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Mother of patient Craig

Why are we Discussing the Importance of Diagnostic Tests at an AACC Meeting ?

1. Most lab directors rarely leave the lab to see patients undergoing evaluation – seeing the patient shows the importance first hand

2. Automation and technically complex methodologies are re-focusing many lab directors more on non-clinical issues and the automation processes

3. There is a nationally recognized need to build communications between lab directors & treating physicians about which tests to order and interpretation of the test results

4. Errors can have tragic consequences

Background Information

Can a bruised or bleeding child suffer a minor unintentional injury and be mistakenly identified as an abused child ?

DIAGNOSIS OF CHILD ABUSE

- Many child abuse cases are brought to attention by bruises or other bleeding symptoms
- Overdiagnosis of child abuse is clearly not as large a problem as the underreporting of child abuse
- However, any incorrect conclusion is catastrophic to children and parents.

DIAGNOSIS OF CHILD ABUSE

- **The medical literature contains many case reports in which child abuse was overdiagnosed in children with hemorrhagic coagulopathies**
- **A major concern is that overdiagnosis may be more common than is currently believed because of the high prevalence of von Willebrand's disease, which may be on the order of 1% in the general population**

DIAGNOSIS OF CHILD ABUSE

- **In 1996, an estimated 3,126,000 child abuse cases were reported to Child Protective Services (CPS) agencies, approximately 31,260 (1%) of which may have a coagulopathy such as von Willebrand's disease**
- **Thus, there is an absolute need to rule out a hemorrhagic coagulopathy with appropriate testing in children who are allegedly victims of child abuse**

SYMPTOMS THAT SUGGEST CHILD ABUSE AND NONINFLICTED ENTITIES THAT MIGHT CAUSE THEM

Physical Symptom	Possible Noninflicted Cause
Burns and Scalds	Impetigo
	Dermatitis
	Fixed drug eruption
	Mechanical abrasion
	Accidental exposure to commercial grade vinegar

Am J Clin Pathol 2005;123(Suppl 1):S119-S124

SYMPTOMS THAT SUGGEST CHILD ABUSE AND NONINFLICTED ENTITIES THAT MIGHT CAUSE THEM

Physical Symptom	Possible Noninflicted Cause
Bruises	von Willebrand disease
	Hemophilia A and B
	Idiopathic thrombocytopenic purpura
	Thrombocytopenia with lymphoblastic leukemia
	Vitamin K deficiency
	Purpura fulminans
	Meningitis with disseminated intravascular coagulation
	Hemorrhagic disease of the newborn
	Henoch-Schönlein purpura
	Ruptured subarachnoid vascular formation

Am J Clin Pathol 2005;123(Suppl 1):S119-S124

COMPARISON SLIDES OF CHILD ABUSE VS. COAGULOPATHY – Which case is abuse and which case is a child with a bleeding disorder who experienced a minor injury?

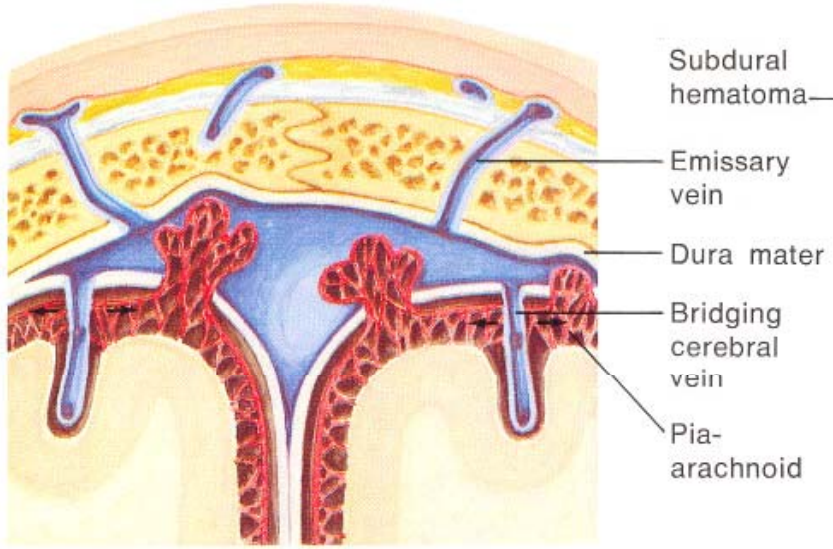
Major Findings with

Shaken Baby Syndrome

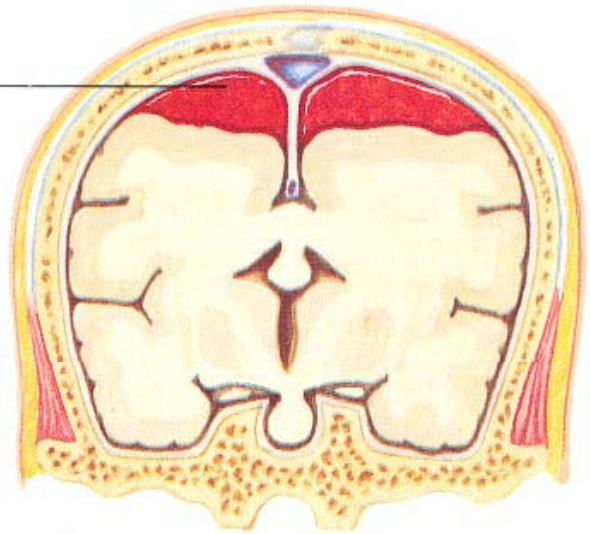
FINDINGS ON EXAM

- **Bilateral Retinal Hemorrhages**
- **Subdural Hematoma**
- **No Bruises Anywhere**

