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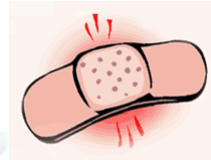
Holiday Inn By The Bay
NORTHEAST LABORATORY CONFERENCE
October 21-23
2009
PORTLAND, MAINE

Hemophilia Therapy

From Rasputin to Recombinants



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Hemophilia
Rasputin to Recombinants

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The Fritsma Factor; Your Interactive Hemostasis Resource
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Hemophilia etiology, pathology and treatment

Hemophilia in history

Alexis and Rasputin

Advances 1920–70

AIDs and recombinants

Future therapy

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Hemophilia

- Anatomic bleeding caused by congenital single-factor deficiencies
- 85% factor VIII deficiency (hemophilia A)
  - 1 in 10,000 male births
- 14% factor IX deficiency
  - Hemophilia B or Christmas disease
  - 1 in 30,000 male births
- 1% XI (autosomal, Rosenthal syndrome)
- Rare autosomal recessive single factor deficiencies
  - Prothrombin, V, VII, X, XIII

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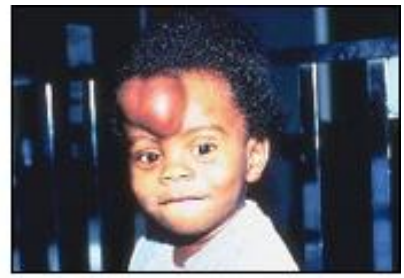
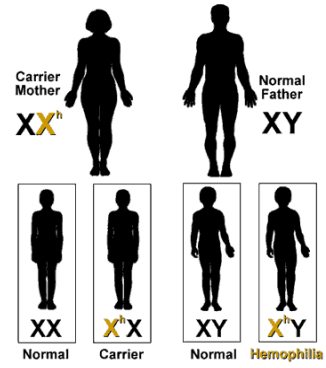
Hemophilia A Inheritance

- Sex-linked recessive, 1/10,000–20,000
- 25–30% spontaneous mutations





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Hemophilia A Symptoms

Spontaneous anatomic (soft-tissue) bleeds

- Bleeding at umbilical stump, circumcision
- Delayed bleeding following injury
  - Joints, muscles, body cavities, GI, soft tissue, tongue, kidney, testicles, CNS
- Often spontaneous, especially joints
- Inflammation, hematomas, hemarthroses

Mild	Moderate	Severe
15%	15%	70%
6-30% VIII	1-5% VIII	<1% VIII
Bleed after major trauma	Bleed after minor trauma	Spontaneous bleeding

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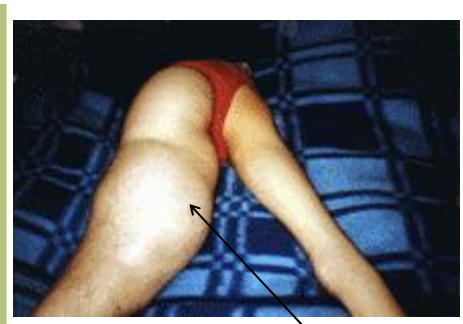

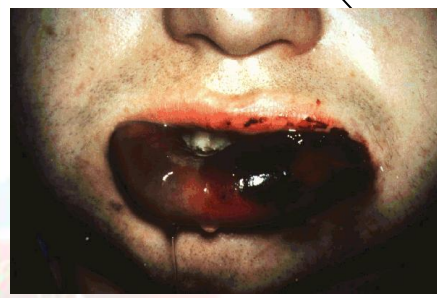

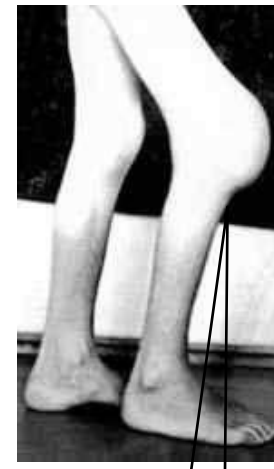

Hemarthroses

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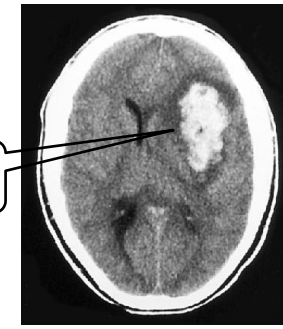
Other Complications

- Lifestyle
- Economic
- Vocational
- Neurologic
- Psychological
- Lack of insurance
- Narcotics addictions
- Social: Russian revolution, for example



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Hemophilia A Genetics

- 186 kb gene on X chromosome
  - Deletions, stop codons, missense and nonsense point mutations
  - 25−30% spontaneous mutation rate
  - Predominantly quantitative deficiency
  - Male hemizygotes are affected
- Hemophilia A in females is rare
  - Acquired anti-coagulation factor VIII
  - Autosomal hemophilia or VWD type N (Normandy)
  - Random excess Lyonization
  - Hemophilic father, carrier mother

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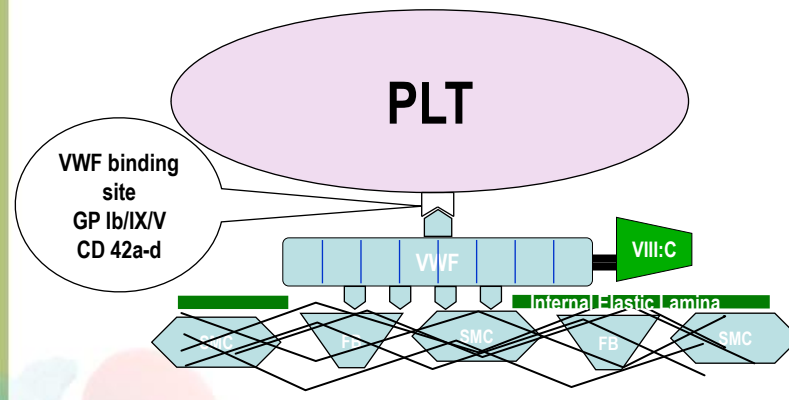
VIII/VWF Interaction with Platelets



