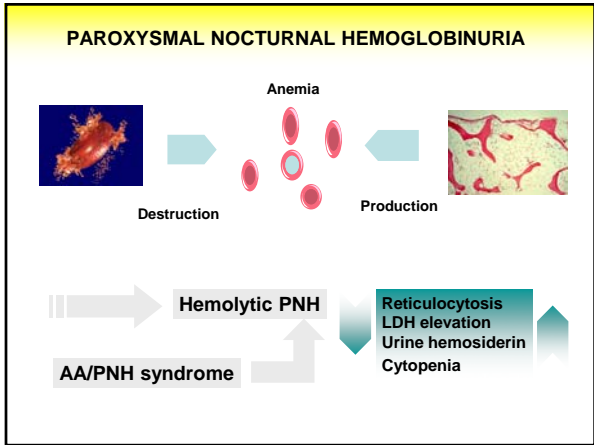


**PAROXYSMAL NOCTURNAL HEMOGLOBINURIA
MECHANISMS OF ANEMIA**

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CAUSES OF ANEMIA IN PNH

Potential Indicators of the Major Cause of Anemia in PNH


Chronic Hemolysis Destruction problem	Impaired Erythropoiesis Production problem
<ul style="list-style-type: none"> • CBC shows anemia only • Elevated reticulocyte count • Elevated LDH • Hemoglobinuria (typically only intermittently present) • Low or undetectable levels of haptoglobin • Iron deficiency (due to hemoglobinuria and/or hemosiderinuria) 	<ul style="list-style-type: none"> • CBC shows thrombocytopenia and/or neutropenia in addition to anemia • Low reticulocyte count • Normal LDH • Highly elevated levels of erythropoietin (EPO) • Normal haptoglobin levels

In cases where both are present, they can/should be addressed concomitantly

THERAPY OF FAILED PRODUCTION

- Immunosuppression when bone marrow failure present (blood cell production is impaired)
- AA/PNH syndrome: PNH clone size usually smaller
 - low platelet counts
 - low reticulocytes
 - low white cell count
- When blood counts not depressed and reticulocyte count is high, no benefit of immunosuppression. i.e. primary hemolytic PNH
- Therapies of bone marrow failure
 - CsA
 - ATG/CsA
 - Newer agents

HEMOLYSIS



Hemolysis in PNH is complement mediated

WHAT IS COMPLEMENT AND WHAT DOES IT HAVE TO DO WITH PNH?

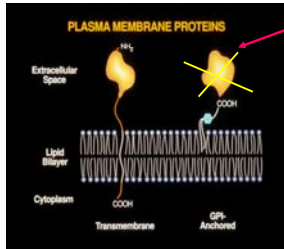
- Complement is the name given to a group of blood proteins that act together to help the body get rid of microbiological invaders
 - One of the ways it does this is by penetrating the membrane (outside surface) of the invading organism
 - When this happens to red cells, they burst, releasing their hemoglobin
 - It is activated spontaneously and by a variety of events (infections, trauma, etc.)
 - Complement circulates in an inactive form
 - It is normally activated more at night

HOW ARE OUR CELLS NORMALLY PROTECTED FROM COMPLEMENT

- Proteins in the serum inactivate complement when it is activated
- Proteins on the cell surface inactivate complement to prevent breakdown (lysis)
 - The most important of these is CD59, which is missing on the abnormal cells of PNH
 - For this reason, PNH red cells are extremely sensitive to very small amounts of activated complement

PNH RED CELLS LACK PROTECTION FROM COMPLEMENT

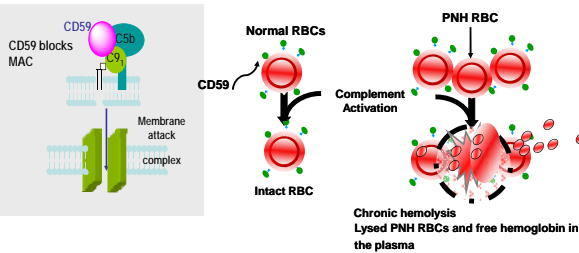
The most important of proteins protecting red cells are CD55 and CD59, which is missing on the abnormal cells of PNH. For this reason, PNH red cells are extremely sensitive to very small amounts of activated complement.