HEAD INJURIES



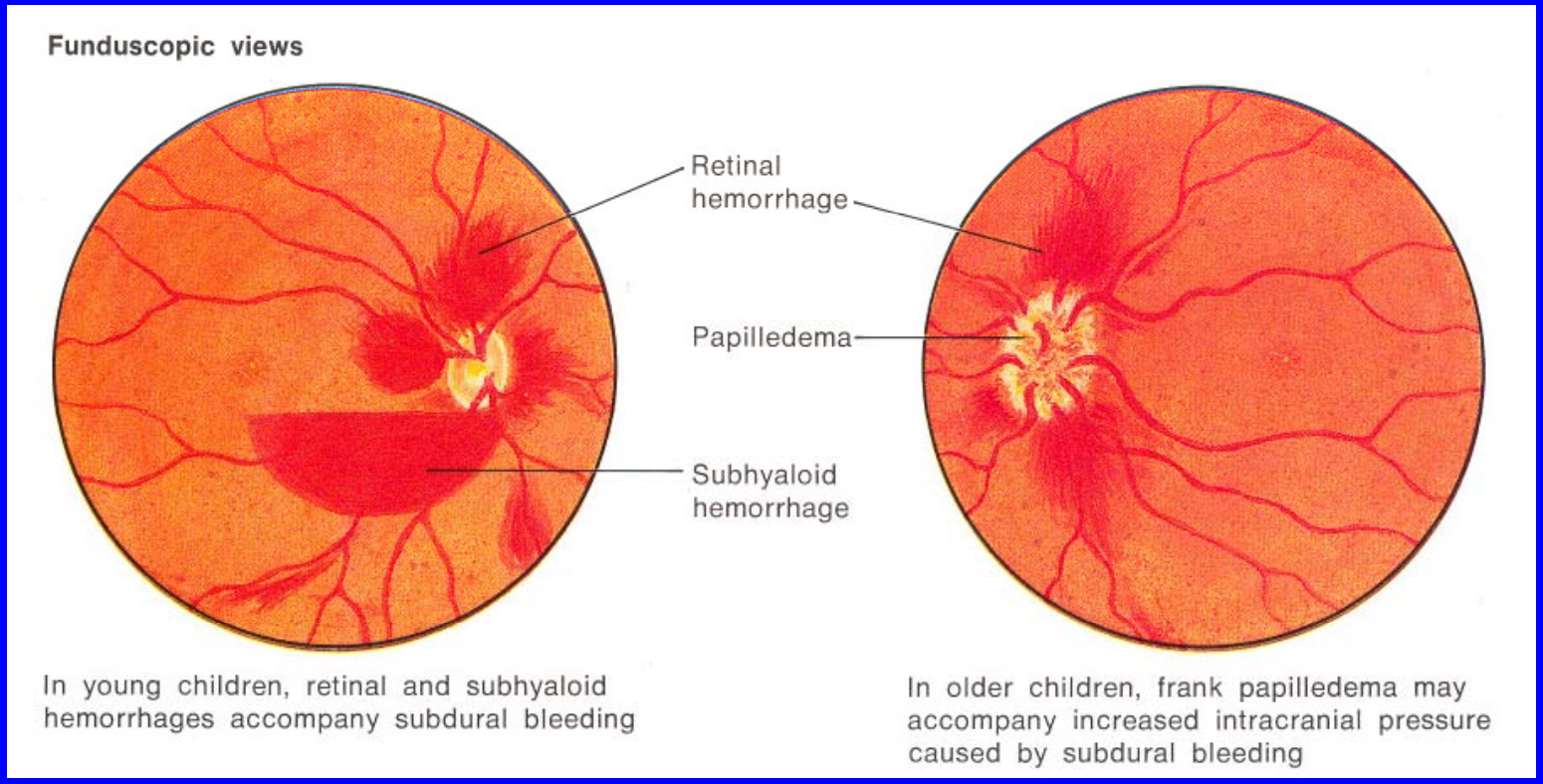
In children, bridging cerebral veins are poorly supported as they pass through subdural space. Violent shaking may cause vulnerable veins to tear, creating subdural hematoma



Bilateral subdural hematomas, with or without evidence of skull fracture, can occur from head injuries. Seizure or coma may be first clinical sign

Clinical Symposia. 1977; 29(5):16-23

HEAD INJURIES



Clinical Symposia. 1977; 29(5):16-23

Brief synopsis of the 2 Cases

Jazmin case

HISTORY OF THE CASE

- **Father alleges he dropped his 3 month old daughter as he was feeding her a bottle**

- **Claims to have caught her by the right ankle and lifted her up sharply before she struck the ground**

RELEVANT HISTORY

- **Child is known to bruise easily in routine daily interactions**
- **A seatbelt has been shown to cause bruising**

MODIFIED DIAGNOSIS

Shaken Baby Syndrome,

UNLESS a hemorrhagic coagulopathy can be identified

TESTING FOR A HEMORRHAGIC COAGULOPATHY

PT/PTT/Platelet count/ von Willebrand factor/ristocetin cofactor

- Values for Platelet count, PT and PTT normal
- Values for von Willebrand factor and ristocetin cofactor in the low end of the adult normal range

