MEDICAL GRAND ROUNDS

Parkland Memorial Hospital
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THE CLINICAL AND LABORATORY APPROACH TO THE BLEEDING PATIENT

CASE #1: [redacted]

This 4-year-old [redacted] male was essentially well until six days prior to his admission in [redacted] 1963, at which time, while running, he fell and developed a minor abrasion of his right upper lip from which bleeding continued with increasing intensity over the six days prior to admission. He was treated with ice packs and topical gel-foam in the emergency room without effecting hemostasis. The patient was otherwise asymptomatic and doing well.

Pertinent past history revealed that at age 3 he had prolonged bleeding following a cut finger that lasted for two to three days in spite of pressure dressings. Six months prior to his admission he had a superficial scalp laceration which required suturing on three occasions. This boy was otherwise asymptomatic; he had not had any other bleeding. The child had been born at Parkland Hospital and had had a circumcision without difficulty.

Physical examination was within normal limits except for a superficial bleeding laceration of the right upper lip.

Our laboratory studies revealed a hemoglobin of 4.9 gm.% with a hematocrit of 17 vol.%, white count 12,000 with normal differential. Platelets were 110,000 and reticulocytes 5.2%. The sickle cell prep was negative and the peripheral smear demonstrated a normochromic, normocytic anemia. The Duke bleeding time was 4.5 minutes, the Lee-White clotting time 6.5 minutes. The prothrombin time was 12 seconds with a control of 12 seconds. The partial thromboplastin test was 195 seconds (normal 60-90 sec.). A prothrombin consumption test was 9 seconds (normal +21 sec.). The thromboplastin generation test demonstrated prolongation of clotting that was corrected by fresh plasma and $Al(OH)_3$-adsorbed plasma.

Diagnosis: Hemophilia - Factor VIII deficiency type (classical AHG deficiency)

Subsequent to this, the patient was treated with fresh frozen plasma for a total of 5 days. All bleeding stopped by the second day of therapy and then with decreased amounts of fresh frozen plasma the ooze began again on the third hospital day, requiring re-institution of more intensive therapy. The initial therapy consisted of 5 ml./lb. followed by 3 ml./lb. q6h. One-half unit of fresh whole blood was also administered to raise the hemoglobin.

The patient's convalescence was unremarkable and he has remained asymptomatic to date.

CASE #2: [redacted]

This 21-year-old white male was in good health until an auto accident two months prior to his admission to this hospital. At that time he sustained a fracture of the left maxillary sinus with multiple facial lacerations. He was hospitalized in his home community, where he bled considerably and required 5 units of whole blood. He was finally referred to another medical center for evaluation of his bleeding state. He was evaluated over a two-week period, during which time he continued to have a slight ooze from his maxillary sinus. A diagnosis of classical hemophilia was made and the patient was returned to his family physician with the directions to avoid any surgical interference and to treat the lesion on a prn basis with fresh plasma.

The patient's past history was completely negative, as was his family history. He had never had joint problems or joint bleeding, gingival bleeding, nosebleeds or increased bleeding from minor lacerations. He had never had any previous tooth extractions or surgical procedures.

The patient was referred to this center because, during the four weeks after being seen at the other hospital, he had progressive enlargement of his maxillary sinus, progressive discoloration of the anterior part of his face and a large massive bulge over the left maxillary sinus.

Physical examination revealed a large mass over the anterior aspect of the left maxillary sinus that was somewhat blue. There was a large perforation along the left upper gingival border with a bleeding fungating mass protruding into the oral cavity and constantly oozing blood. Multiple nasal polyps were also present. The remainder of the exam was within normal limits.

Our laboratory studies revealed a hemoglobin of 9.4 gm.% and a hematocrit of 30 vol.%. Pertinent clotting studies revealed a platelet count of 310,000, a bleeding time by the Duke method of 3 minutes, and a whole blood clotting time of 8 min. 30 sec. His partial thromboplastin time was 60 sec. and 70 sec. His prothrombin time was 14 sec. with a control of 12 sec., yielding 80%, and a repeat prothrombin time was 12 sec., or 100%. The recalcified clotting time was 87 sec. The prothrombin consumption test was 27 and 33 sec. Clot retraction was good at one hour. In light of the fact that a previous diagnosis of hemophilia was made, a thromboplastin generation time was carried out and revealed completely normal thromboplastin generation.