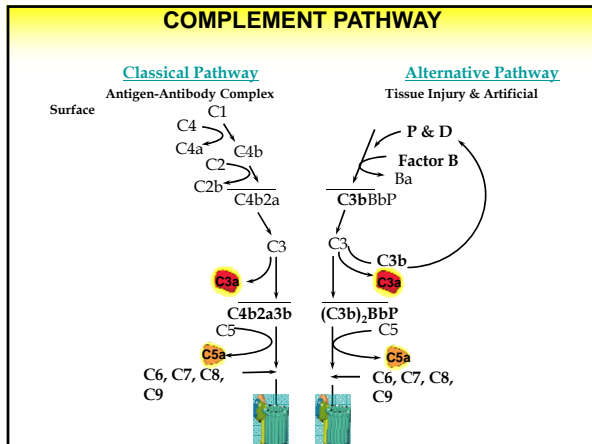


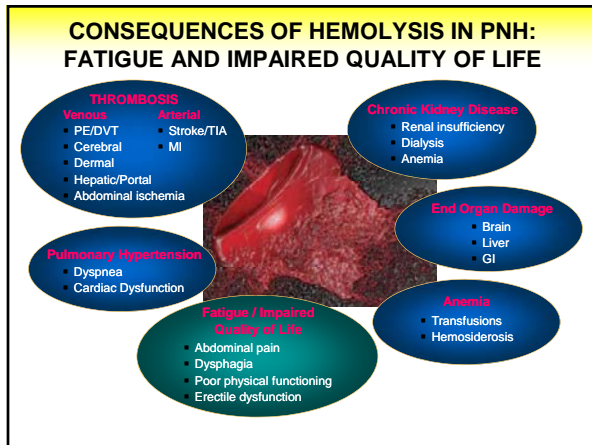
CD55 and CD59

What happens in PNH when complement is activated?
• Complement successfully attacks the red cells and they break up (hemolysis)
• The red cells are destroyed, resulting in anemia

MECHANISM OF HEMOLYSIS





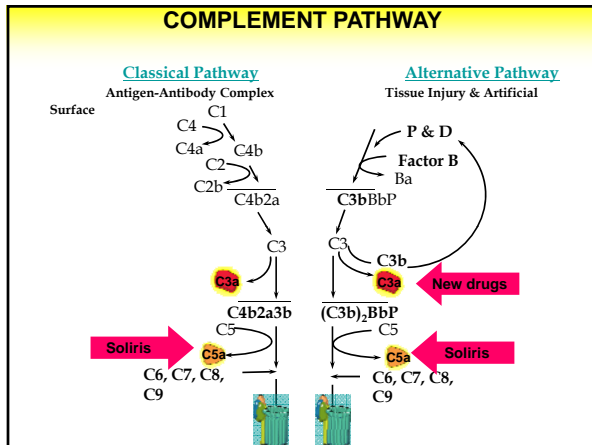


HEMOLYSIS CAUSES FATIGUE INDEPENDENT OF ANEMIA

- "Many patients note a feeling of fatigue that may be disabling during periods of hemoglobinuria."
- This is not related to hemoglobin level (anemia), as it disappears when the hemoglobinuria stops."
- "PNH patients frequently complain of disabling fatigue that is often out of proportion to the degree of anemia."
- Univariate analyses indicate hemolysis and anemia associated with fatigue
- Multivariate analysis indicates hemolysis drives fatigue in PNH – not anemia

THERAPY OF HEMOLYSIS

- Replace hemolysed blood
- Increase blood production
 - Iron (if deficient)
 - Folate
 - Erythropoietin
 - Treat immune bone marrow failure with immunosuppression
- Stabilize complement
 - Prednisone
 - Androgenic steroids
- Block complement activation
 - Soliris
 - Other complement blocker under development



COMPLEMENT BLOCKADE WITH ECUUZUMAB

Hillmen et al, NEJM 2007

WHAT DOES SOLIRIS® DO?

- Quickly and markedly reduces hemolysis
 - Stops hemoglobinuria
 - Increases hematocrit and hemoglobin level
 - Reduces transfusions
 - Hematocrit may not be quite normal
- Stops the symptoms associated with hemolysis
 - “Fatigue”
 - Esophageal and abdominal spasm
 - Erectile dysfunction
 - Improves sense of well being
- Appears to reduce thrombosis and thereby change role of chronic blood thinning

ECULIZUMAB

- Issues
 - Cost vs. benefit
 - Partial responders
 - Inconvenience
 - Stopping
 - Risks

- How to improve the response in patients who showed less than “perfect response”