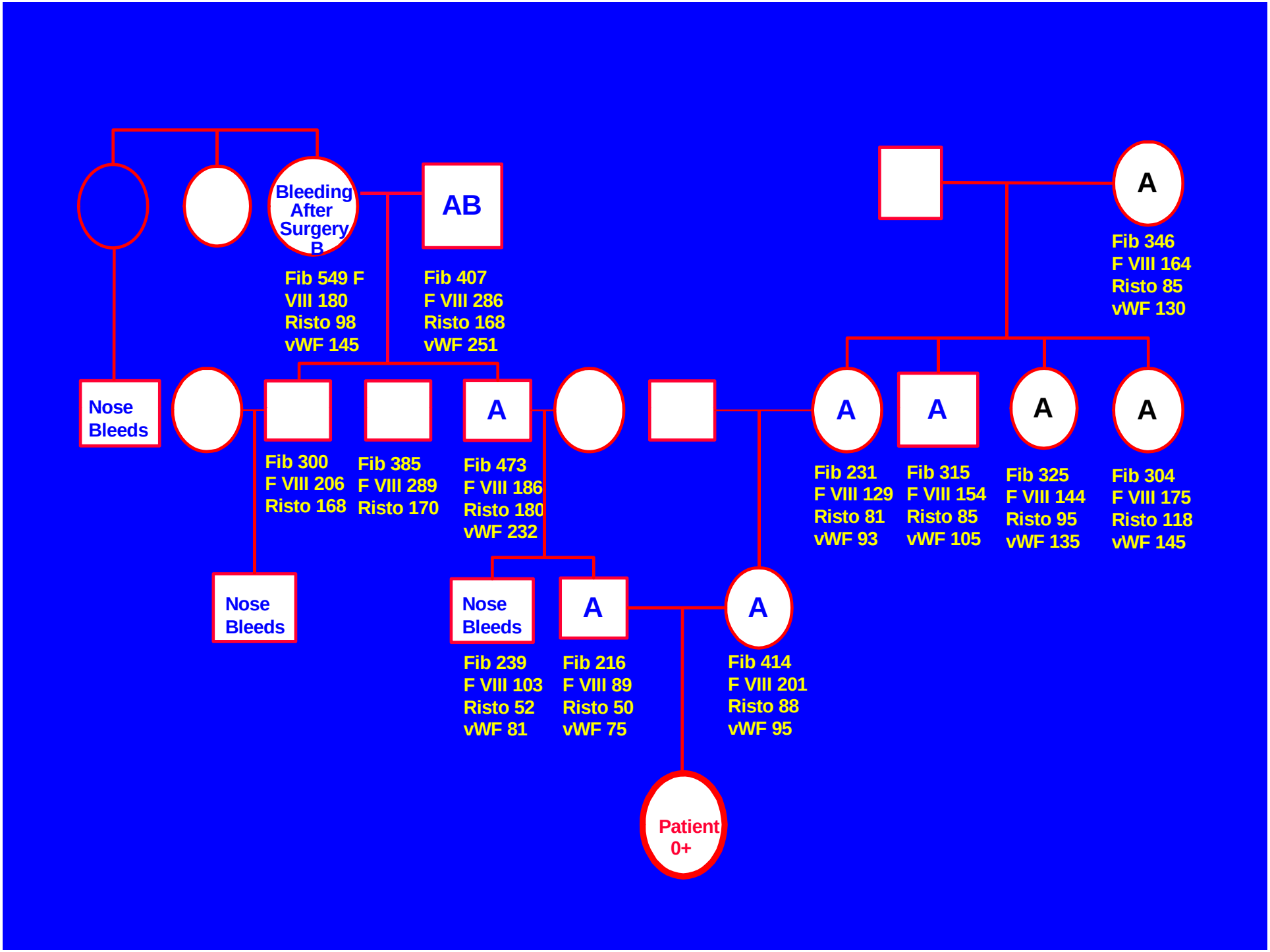
ACTIONS

- **Child placed in foster care**
- **Father indicted for child abuse and subsequently imprisoned**

IN FOSTER CARE

After 3 months in foster care, the child develops meningitis and a new subdural hemorrhage -

flown to MGH in critical condition


Bleeding After Surgery B
AB
Fib 549 F VIII 180 Risto 98 vWF 145
Fib 407 F VIII 286 Risto 168 vWF 251
A
Fib 346 F VIII 164 Risto 85 vWF 130
Nose Bleeds
Fib 300 F VIII 206 Risto 168
Fib 385 F VIII 289 Risto 170
A
Fib 473 F VIII 186 Risto 180 vWF 232
A
A
A
A
Fib 231 F VIII 129 Risto 81 vWF 93
Fib 315 F VIII 154 Risto 85 vWF 105
Fib 325 F VIII 144 Risto 95 vWF 135
Fib 304 F VIII 175 Risto 118 vWF 145
Nose Bleeds
Nose Bleeds
A
A
Fib 239 F VIII 103 Risto 52 vWF 81
Fib 216 F VIII 89 Risto 50 vWF 75
Fib 414 F VIII 201 Risto 88 vWF 95
Patient 0+

CONCEPTS IN THE DIAGNOSIS OF VON WILLEBRAND'S DISEASE UNLIKELY TO BE KNOWN TO A NON-EXPERT

- **vW Factor can increase 2-3 fold with injury, infection or other acute phase reactant stimulus**
- **A 30% vW factor at baseline at the time of an accident can rise to 90% by the time patient is tested**

CONCEPTS IN THE DIAGNOSIS OF VON WILLEBRAND'S DISEASE UNLIKELY TO BE KNOWN TO A NON-EXPERT

- **The normal range for vW factor is higher in children < 6 months of age than adults**
- **An abnormal value for a 3-month old child may be normal for an adult**

HOW WAS THE MISTAKE MADE ?

A low value was missed because --

The physician did not know that the patient's von Willebrand level increases after injury and that re-testing of the patient is ABSOLUTELY NECESSARY to determine the baseline level of von Willebrand factor

The physician did not know that the reference range for von Willebrand factor in children <6 months is higher than it is for adults

INTERPRETATION OF TEST RESULTS FOR VON WILLEBRAND'S DISEASE

	VWF (%)	RCoF (%)	Fibrinogen (mg/dL)
Initial Presentation at Outside Hospital (3 months old)	65	78	326 & 279
Stated Reference Range	50-150	50-150	180-460

INTERPRETATION OF TEST RESULTS FOR VON WILLEBRAND'S DISEASE

	VWF (%)	RCoF (%)	Fibrinogen (mg/dL)
Initial Presentation at MGH (6 months old)	50	50	865
2 Weeks After Initial Presentation at MGH	40	34	504
4 Weeks After Initial Presentation at MGH	33	31	

Type 0 blood mean vWF value for adults for this blood type = 74%. No stated normal range at the MGH.

Craig case

HISTORY OF THE CASE

- **Father alleges his child fell off a bed when playing with his older siblings while he was preparing a bottle of formula for the child**
- **The children – ages 2 and 4 - say their baby brother fell off the bed directly onto the hardwood floor about 3 feet above the floor**

ACTIONS

- **Father not permitted to be home alone with the children for a period of more than one year – had to sleep at the neighbor's home**

- **Father indicted for attempted murder of his son**

HOSPITAL CARE IN
2 MAJOR MEDICAL CENTERS

After months of evaluation, including neurosurgery to address his subdural hematoma, multiple esoteric studies were performed to assess the child for inborn errors of metabolism - and NO full assessment for bleeding was performed

AFTER DISCHARGE

After father's attorney finds a coagulation service for evaluation, von Willebrand's disease identified in the child and his 2 siblings

TESTING FOR A HEMORRHAGIC COAGULOPATHY

- **Values for PT and PTT and platelet count normal on multiple occasions**
- **Values for von Willebrand factor and ristocetin cofactor for the affected child in the 60% range on first testing with rhinorrhea, then in the 50% range finally in the 30% range**

LABORATORY TESTING

Siblings reported to bruise easily

Testing of siblings reveals values in the 20% range for brother and 50% range for sister for vWF and ristocetin cofactor

Schedule for Presentations in this Session

Speaker	Time
Mike Laposata	Introduction of Cases
Corinne Smith and Rosemary Jaromin	Part 1 of Patient Narratives with Discussion
Mike Laposata	Evaluation of the bleeding patient
Corinne Smith and Rosemary Jaromin	Part 2 of Patient Narratives with Discussion
Mike Laposata	von Willebrand's Disease
Corinne Smith and Rosemary Jaromin	Part 3 of Patient Narratives with Discussion
Mike Laposata	Analysis of the Misdiagnoses
	BREAK WILL OCCUR AT MID-POINT

Full evaluation of the patient with bleeding

Is the Bleeding Traumatically Induced?

↓

YES

Is There Any Reason At All to Consider a Pre-existing Bleeding Disorder That Was Present at the Time of Trauma?

↓

NO

No Evaluation for an Underlying Cause for Bleeding is Needed – Bleeding is Fully Explained by Trauma

Is it Spontaneous Bleeding or Was there Trauma with a Potentially Underlying Bleeding Disorder ?

YES

Evaluate the Patient for –

- **Coagulation factor deficiencies with PT and PTT**
- **Abnormal platelet count**
- **von Willebrand's Disease with VW antigen, Ristocetin cofactor, factor VIII, fibrinogen, and blood type**
- **Platelet function studies with a platelet aggregation test**
- **Factor XIII and Antiplasmin deficiencies (rare, but identifiable with simple tests)**

Which tests for bleeding were not done in Jazmin's Case ?