SMC: Smooth muscle cell
FB: Fibroblast
Lines: Collagen

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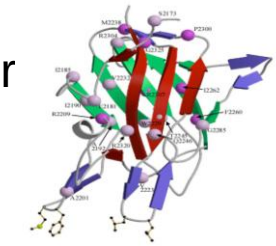
Factor VIII Glycoprotein Cofactor



- 285,000-D heterodimer
  - Translated from the X chromosome
- Cleaved by thrombin, leaving a Ca^{++}-dependent portion that detaches from VWF and binds factor IXa and phospholipid
- Stabilizes IXa in the “tenase” reaction
- Deficiency slows thrombin production
- In vitro, deteriorates 5%/h at 18–24°C

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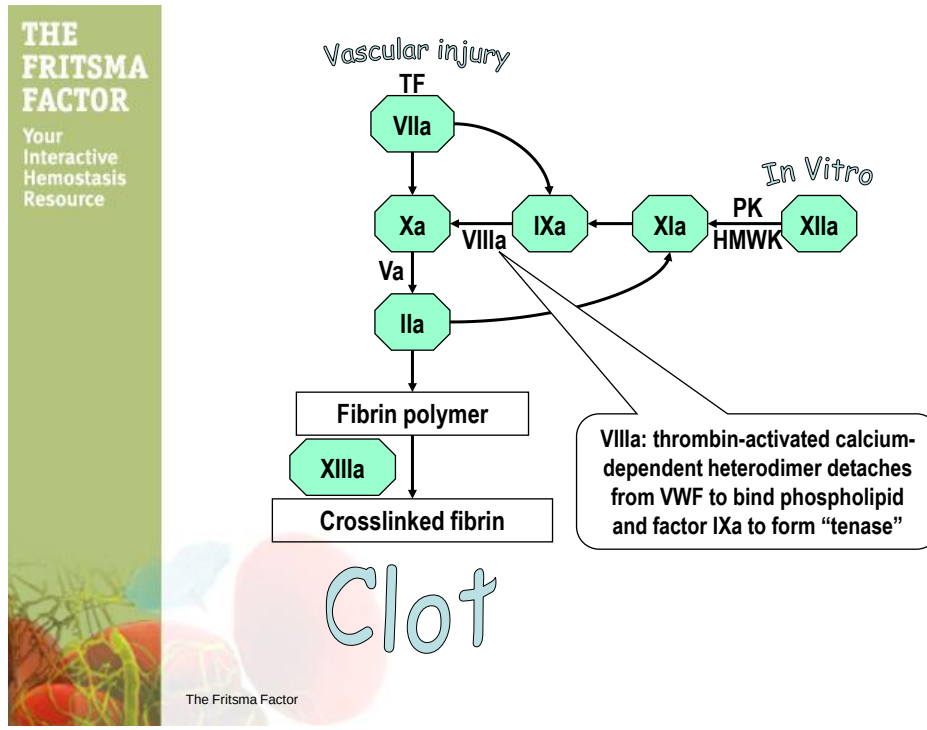

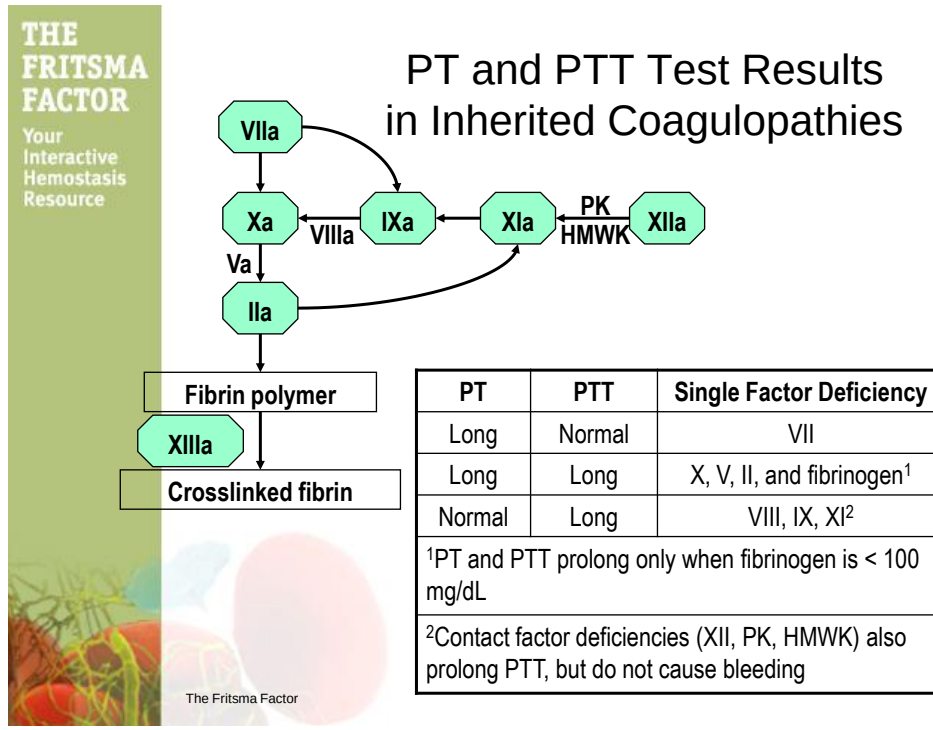

PT	PTT	Single Factor Deficiency
Long	Normal	VII
Long	Long	X, V, II, and fibrinogen[1]
Normal	Long	VIII, IX, XI[2]
[1]PT and PTT prolong only when fibrinogen is < 100 mg/dL		
[2]Contact factor deficiencies (XII, PK, HMWK) also prolong PTT, but do not cause bleeding		

