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**National Organization for Rare Disorders
Regional PNH Patient Support Meeting
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Chicago, IL**

What Is PNH?

And What Can Be Done About It.

PNH Is:

- A disorder of blood
- Rare
- Due to a glitch in a gene in a single cell
- Manifest in a variety of ways
- Able to be treated

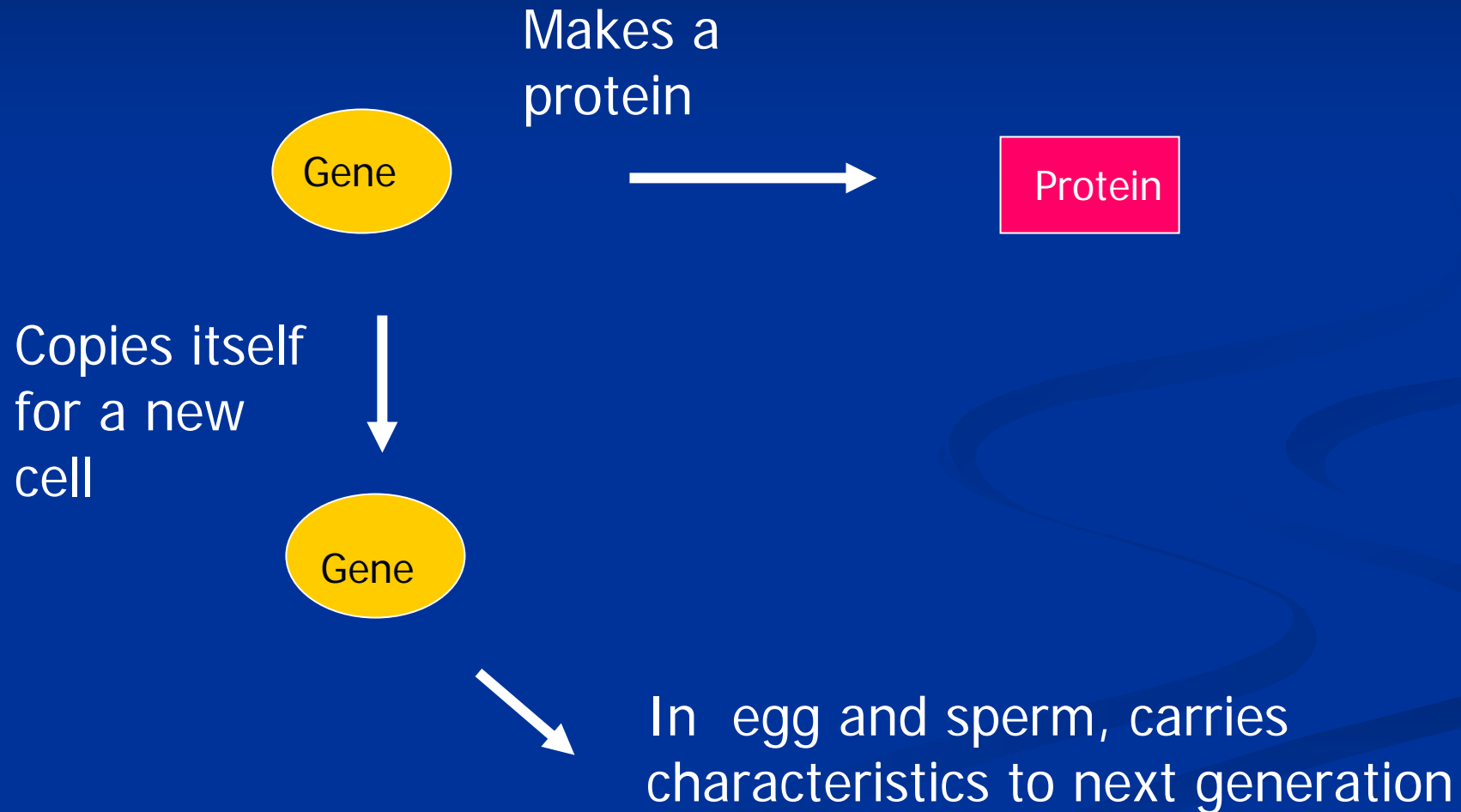
What We Will Cover Today

- How does PNH get started?
- What are the ways PNH affects one?
- What can be done to treat PNH?