Von Willebrand's Testing was done,
but the test results were misinterpreted

No Platelet Function Studies

No Assessment for Rare Disorders

Which tests for bleeding were not done in Craig's Case ?

- No Von Willebrand's Studies
- No Platelet Function Studies
- No Assessment for Rare Disorders

How easy is It to obtain a patient-specific, expert driven narrative interpretation of the test results - as done in radiology?

- ❑ **PT/PTT Prolongations**
- ❑ **Von Willebrand Study**
- ❑ **Antiphospholipid Antibody Evaluation**
- ❑ **Hypercoagulability Evaluation**
- ❑ **Other _____**

All of these "Special" coagulation studies are automatically interpreted without further request, by an expert lab director & the results are included in the lab report

How easy is it to order the right tests with reflex testing ?

x **Von Willebrand Panel**

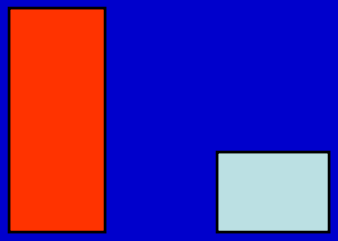
A check means all the tests in the von Willebrand Panel are performed – omission of even 1 test can make it impossible to make or rule out a diagnosis – and with reflex testing, omissions do not occur

The Increasingly Glaring Safety Issue Involving Clinical Laboratories

Clinical lab test menu enlarges in size and complexity → **Physicians highly uncertain about correct tests to order and how to interpret test results**

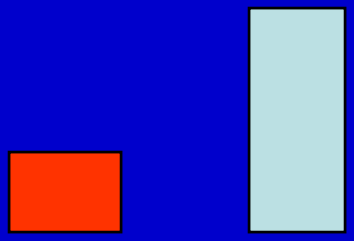
PROBLEM : Clinical lab directors focus on operations - radiologists had the same issue in the 1980s and chose to focus on consultation with physicians ordering tests

Radiology



CLINICAL OPERATIONAL

Clinical Labs



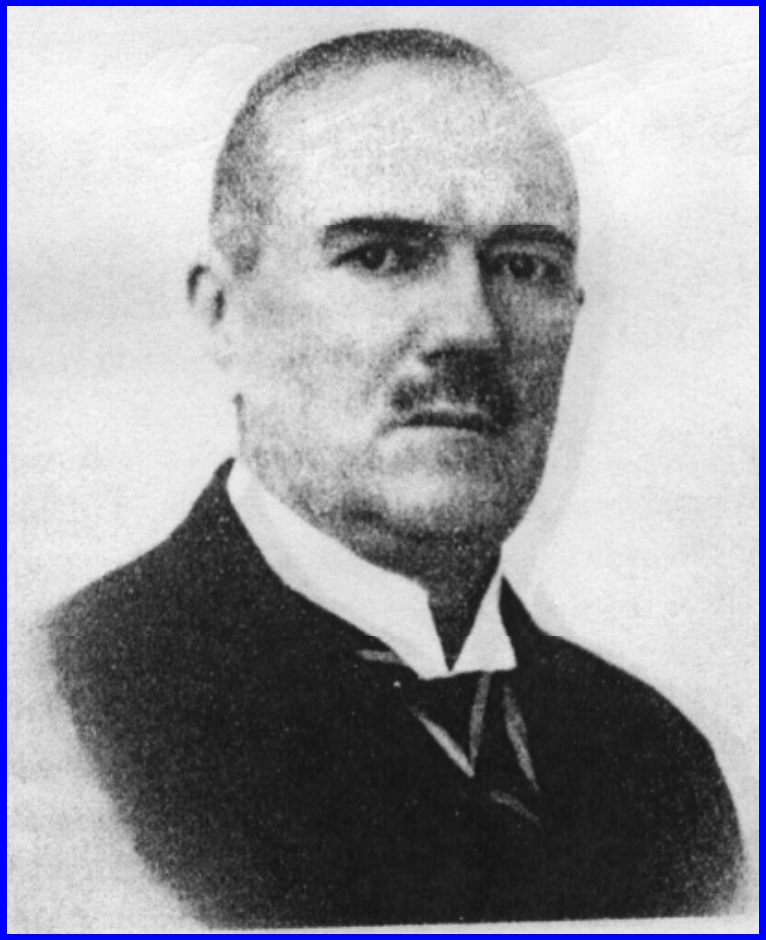
CLINICAL OPERATIONAL

In both of these cases, until the patients arrived for evaluation and testing at the Massachusetts General Hospital --

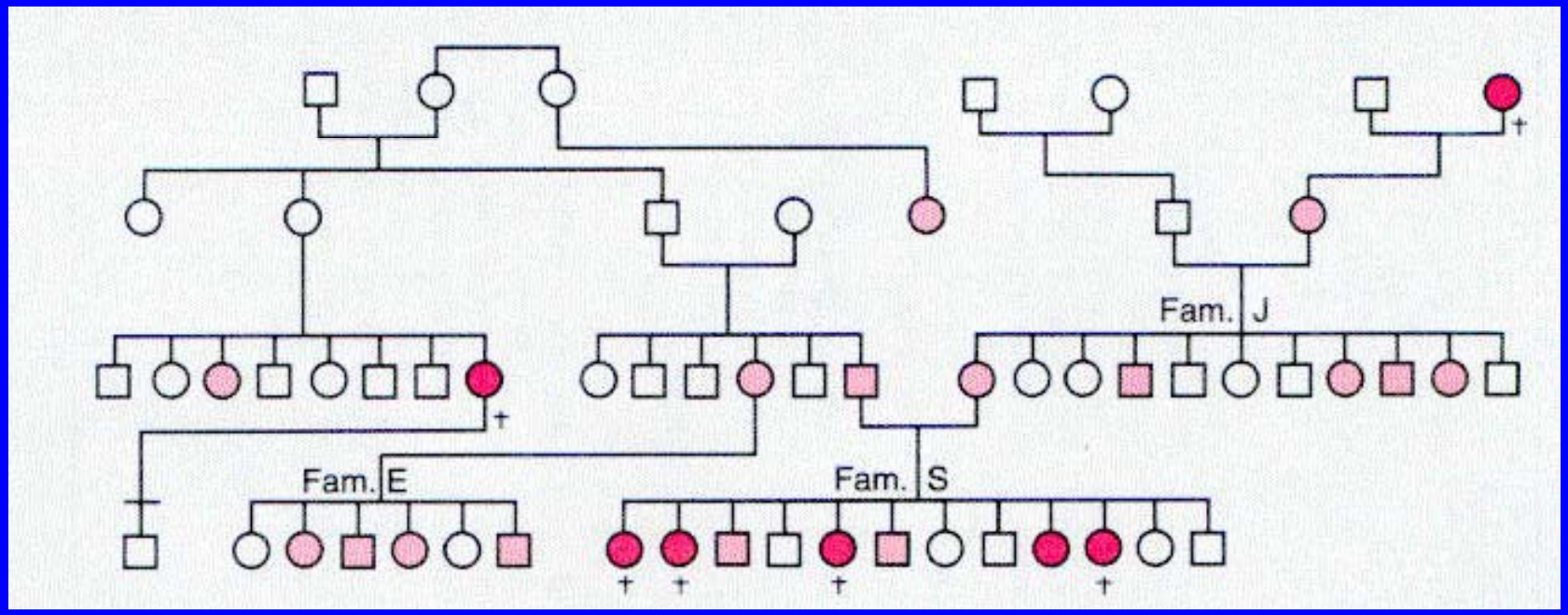
There was NO systematic interpretation of test results or use reflex testing to guide test selection for evaluation of bleeding disorders