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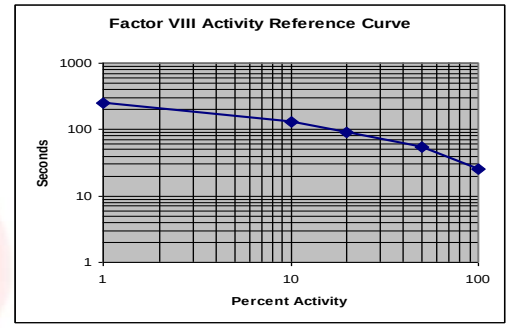
Factor VIII, IX, or XI Assay

- Dilute plasma 1:10, add factor-depleted reagent plasma 1:1
- Add PTT reagent, incubate 3 minutes
- Add $CaCl_2$, record interval to clot formation
- Compare result in seconds to dilution curve



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Factor VIII Assay Dilutions Parallelism Indicates No Inhibitor

Plasma Dilution	Seconds	Raw Factor VIII Activity	Computed Factor VIII Activity (× dilution)
1:10 (undiluted)	90 s	20%	20%
1:20	104 s	10%	20% (parallel)*
1:40	107 s	5%	20% (parallel)
1:80	110 s	2.5%	20% (parallel)

* < 10% difference from undiluted implies parallelism;
> 10% difference from undiluted = non-parallel, implies inhibitor

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Factor VIII, IX, XI Assays at Four Dilutions: Lupus Anticoagulant

Plasma Dilution	F VIII	F IX	F XI
1:10 (undiluted)	17 %	20 %	5 %
1:20	26 %	22 %	6 %
1:50	50 %	30 %	12 %
1:100	74 %	32 %	17 %

- 10% change between dilutions = non-parallel
- Proceed to lupus anticoagulant and anti-phospholipid antibody profiles

Kasper CK. Laboratory diagnosis of factor VIII inhibitors. In Kessler C, Garvey MB, Green D, Kasper C, Lusher J. Acquired Hemophilia 2nd Edition. Excerpta Medica 1995

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Hemophilia A Therapy

- Monoclonally purified VIII concentrates available from many distributors
  - (Monarch M, Monoclate-P, Hemofil M)
- Recombinant factor VIII concentrates for PUPs (Recombinate, Kogenate)
  - Also B-domain-deleted factor VIII

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Calculating Factor Dosage for Hemophilia A, B, or VWD

- One unit of factor = amount of activity in 1 mL normal plasma, same as 100%
- Determine plasma volume:
  - Blood volume (mL) = weight (kg) x 70 mL/kg
    - Use 60 for obese, BMI 25-30, 50 for BMI > 30
  - Plasma volume (mL) = blood volume (mL) x (100%-HCT%)
- Determine units of factor required:
  - Units of factor required = (desired factor level in units/mL - initial units/mL) x plasma volume (mL)

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Example Factor Dosage for Factor VIII, IX, or VWF

- Patient: 80 kg, HCT 40%, 0 factor level
- Determine plasma volume:
  - Blood volume (mL) = 80 kg x 70 mL/kg = 5600 mL
  - Plasma volume (mL) = blood volume (5600 mL) × (100%−40% = 60%) = 3360 mL
- Determine units of factor required:
  - Wish to reach 80% factor level (0.8 U), therefore…
  - Units of factor required =(0.8 U/ mL −0) x 3360 mL = 2688 (2700) U
  - Typical factor vial provides 1000 U
- Apply formula to conserve therapeutics

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If Factor Assay not Available

- When factor assay not available and timing is critical, assume 0 activity or…
- The PTT may be correlated to factor levels

Factor	PTT
40%	35 s
30%	50 s
20%	65 s
10%	90 s
1 %	120 s
Example only, do not use	

- Draw specimen and freeze, assay later
- Maintain patient database

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Hemophilia A & B Inhibitors

- Assay factor VIII or IX
  - 30% of treated boys
  - Some dose and severity response
  - If > 30% factor VIII, no inhibitor is present
  - 3% of factor IX deficiencies
- Perform Bethesda titer
  - Reciprocal of patient titer that neutralizes 50% of factor VIII or IX in normal plasma

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Factor VIII Assay Dilutions non-Parallelism Indicates Inhibitor

Plasma Dilution	Seconds	Raw Factor VIII Activity	Computed Factor VIII Activity (× dilution)*
1:10 (undiluted)	80 s	10%	10%
1:20	93 s	8%	16%
1:40	107 s	5%	20%
1:80	108 s	4%	32%

* < 10% difference from undiluted implies parallelism;
> 10% difference from undiluted = non-parallel, implies inhibitor

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Factor VIII Inhibitor Therapy

- Factor IX complex, activated prothrombin complex concentrate (PCC), prepared by extraction
  - FEIBA, Autoplex are activated PCCs
  - Thrombosis (DIC) potential
- FEIBA dosage
  - 50 U/kg/12 h standard
  - 70 U/kg/8 h hemorrhage
  - Limit 200 U/kg/24 h to avoid DIC
  - Cannot monitor in laboratory

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Recombinant VIIa Concentrate

- Effective dosage: 90 μg/kg
- Cannot monitor in laboratory
- Repeat full dosage every 3–6 h
  - 6h factor VII half-life
- $0.83/μg
- For a 75 kg patient, one dosage = $5600

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1st Documented Bleeder's Disease

2nd century: Talmudic ruling of *Rabbi Judah the Patriarch* exempts a woman's 3rd son from circumcision if two elder brothers had died of bleeding after circumcision

2nd century: *Rabbi Simon ben Gamaliel* forbade a boy to be circumcised after sons of his mother's three elder sisters had died after circumcision

11th century: Arabic surgeon *Albucasis* describes village males who bled to death from "trivial" wounds

Ingram GIC. The history of haemophilia. J Clin Pathol 1976; 29: 469-79.