How Does PNH Get Started?

- PNH is due to a change in a gene in a blood stem cell

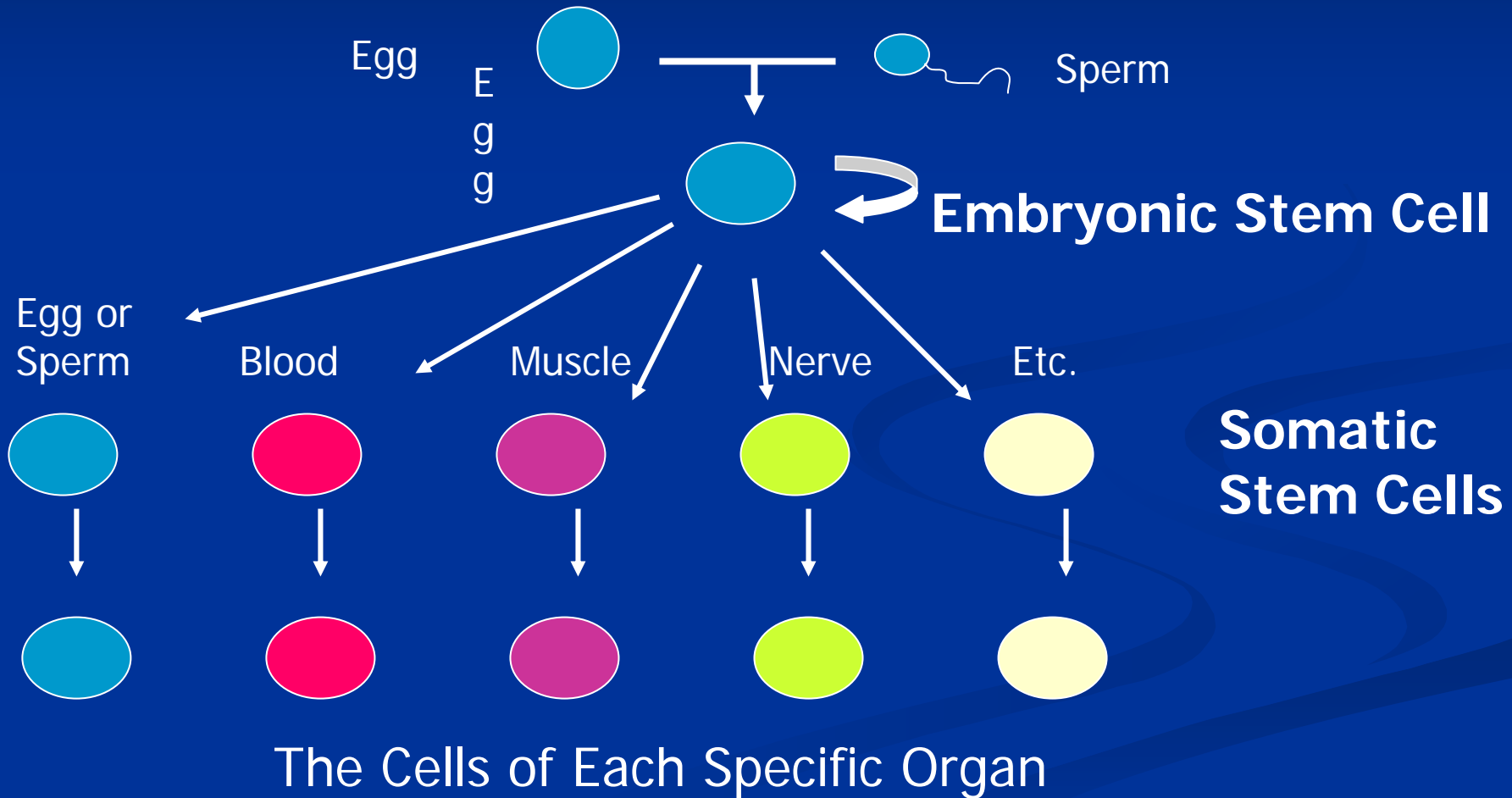
What A Gene Does



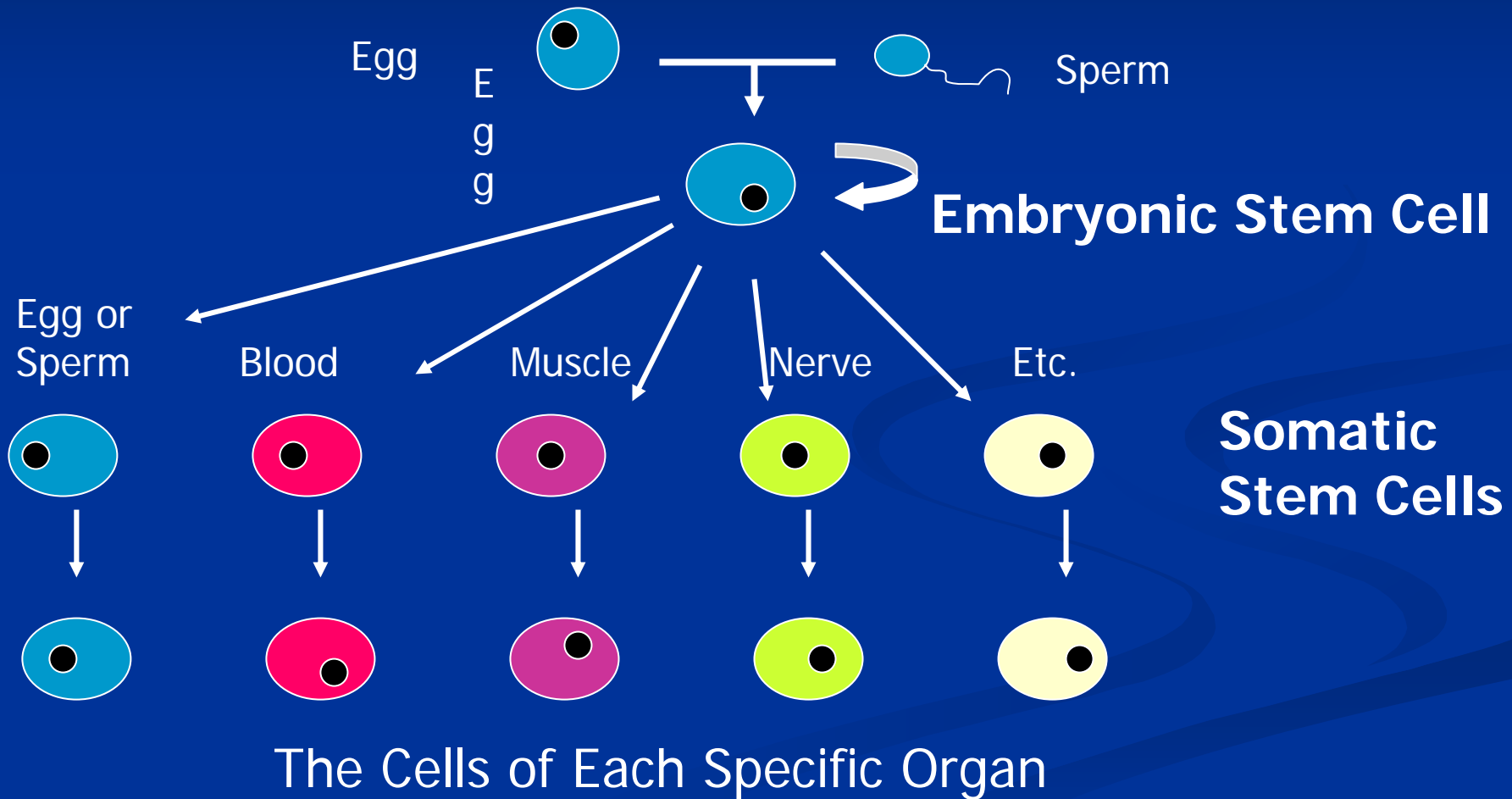
What Is A Mutation?