VON WILLEBRAND'S DISEASE (VWD)
Outline of Presentation

- Introduction
- Synthesis, secretion, metabolism, action and transport
- Clinical laboratory assays
- Types and subtypes
- Treatment



First described by Erik von Willebrand based on a 1926 study of inhabitants of the Aaland island in the Gulf of Bothnia



Female nonbleeders

Male nonbleeders

Female bleeders

Male bleeders

Severe female bleeders

Severe male bleeders

† hemorrhagic deaths

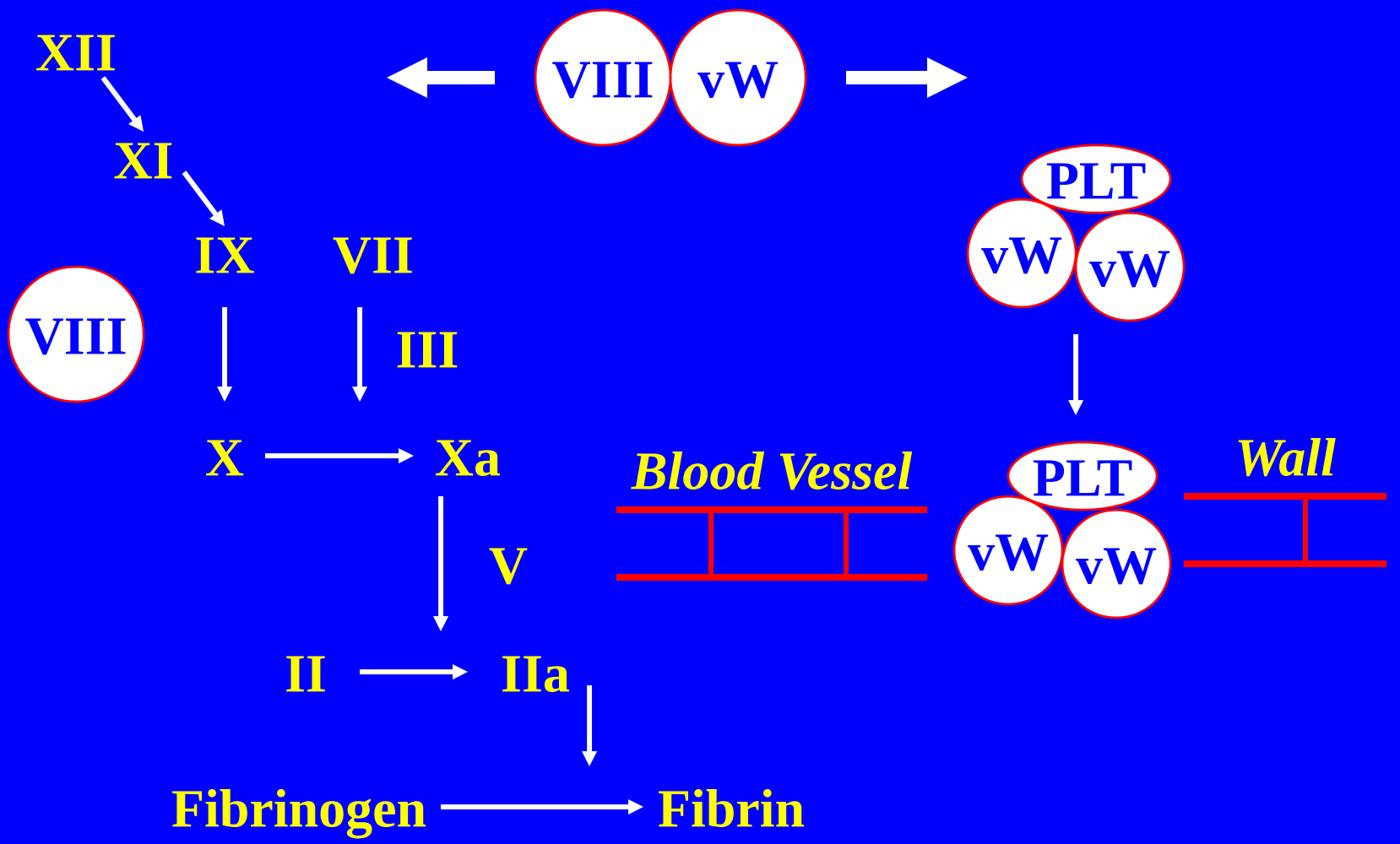
EARLY STUDY OF CONGENITAL BLEEDING DISORDERS IN SWITZERLAND

	Severity of Bleeding Disorder		
	Severe	Moderate	Mild
Hemophilia	18	8	3
Von Willebrand's Disease	4	13	25