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1791–1803: British & American Families

- 1000–1800: Several references to “bleeders”
- 1791 (Britain), Zoll: 6 brothers bled to death after minor injuries
  - Half-siblings by a different mother were unaffected
- 1803 (Philadelphia), Otto: “A hemorrhagic disposition existing in certain families”
  - Recorded males in his own family with symptoms and recognized transmission through asymptomatic women
  - Traced pedigree to a woman named Smith in Plymouth, 1720–30

Otto quoted in Bulloch W, Fildes P. Treasury of human inheritance, parts V & VI, section XIVa, Haemophilia, 1911.

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1800–28: Documented Names

- Bleeding disease
- Haemorrhoea
- Idiosyncrasia haemorrhagica
- Hereditary haemorrhagic diathesis
- 1828: first use of "haemophilia" (blood-loving) appears in the title of a treatise by Hopff at University of Zurich

Hopff F. Cited by United States Surgeon General’s catalogue, 1st series: Hemophilia, 1828.

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Bulloch and Fildes

Bulloch W, Fildes P. *Treasury of human inheritance, parts V and VI, section XIVa, haemophilia*.

Published as Eugenics Laboratory memoirs XII, Francis Galton Laboratory for National Eugenics, University of London; 1911, Dulau and Co, 37 Soho Square, London.

- 1000 references and case reports
- 200 pedigrees
- Identified haemophilia as sex-linked, but carrier status not understood
- Meticulously traces the current spread of the mutation throughout Queen Victoria's family

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Alexandrina Victoria; May 24, 1819–Jan 22 1901, was *Queen of the United Kingdom of Great Britain and Ireland* from June 20, 1837 until her death, altogether 63 years and 7 months. The Victorian era was a time of UK industrial, political, imperial, and military progress.

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Queen Victoria

- Presumed spermatogenesis mutation in father; Edward, Duke of Kent, who was in his 50s when Victoria was conceived
- Victoria's seventh child, Leopold, was hemophilic
  - Stigmatized as a "weak" invalid by his mother
  - Married at 29
  - Died of cerebral hemorrhage following a fall at 31
- Two daughters, Alice (2nd) and Beatrice (8th) were carriers

Massie RK. Nicholas and Alexandra. (1968). Gollancz, London.

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Queen Victoria and Family

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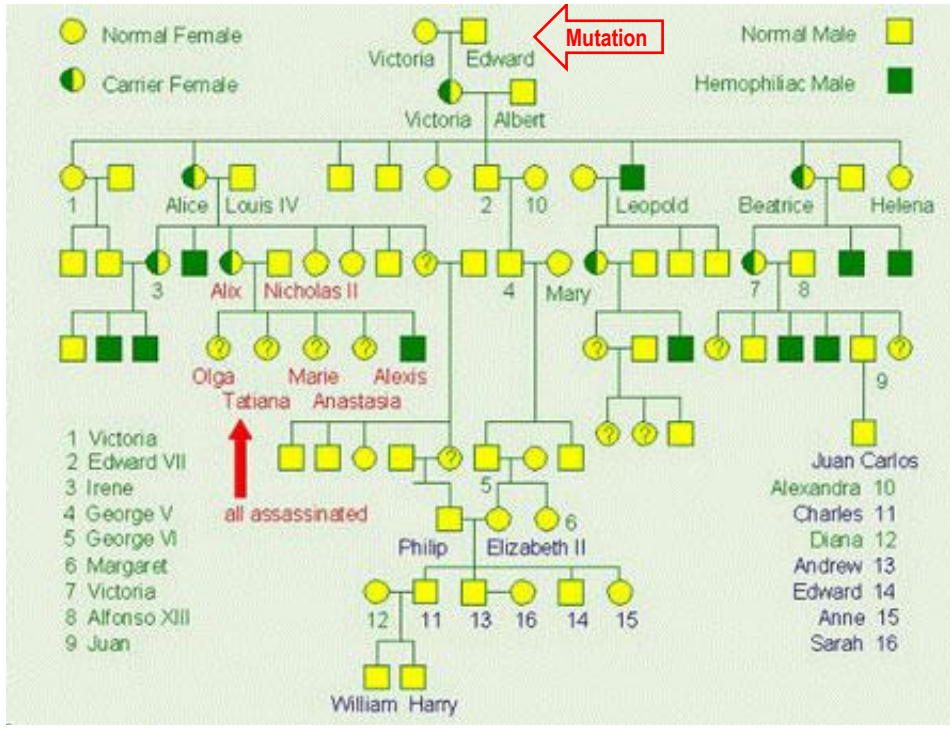

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Victoria Eugenie (Ena) Battenberg