Because we could not document an abnormal coagulation defect, and in light of the persistent bleeding and progressive disfiguration of his face, it was elected to explore the maxillary sinus. Fresh frozen plasma was available in the operating room. At the time of exploration, our oral surgeons identified a transected free bleeding vessel in the left maxillary sinus. Hemostasis was achieved by suture and a plastic repair carried out. The patient made a completely uneventful post-operative recovery and has continued to do well. A re-check on his coagulation studies two months post-operatively failed to demonstrate any abnormal clotting defect.

TABLE I

DISTINCTION BETWEEN CLOTTING AND CAPILLARY DEFECTS

FEATURE	CLOTTING DEFECT	CAPILLARY DEFECT
Bleeding from small superficial cuts	Often no excessive bleeding	Bleeding often profuse
Time of onset of bleeding	Often delayed 1-3 hours	Immediate
Effect of pressure on bleeding	Restarts after release	Often permanent stasis
Common sites affected	Joints, muscles and subcutaneous tissue (large bruises) Any form of internal hemorrhage is common	GI bleeding, epistaxis and menorrhagia most common
Symptoms in mildly affected case	Large hematoma following injury. May yield dangerous bleeding after trauma	Bleeding as above. Less dangerous
Inheritance	Most are sex-linked recessive	Most are dominant
Lab tests	Clotting time (or PTT) Prothrombin consumption T.G.T. assay for individual factors	Bleeding time Tourniquet test Platelet count

After Biggs and MacFarlane

Table II

NOMENCLATURE FOR BLOOD COAGULATION FACTORS

FACTOR	SYNONYMS
I	Fibrinogen
II	Prothrombin
III	Thromboplastin (tissue)
IV	Calcium
V	Labile factor; Proaccelerin; Accelerator globulin
VI	
VII	Stable factor; Proconvertin; Serum prothrombin conversion accelerator (SPCA); Autoprothrombin I
VIII	Antihemophilic factor (AHF); Antihemophilic globulin (AHG); Platelet cofactor I
IX	Christmas factor; Plasma thromboplastin component (PTC); Platelet cofactor II; Antihemophilic factor B; Autoprothrombin II
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent (PTA)
XII	Hageman factor

THE COAGULATION MECHANISM (1963)