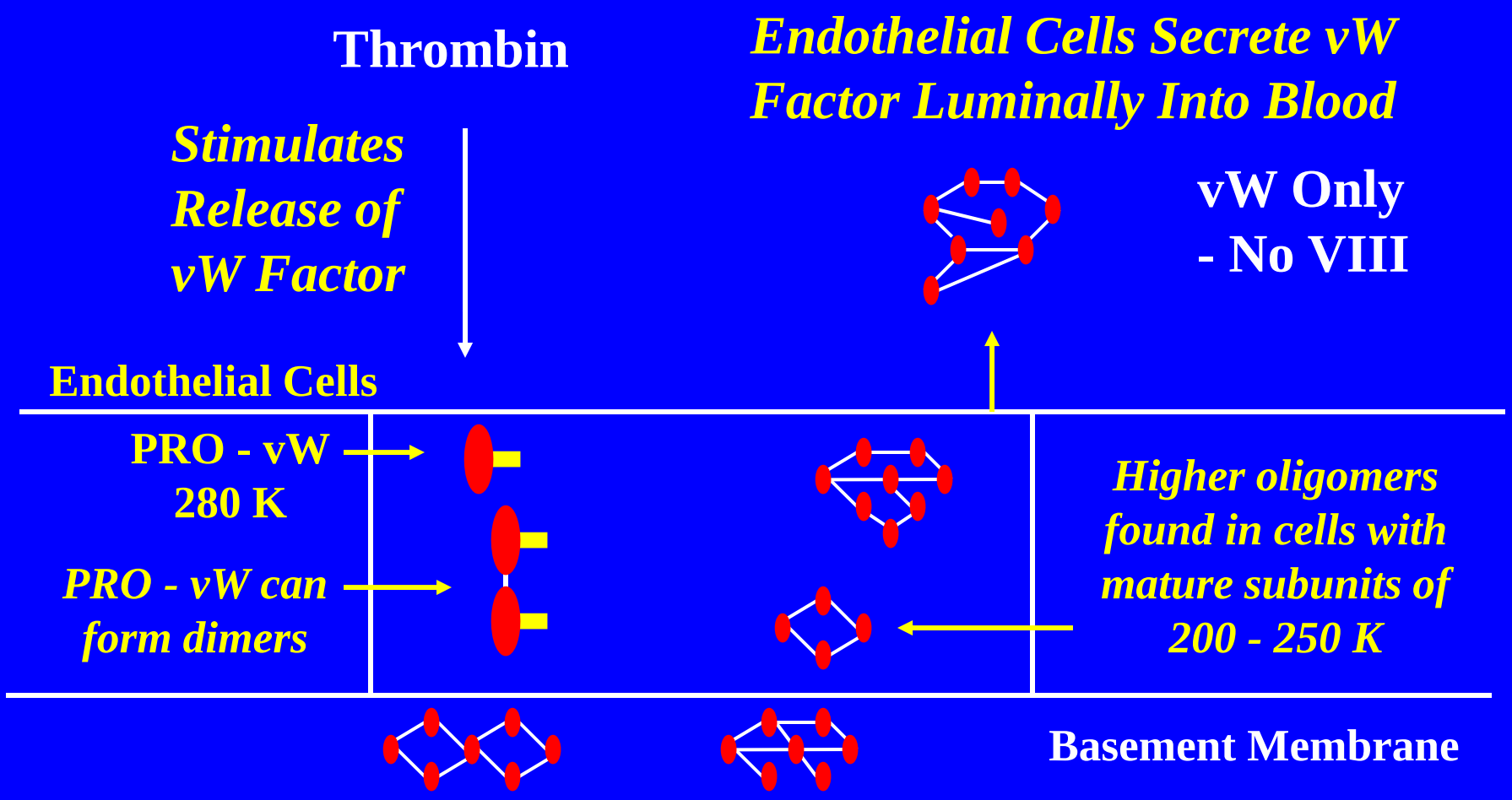
VON WILLEBRAND'S DISEASE

Synthesis, Secretion, Metabolism, Action, and Transport

THE TWO DIFFERENT ACTIVITIES OF THE FACTOR VIII-VON WILLEBRAND FACTOR COMPLEX



SYNTHESIS AND SECRETION OF VON WILLEBRAND FACTOR



Endothelial Cells Secrete vW Factor Basally to Subendothelium

VON WILLEBRAND'S DISEASE

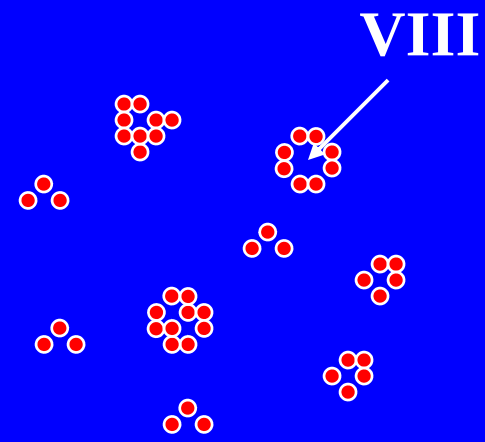
Major Types and Subtypes

TYPE 1
VON WILLEBRAND'S DISEASE

Common Defect:

Slow release of normal vW factor from stores

TYPE 1
VON WILLEBRAND'S DISEASE



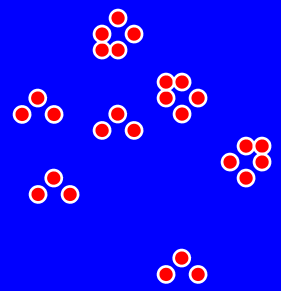
Quantitative disorder with normal multimer distribution - von Willebrand factor and ristocetin cofactor decreased approximately equally

Factor VIII may be normal or low

TYPE 1
VON WILLEBRAND'S DISEASE

DDAVP can completely correct entire defect if it is mild, by stimulating vW Factor release from endothelium

TYPE 2A
VON WILLEBRAND'S DISEASE



Decrease in high molecular weight multimers in plasma and sometimes in platelets

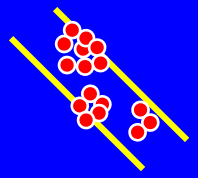
Synthesis of large multimers defective or increased proteolysis of large multimers

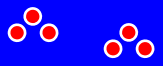
Ristocetin cofactor and von Willebrand factor antigen both very low

TYPE 2B

VON WILLEBRAND'S DISEASE

Platelet Membrane





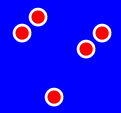
Plasma

Decrease in high molecular weight multimers in plasma only

High molecular weight multimers of vW factor removed from plasma by binding to normal platelets

Plasma ristocetin cofactor and von Willebrand factor antigen both very low

TYPE 3



Quantitative disorder with nearly undetectable levels of von Willebrand antigen and ristocetin cofactor

Either markedly reduced synthesis of normal von Willebrand factor or synthesis of a highly dysfunctional von Willebrand factor

INFLUENCE OF ABO BLOOD GROUP ON vW FACTOR ANTIGEN VALUES IN VOLUNTEER BLOOD DONORS

ABO Type	n	von Willebrand Factor Mean Value
O	456	74.8
A	340	105.9
B	196	116.9
AB	109	123.3

