therapeutic use as an antibiotic.