- Beatrice's daughter, 2 hemophilic brothers
- Alfonso XIII of Spain married her in 1906
  - Warned by Spanish Embassy, but trusted his luck
- Alfonso XIV b. 1907 bled from circumcision
  - Alfonso blamed Ena, grew to despise her
  - Jaime, deaf-mute; Gonzalo, hemophilic
  - Spaniards blamed the British
- Juan b. 1913, normal
  - Son Juan Carlos is current King
- 1931, royal family in exile in Rome
  - Alfonso was too ill to appear
  - 1933, marries Cuban commoner and abdicates

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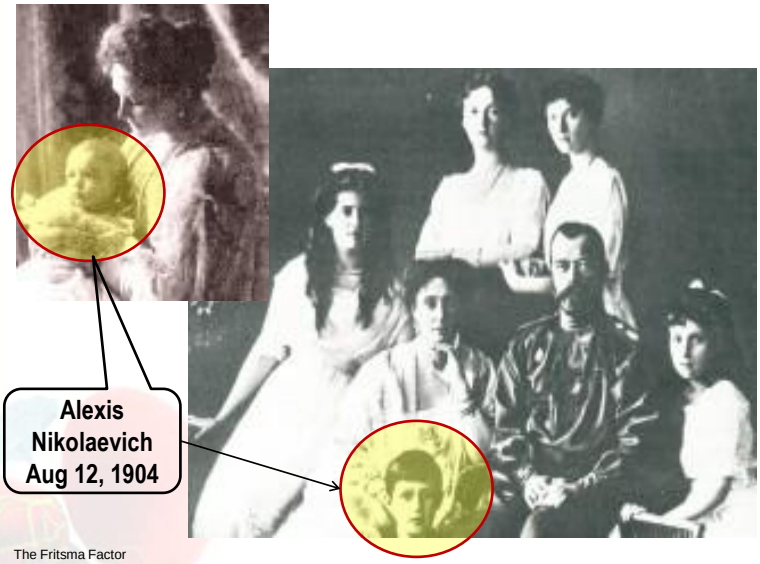
The Romanovs: Tsar Nicholas II, Alexandra (Alix, granddaughter of Victoria) and Family



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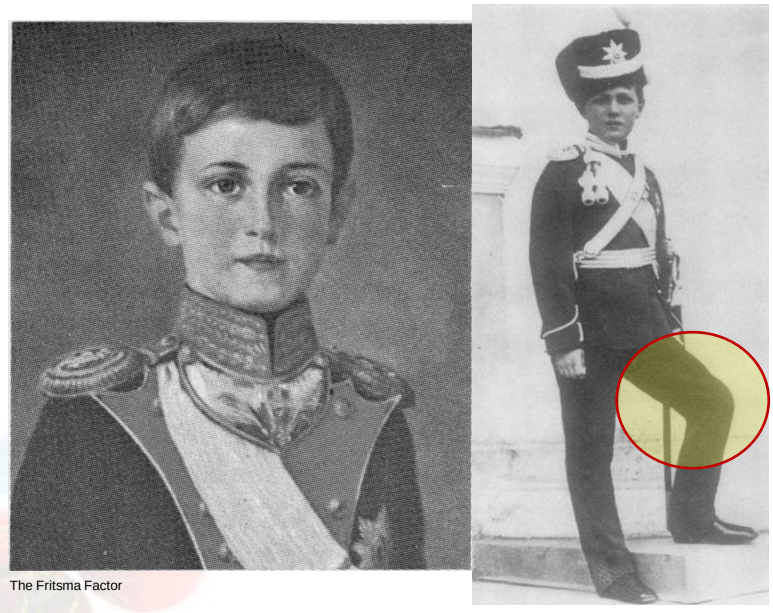
Prince Alexis, 1912



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Grigori Yefimovich Rasputin
1869–1916

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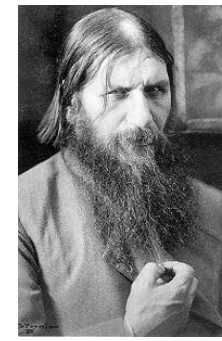
Rasputin



- 1869, Pokrovskoye, Siberia
- Two sibs drowned
- 1887: three months in Verkhoturye Monastery
- 1901: *strannik* (pilgrim) wandered through Greece, Jerusalem
- 1903: Saint Petersburg, *starets* (holy man) with healing & prophetic powers
- 1905: Alexandra introduced by Anna Vrubova to get help for 1 YO Alexis

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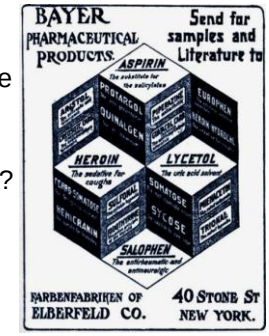
Rasputin's Power: 1905–16

- Calming influence?
  - 1912 in Spala, Poland "Don't let the doctors bother him too much; let him rest" (by telegram)
  - Distraction, causing Alexis to relax?
- Faith healer, hypnotism?
- Leeches?
- Aspirin?



Alexandra believed God spoke through Rasputin, and he became the czar's primary adviser and gatekeeper, used his power for financial gain and debauchery, and was increasingly hated by the Russian nobles, though loved as a prophet by many of the peasants.

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The Romanovs in 1912

Pierre Gilliard, Alexis' tutor, wrote: "*The illness of the Tsarevich cast its shadow over the whole of the concluding period of Tsar Nicholas II's reign. Without appearing to be, it was one of the main causes of his fall, for it made possible the phenomenon of Rasputin and resulted in the fatal isolation of the sovereigns who lived in a world apart, wholly absorbed in a tragic anxiety which had to be concealed from all eyes*."

Historians have since disputed the contribution of Alexis' hemophilia to Russian politics, but the strain on the royal household is clear enough.