Blood 69, 1691-1695, 1987

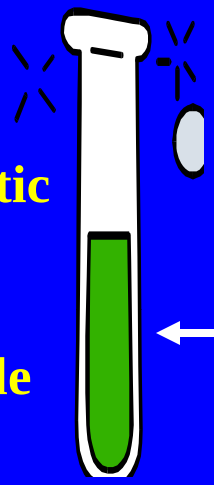
VON WILLEBRAND'S DISEASE

Clinical Laboratory Assays

THE RISTOCETIN COFACTOR ASSAY

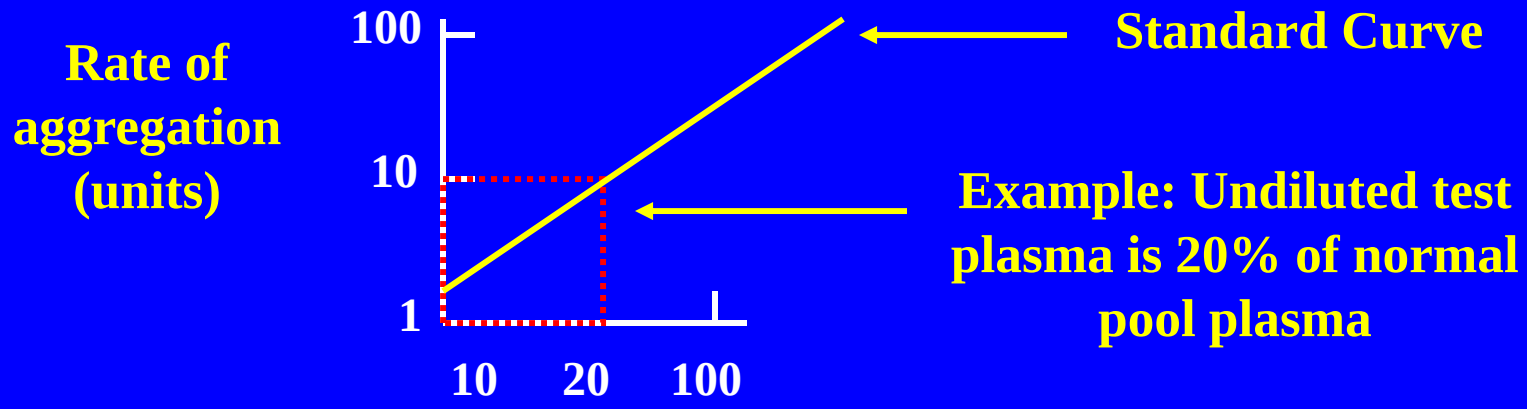
Ristocetin:

Glycopeptide antibiotic from nocardia which aggregates platelets when vWF is available as a cofactor