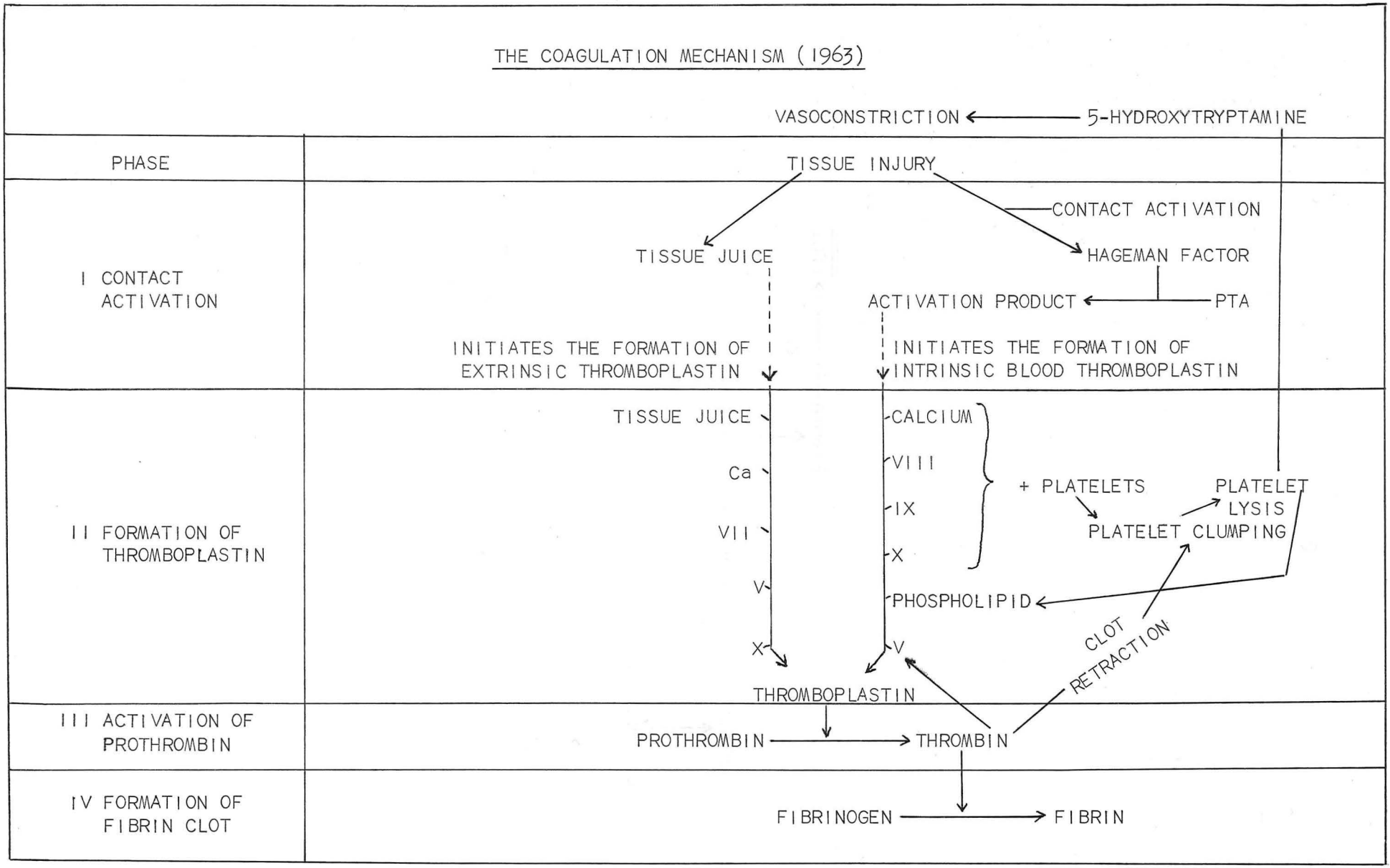
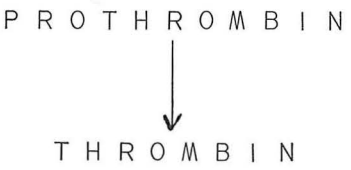