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Rasputin and Admirers, 1914

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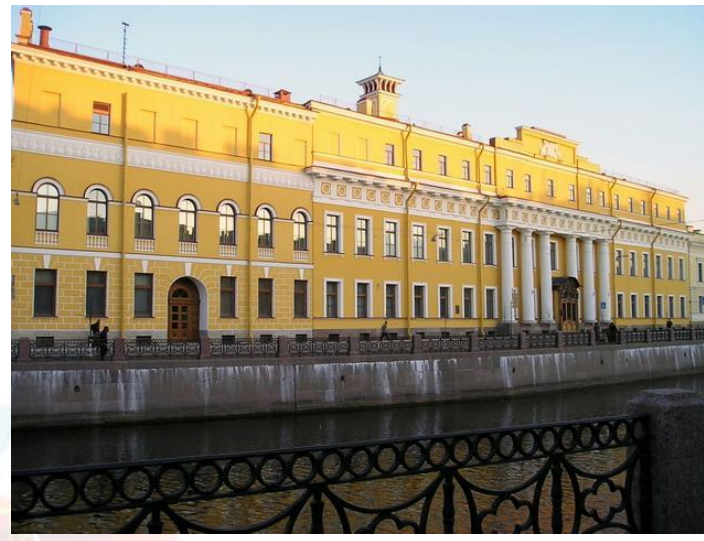
Yusupov Moika Palace, St. Petersburg



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Maj. Felix Yusupov: Dec 16, 1916

(Wax figures)

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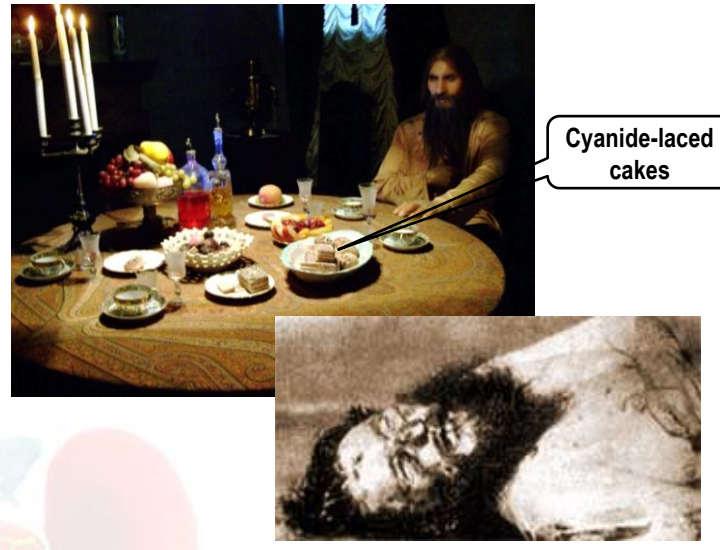
Poisoning Rasputin



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Treatment Attempts 1901-1942

- Lime
- Gelatin
- Oxygen
- Splenectomy
- Bone marrow
- Sodium citrate
- Calcium lactate
- Witte's peptone
- Hydrogen peroxide
- Induced anaphylaxis
- Antidiphtheric serum
- The 'galvanic needle'
- Animal and human sera
- Adrenaline
- Bird's muscle
- IV oxalic acid
- Vitamin therapy
- X-ray irradiation
- Serum from the mother
- Tissue fibrinogen by mouth
- Bromide extract of egg white; sedative
- Blood—both injected and withdrawn therapeutically, auto-hemotherapy
- Female hormone therapy (in the belief that femininity prevents the expression of the hemophilic gene)

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Effective Treatments

- 1926, Surgeon General: 12 referenced attempts at whole blood transfusion
- 1934, McFarlane: topical application of Russell viper venom
- 1937, Patek and Taylor first characterization of anti-hemophilic globulin
- 1938, McFarlane: fresh whole plasma
- 1950s: EJ Cohn fractionation of whole human and animal plasma
  - Animal: Biggs and Macfarlane, 1954; Bidwell, 1955
  - Kekwick and Wolf, 1957; Soulier, Gobbi, Larrieu, 1957; Blomback, Blomback, Nilsson, 1958

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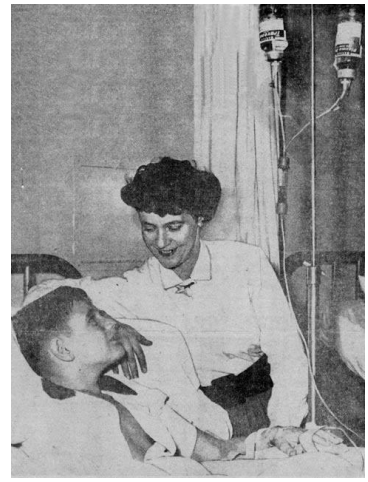

1952: Stephen Christmas
Canadian Hemophilia Society:
Delineation of factor IX deficiency (Christmas disease) from factor VIII deficiency

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1953

Nine-year-old Donald Burns smiles on father's knee. His is believed to be first successful appendectomy operation to a haemophiliac in North America.