Formalin fixed platelets mixed with normal plasma undiluted/ 1:2/1:4/1:5/1:X

Ristocetin added and rate of platelet aggregation measured

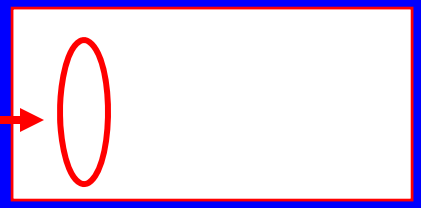


ANTIGENIC VON WILLEBRAND FACTOR ASSAYS

Immunoassays of many different types are available

VWF MULTIMER ANALYSIS BY IMMUNOBLOTTING

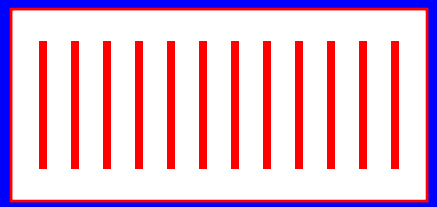
Plasma Added



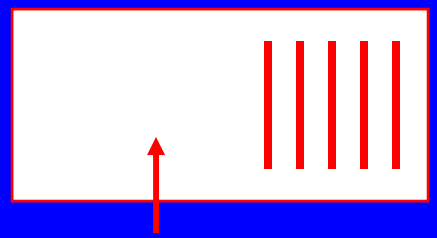
Electrophoresis Separates vW Multimers

Blot Proteins onto Different Surface

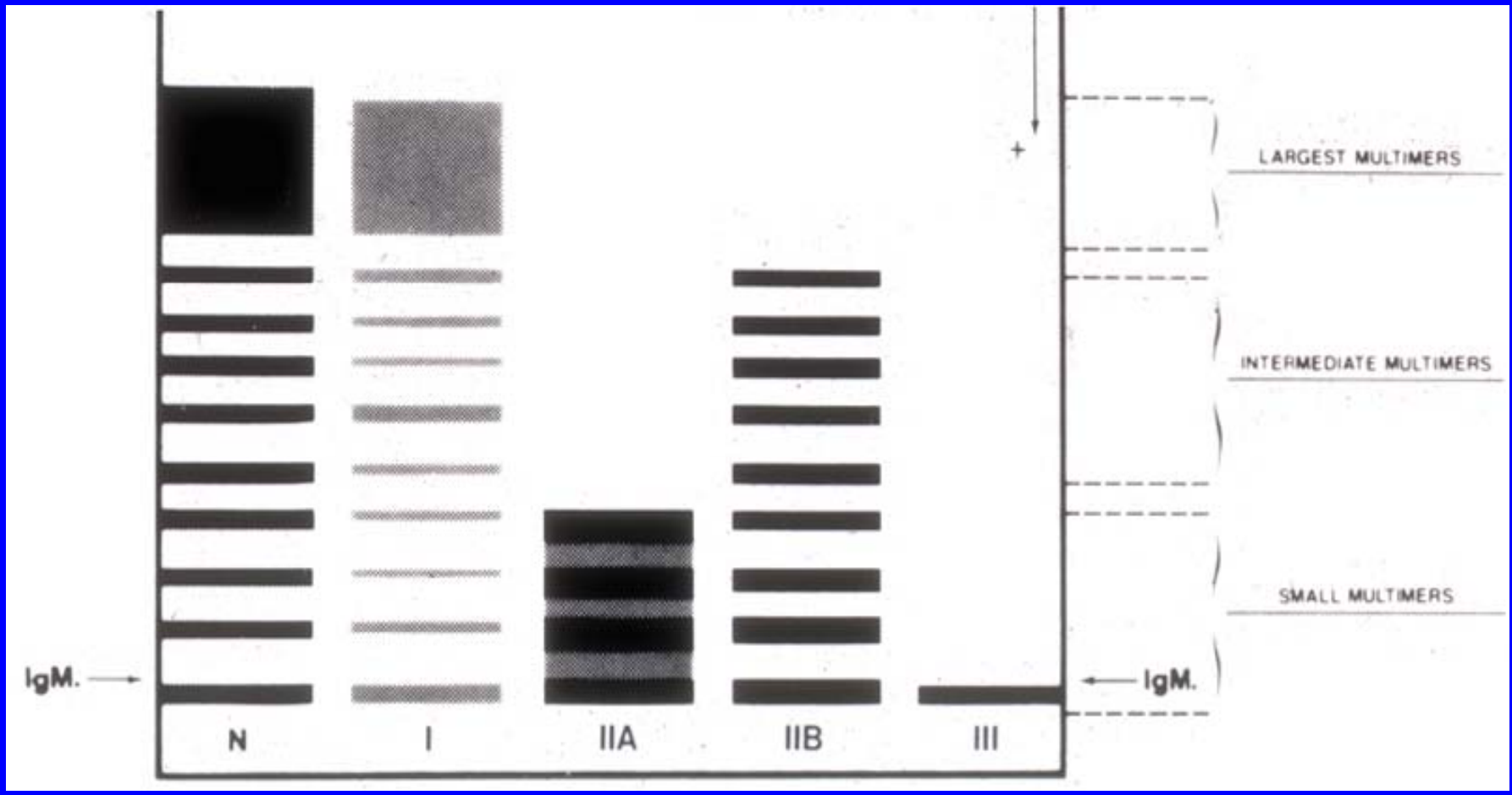
Add Antibody to vW Factor and Stain



Normal



Type 2 vW Disease - High Molecular Weight Multimers Reduced


+
LARGEST MULTIMERS
INTERMEDIATE MULTIMERS
SMALL MULTIMERS
IgM.
IgM.
N
I
IIA
IIB
III

FACTOR VIII ASSAYS

Factor VIII deficient plasma mixed with dilutions of normal pool plasma to construct standard curve

Instrument Detects Clot Formation

Patient sample compared to standard curve to determine patient's value for factor VIII

WHAT IS A NORMAL vWF LEVEL?

- **No general agreement**
- **Guidelines for diagnosis from the NIH are under evaluation – this should lead to a consensus statement on what levels of von Willebrand factor antigen and ristocetin cofactor required for a diagnosis**
- **The impact of blood type on establishing a diagnosis is an important issue that is considered in the consensus guidelines**
- **In the absence of guidelines, 50% von Willebrand factor is not uncommonly used as a threshold for "low vWF"**

VON WILLEBRAND'S DISEASE

Treatment for Acute Bleeding

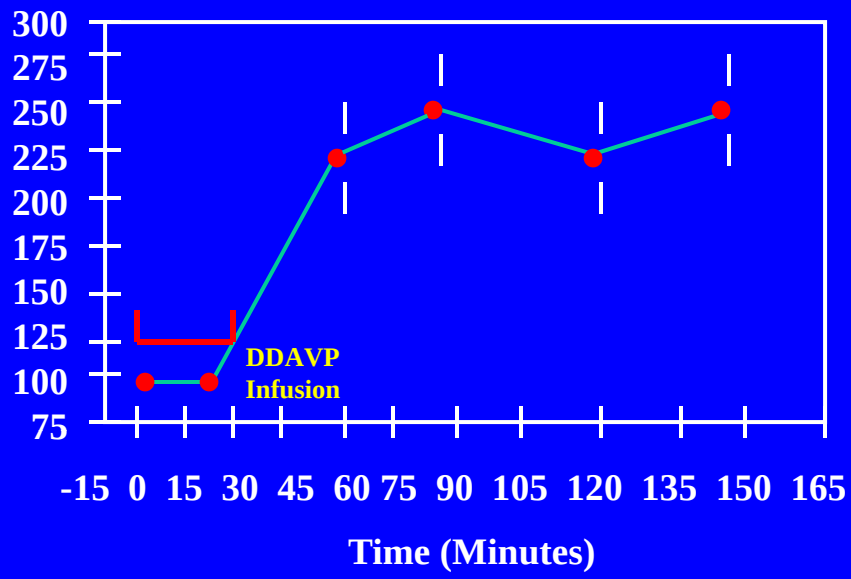
VWD TREATMENT OPTIONS

- **Desmopressin**
- **Cryoprecipitate**
- **Replacement therapy with vWF-containing Factor VIII concentrates**

TEST FOR DDAVP RESPONSE

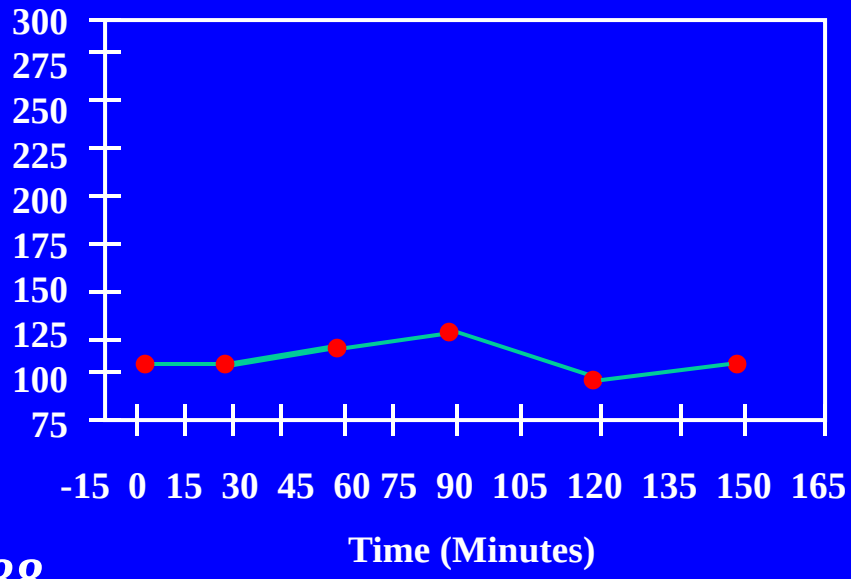
Normal response of a normal subject

vWF



Lack of response

vWF



N. Engl. J. Med., 318-881-887, 1988

THERAPY FOR VON WILLEBRAND'S DISEASE ASSOCIATED BLEEDING

Cryoprecipitate is derived from fresh frozen plasma and contains von Willebrand factor - 1 bag/10 kg daily

May need 2-3 bags/kg/day if breakthrough bleeding

A patient is typically exposed to dozens of donors when cryoprecipitate is used

REPLACEMENT THERAPY FOR TYPE 3, SEVERE TYPE 2, AND SERIOUS BLEEDING IN TYPE 1 VWD PATIENTS

- **Intermediate purity Factor VIII concentrates**
  - **Humate P**
  - **Alphanate**

- **Very high Purity (VHP) vWF**
  - **10:1 ratio of vWF activity to factor VIII**
  - **If factor VIII <20% in vWD patient, also need to replace VIII**

LEGAL SYSTEM

"At the point the case is reported, the legal and medical systems merge in an effort to sort out the evidence as fairly as possible, with maximal "protection" given to the child.

Many issues related to jurisprudence inhibit the sharing of information, while the medical community optimizes clinical outcome by information sharing.

The problem becomes apparent in the evaluation of child abuse when the treating physician is unable to discuss the case with experts brought by the defense who indeed might have specialized knowledge not available to the physician making the diagnosis of child abuse."

Am J Clin Pathol 2005;123(Suppl 1):S119-S124