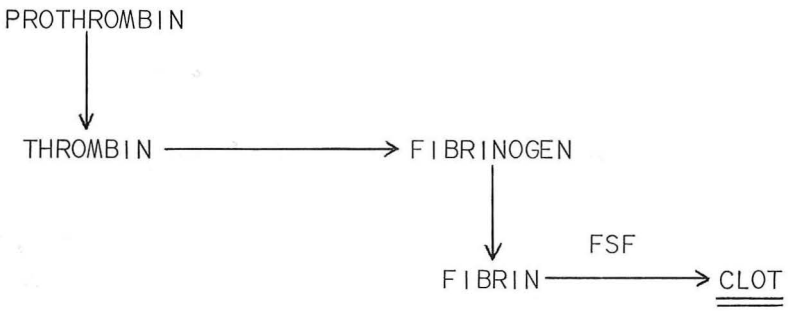
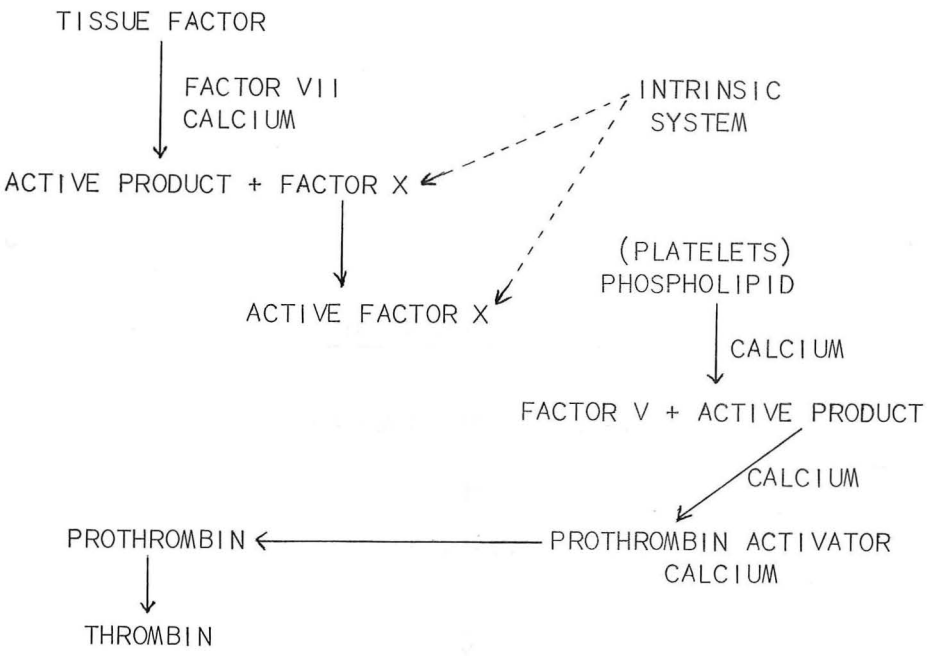