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Breakthroughs

- 1964, Judith G. Pool (1919–75, U of Chi)
  - Cryoprecipitate
  - First opportunity for hemophilic home care
- 1968, Kenneth M. Brinkhous (1908–2000, UNC Chapel Hill)
  - First to chemically characterize factor VIII in 1938
  - Developed AHF with hemophilic dog experiments
  - AHF released through Hyland in 1968

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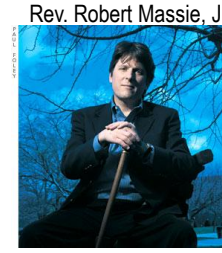
Advances in the 1960–70s

- Dental extractions and minor procedures using Kohn fractions
- Orthopedic correction of hemarthroses using AHF
- Prothrombin complex concentrate, II, VII, IX, X for inhibitor
- Home therapy
- Hemophilia treatment centers 1973
- By 1980, life expectancy was 60
- But high hepatitis rate, 20,000 donors/pool
  - No viral inactivation

Rev. Robert Massie, Jr



Susan Massie

Robert K. Massie

Massie R, Massie K. *Journey*. Knopf, USA 1973

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AIDS

- Fall 1980: *Pneumocystis carinii* pneumonia and Kaposi sarcoma in homosexual males
  - Searched for non-infectious causes such as amyl nitrite "poppers," anti-sperm antibodies or anal intercourse
- Spring 1982: CDC recorded three cases of PCP in hemophilics receiving AHF, all died
  - Reports of similar symptoms in Haitian hemophilics and drug abusers
  - No homosexual behavior or illegal drug use
  - Led to concept of blood-borne viral infection

Evatt BL. The tragic history of AIDS in the hemophilia population, 1982–1984. J Thrombos Haemost 2006; 4: 2295–301.

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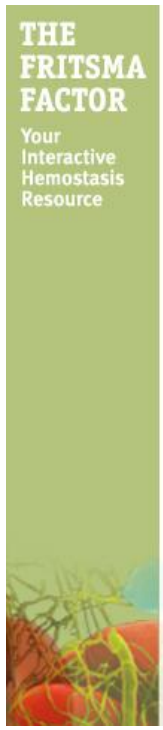

July 27, 1982

- CDC reported to blood and plasma industries, gay organizers, hemophilia organizations, FDA and NIH
- Consensus to not act
  - Evidence of three patients too weak to conclude hemophilics were a risk group
  - Concern it would stigmatize homosexual community
  - Lose homosexual donors to blood and plasma services
  - Millions of dollars to change manufacturing policies
- Fall of 1982: six more cases, including two non-hemophilic blood recipients
  - Donor services would not reveal donor identities to avoid embarrassing and subsequently losing donors
  - One definite identification

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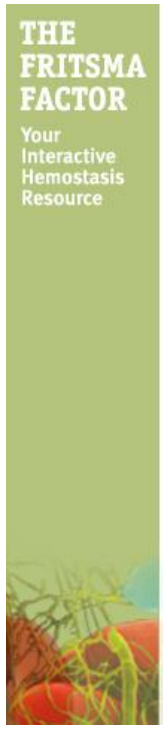

January 4, 1983

- CDC reported the statistical prevalence of hepatitis B was identical in hemophilics and AIDS risk groups (surrogate association)
- CDC reported to the same groups including ARC, AABB, National Hemophilia Foundation, National Gay Task Force, Pharmaceutical Mfrs Association, Council of Community Blood Centers, State and Territorial Epidemiologists, and individuals.
- Again, consensus to not act, debate was irrational, acrimonious and public, harshly critical of BL Evatt and CDC

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January 13, 1983

- CCBC and AABB: "*transfusions are life-saving procedures; some adverse reactions are acceptable to save lives. The rare disorder affecting nine cases is not enough to force a policy change*."
- ARC head Dr Cumming wrote: "*It has long been noted that CDC increasingly needs a major epidemic to justify its existence… In short, we can not depend on the CDC to provide scientific, objective, unbiased leadership*."
- NHF, however, already alarmed, had contacted plasma manufacturers in December, 1982

American Red Cross

National Hemophilia Foundation
for all bleeding and clotting disorders

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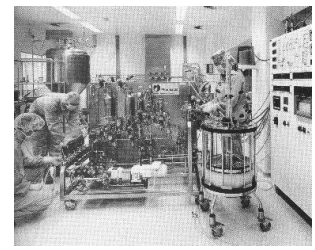
NHF Initiative: 1983

- Dec 1982: *Alpha Therapeutics* began to screen donors
- 20% of commercial plasma came from donor services who refused to screen donors for sexual orientation
- US Public Health Service guidelines, March 4, 1983
  - CDC bypassed FDA, sent guidelines direct to PHS
  - Donor screening and surrogate testing: hepatitis markers
- March, 1983, Baxter Hyland began heat treating plasma
- August, 1983, 26 confirmed cases of transfusion transmitted AIDS, including one F IX deficiency



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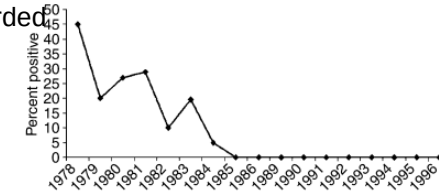
Virus Isolation: 1983

- Mid-1983: Pasteur Institute isolates virus from lymphadenopathy patients
- Feb, 1984: Pasteur Institute isolates virus from AIDS samples provided by CDC
- Sep, 1984: Alpha and Cutter demonstrate heat treatment is safe and does not increase immunogenicity
- Oct, 1984: CDC/PHS screening and heat treatment guidelines published and adopted
- By 1984, 63% of 15,500 US hemophilia patients had HIV
- Since 1/1/1985, not a single new factor-transmitted HIV infection has been recorded



Frequency of HIV infection in US hemophilia birth cohorts. (From medical records)

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Recombinant Clotting Factors

- 4/7/1976: *Genentech* incorporated
- 1981: *Genetics Institute* incorporated
- 1982: rFIX cloned by both (small molecule)
- Aug, 1984: Both cloned rFVIII gene and produced the protein
- 1985: rVWF coexpressed

Pipe SW. Recombinant clotting factors. Thromb Haemost 2008; 99: 840–50.