TABLE III

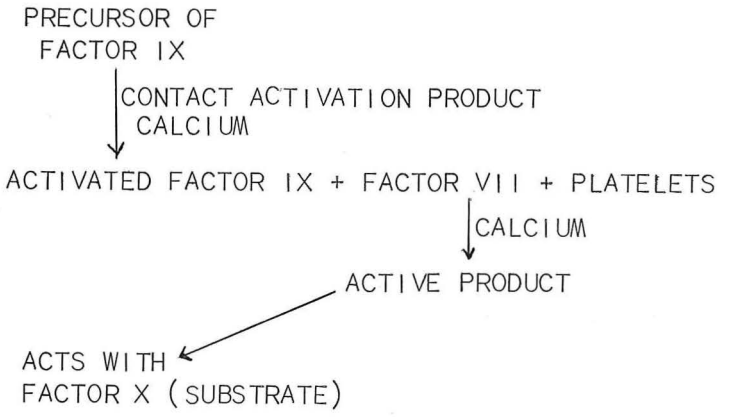

PROTHROMBIN
THROMBIN


PROTHROMBIN
THROMBIN
FIBRINOGEN
FSF
FIBRIN
CLOT

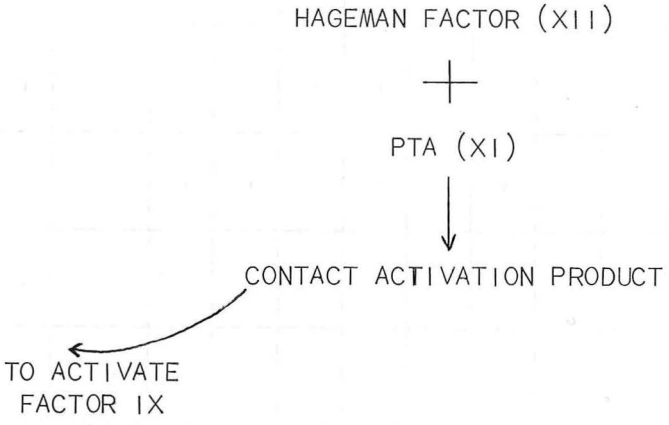
EXTRINSIC PROTHROMBIN ACTIVATION



INTRINSIC PROTHROMBIN ACTIVATION



THE CONTACT SYSTEM



	THROMBOCYTOPENIA	THROMBASTHENIA	CLASSICAL HEMOPHILIA (A)	CHRISTMAS DISEASE (HEMOPHILIA B)	VASCULAR HEMOPHILIA	VASCULAR CHRISTMAS DISEASE	CIRCULATING ANTICOAGULANT	AFIBRINOGENEMIA	FACTOR V DEFIC.	FACTOR VII DEFICIENCY	FACTOR X DEFIC.	PROTHROMBIN DEFICIENCY	PTA DEFICIENCY	HAGEMAN FACTOR DEFICIENCY
PLATELET COUNT	+	-	-	-	-	-	-	-	-	-	-	-	-	-
PLATELET MORPHOLOGY	±	±	-	-	-	-	-	-	-	-	-	-	-	-
BLEEDING TIME	+	±	-	-	+	+	-	-	-	-	-	-	-	-
TOURNIQUET TEST	+	±	-	-	±	±	-	-	-	-	-	-	-	-
CLOT RETRACTION	+	±	-	-	-	-	-	-	-	-	-	-	-	-
CLOTTING TIME-Glass	-	-	+	+	±	±	++	Δ	+	-	+	-	±	++
CLOTTING TIME-Silicone	-	-	++	++	+	+	Δ	Δ	++	-	+	±	±	±
PROTHROM. CONSUMPTION	+	±	+	+	+	+	+	-	+	-	+	-	+	+
1-STAGE PRO. TIME	-	-	-	-	-	-	±	Δ	+	+	+	+	-	-
2-STAGE PRO. ASSAY	-	-	-	-	-	-	-	-	-	-	-	+	-	-
STYPVEN TIME	-	-	-	-	-	-	-	Δ	+	-	+	+	-	-
THROMBIN TIME	-	-	-	-	-	-	-	Δ	-	-	-	-	-	-
TGT - PATIENT'S $Al(OH)_3$ PLASMA	-	-	+	-	+	-	+	-	+	-	-	-	+	-
TGT - PATIENT'S SERUM	-	-	-	+	-	+	+	-	-	-	+	-	+	-
TGT - NORMAL + 10% PATIENT PLASMA	-	-	-	-	-	-	+	-	-	-	-	-	-	-
TGT - PLATELETS	-	±	-	-	-	-	-	-	-	-	-	-	-	-

+ Normal; - Abnormal; ± May be normal or abnormal; Δ Blood incoagulable

LABORATORY INVESTIGATION OF A BLEEDING DIATHESIS

I. SCREENING

1. Platelet count and morphology

2. Bleeding time

3. Tourniquet test

4. Clot retraction

5. Clotting time

6. Prothrombin consumption

7. One-stage prothrombin time

Interpretation:

If all 7 normal - no identifiable abnormality
If 6) abnormal - See II - Investigation of Abnormal Prothrombin Consumption
If 7) abnormal - See III - Investigation of Abnormal One-State Prothrombin Time

II. INVESTIGATION OF AN ABNORMAL PROTHROMBIN CONSUMPTION

Anything that interferes with the formation of blood thromboplastin (deficiency of an essential factor or the presence of an inhibitor) results in defective prothrombin consumption.

The diseases resulting in abnormal prothrombin consumption and the clinical features and laboratory tests used to differentiate them are listed below:

1. Platelet defects

   a. Thrombocytopenia - a platelet count below 75,000 per mm^3 (direct count) may result in abnormal prothrombin consumption. Other tests of platelet function (bleeding time, tourniquet test, clot retraction) are also abnormal.

   b. Thrombasthenia - the platelet count is over 100,000 per mm^3, but they are qualitatively defective. If the platelets are deficient in the phospholipid required for thromboplastin formation they show abnormal morphological features (large, 5-7μ, few granules, no clumping) and function poorly in the TGT. Other tests of platelet function may or may not be abnormal.

2. Deficiency of a plasma factor or circulating anticoagulant

   a. If the 1-stage prothrombin time is normal, the defect may be a deficiency of Factor VIII, IX, PTA, Hageman or a circulating anticoagulant.

To identify the defect, the TGT is done, and the following mixtures are tested:

Mixture	$Al(OH)_3$-adsorbed plasma	Serum	Indications
A.	Normal	Normal	Routine
B.	Patient	Patient	
C.	Patient	Normal	
D.	Normal	Patient	
E.	Normal + 10% patient's plasma	Normal	If circulating anticoagulant suspected

The differentiating features of the diseases in this group are:

(i) Factor VIII Deficiency

Classical Hemophilia - Mixtures B and C abnormal in TGT. Bleeding time normal. Usually a male with a family history suggesting a sex-linked recessive mode of inheritance.

Vascular Hemophilia - Mixtures B and C abnormal in TGT. Bleeding time prolonged. May be a male or female, family history suggesting dominant mode of inheritance.

(ii) Factor IX Deficiency

Christmas Disease - Mixtures B and D abnormal in TGT. Bleeding time normal. Usually a male, with family history suggesting sex-linked recessive mode of inheritance.

Vascular Christmas Disease - Mixtures B and D abnormal in TGT. Bleeding time prolonged. May be a male or female, with family history suggesting a dominant form of inheritance.

(iii) Circulating Anticoagulant - Mixtures B, C, D, and E abnormal in TGT. This is the only coagulation defect in which the addition of 10% of the patient's plasma to normal ingredients in a TGT interferes with thromboplastin formation.

(iv) PTA Deficiency - Mixture B abnormal, C and D usually normal, because PTA is present in the normal $Al(OH)_3$-plasma and serum, and this corrects the defect.

(v) Hageman Trait - The same pattern of results with TGT as for PTA. A deficiency of the Hageman Factor is differentiated from PTA on the basis of the following:

	Hageman	PTA
History	No bleeding tendency	Mild bleeding after trauma
Clotting	Very prolonged in glass tubes	Normal or slightly long in glass tubes
	Normal or only slightly prolonged in siliconed tubes	Normal or slightly long in siliconed tubes
Other	Correction of defect by addition of blood from patient with PTA deficiency	Correction of defect by addition of blood from patient with known Hageman Trait

b. If the one-stage prothrombin time is prolonged, the cause of the abnormal prothrombin consumption may be a deficiency of Factor V or X. The differentiation of these diseases is discussed in the next section.

II. INVESTIGATION OF A PROLONGED ONE-STAGE PROTHROMBIN TIME

A prolonged one-stage prothrombin time may be due to a deficiency of one of the factors that reacts with tissue thromboplastin (Factor V, VII or X), an inhibitor of this reaction (e.g., heparin), or a deficiency of prothrombin or fibrinogen.

1. The clinical history is often very helpful. Check especially for the following:

   a. The possible previous use of anticoagulants such as heparin or protamine

   b. Ingestion of one of the coumarin group of drugs, or ingestion of rat poisons containing warfarin. The coumarin drugs cause a combined deficiency of Factors VII, IX, X and prothrombin.

   c. The possibility of Vitamin K deficiency, e.g., associated with steatorrhea, prolonged antibiotic therapy or in the newborn. The coagulation defect of Vitamin K deficiency is a combined deficiency of Factors VII, IX, X and prothrombin.

   d. Marked hepatic insufficiency also causes a combined deficiency of Factors VII, IX, X and prothrombin.

TESTS OF COAGULATION WORK-UP

Ivy Bleeding Time:

Apply blood pressure cuff to arm and inflate to 40 mm.Hg and keep pressure constant. Incise forearm with commercial lancet (disposable). Touch (scoop) blood every 30 seconds until bleeding has stopped.

Normal 3-5 minutes

Qualitative Fibrinogen Assay (Page)

Useful operating room technique:

1. Maintain in refrigerator clean Pyrex tubes (13 x 100 mm) scored at 1 ml. mark to which is added 0.1 ml. of TOPICAL THROMBIN (1000 N.I.H. units/ml.).

2. Add venous blood to 1 ml. mark

Normal clots in 18 seconds

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