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rFVIII Barriers

- Extensive post-translational modification
  - Need for mammalian cloning system
  - Chinese hamster ovary cells
- rFVIII affinity for phospholipid
  - CHO membrane binds and degrades FVIII
  - CHO cells transfected with FVIII and VWF genes
  - Resolved by rVWF coexpression—higher affinity
- Need for serum-free cloning system
  - Eliminate animal viruses, ease purification
- High-volume fermentation process
  - Immunoaffinity, ion-exchange, pasteurization, solvent-detergent, nanofiltration reduces 7000 L to 1 L.

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rFVIII to Market

- Regulatory uncertainty
  - Sterility, consistency questions generate 600 tests/lot
- Baxter Hyland and Genetics Institute produced Recombinate®
- Bayer Miles Lab/Cutter Biological and Genentech produced Kogenate®
- 3/27/1987: UNC Chapel Hill, first phase II infusion into a 39 year-old hemophilic
- Recombinate® cleared 1992, Kogenate® 1993

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Post-market Advances

- B-domain deleted: ReFacto®
- Removal of human and animal protein additives (albumin): Advate®
- Hemostatic efficacy: 90% cessation of bleeding
- Risk of inhibitor formation in previously untreated persons (PUPs) is approximately double plasma-derived FVIII (pdFVIII)
- Risk of inhibitor formation in PTPs < 1%

Pipe SW. The promise and challenges of bioengineered recombinant clotting factors. J Thromb Haemost 2005; 3: 1692–1701.

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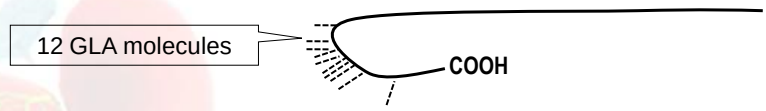
rFIX

- 1998: Genetics Institute BeneFix®
- Barrier: γ-carboxylation of 12 glutamic acids at amino terminus
  - Vitamin K
  - Coexpressed γ-glutamyl carboxylase
  - Coexpression of furin
- 90% bleeding cessation using 1–2 infusions
- PUPs—3% high titer inhibitors



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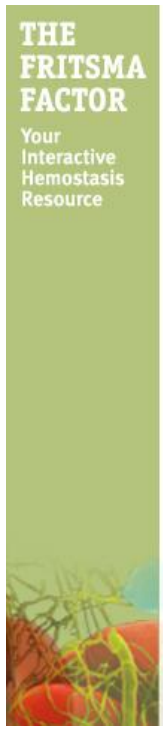

1999: rFVIIa

- Same γ-carboxylation issue
- For inhibitors: generates no DIC compared to activated prothrombin complex concentrates
- Activates through tissue factor and platelet surface binding
- Activates thrombin activatable fibrinolysis inhibitor (TAFI) to control fibrinolysis
- Novel variants in animal models

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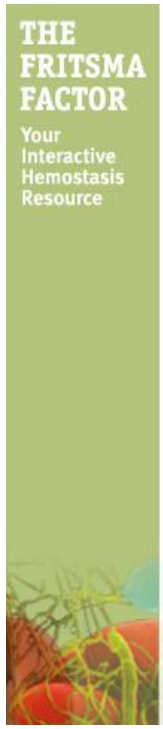

Primary Prophylaxis in Children

- 2005: Joint damage outcome study
  - 25 IU/kg every other day generates 6X decrease in joint deterioration by MRI vs on-demand (OD) Rx up to 6 YO
- 2009 Italian study on prophylaxis
  - 10 Y f/u on 25 IU/kg 3X a week showed 0.52 vs 1.08 total bleeds and 0.2 vs 0.52 joint bleeds/patients/month in OD
- 2009 Danish/Russian study
  - Orthopedic issues 15.6 in OD vs 2.2 in prophylaxis

Franchini M, Coppola A, Molinari AC, et al. Forum on the role of recombinant factor VIII in children with severe haemophilia A. Haemophilia 2009; 1–9.
Gringeri A, Lundin V, von Mackensen S, et al. Primary and secondary prophylaxis in children with haemophilia A reduces bleeding frequency and arthropathy development compared to on demand treatment; a 10-year, randomized clinical trial. J Thromb Haemost 2009;7
Ingerslev J, Lethagen S, Hvitfeldt Poulsen L, et al. A case-controlled Danish-Russian comparative study of clinical outcomes in younger severe haemophilia patients treated with prophylaxis compared to those managed with on-demand treatment. J Thromb Haemost 2009;7

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Primary Prophylaxis in Children

- Encouragement
  - Abundant safe rFVIII
- Barriers
  - Venous access with clotting, cost, compliance, duration
- Inhibitor formation in severe hemophilics
  - Meta-analysis of 20 trials
  - 1248 patients, 798 severe, 632 treated exclusively with plasma-derived and 616 with recombinant FVIII, median age 12
  - Combined trials data: 14% inhibitors in PD FVIII, 25% in rFVIII
  - High titer: 8.8% PD, 12.3% recombinant

Iorio A, Marcucci M, Marchesini E, Mannucci P. Plasma derived and recombinant factor VIII concentrates include a different rate of inhibitor development in hemophilia A patients. A systematic review of the literature. J Thromb Haemost 2009;7

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Future

- rVWF
- rXIII
- Gene transfer
  - One human trial was negative
  - Animal trials in progress
- Need for new bioassays
  - Chromogenic FVIII
  - Activated FVII
- Need for humane public policies

Lozier J. Gene therapy of the hemophilias. Semin Hematol 2004; 41:287–96.

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