- A mutation is a “mistake” in a gene that arises during copying and is not corrected
- The mutation is transmitted to daughter cells
- The effect of a mutation:
 - None
 - An altered protein
 - No protein is produced

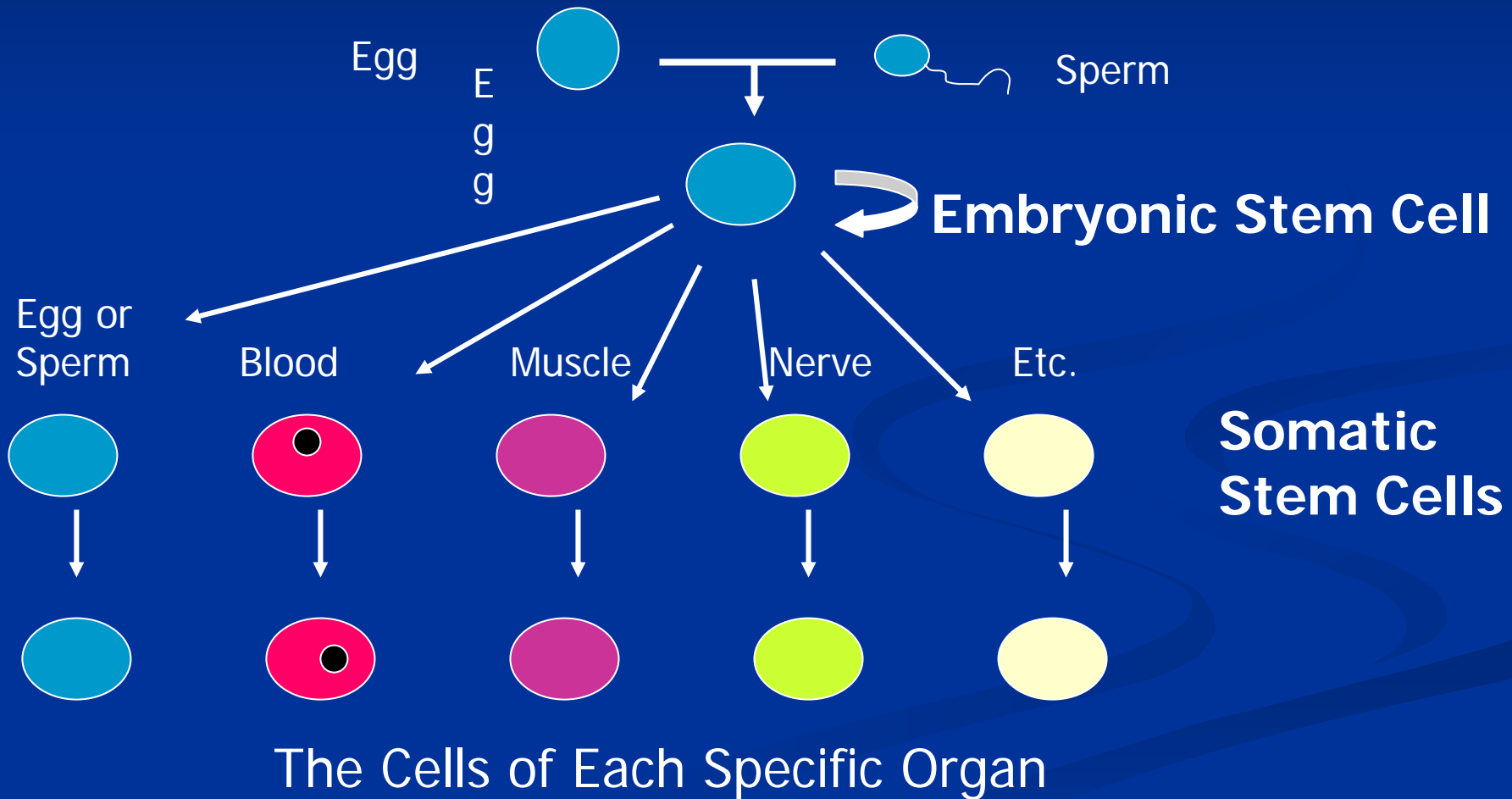
Stem Cells



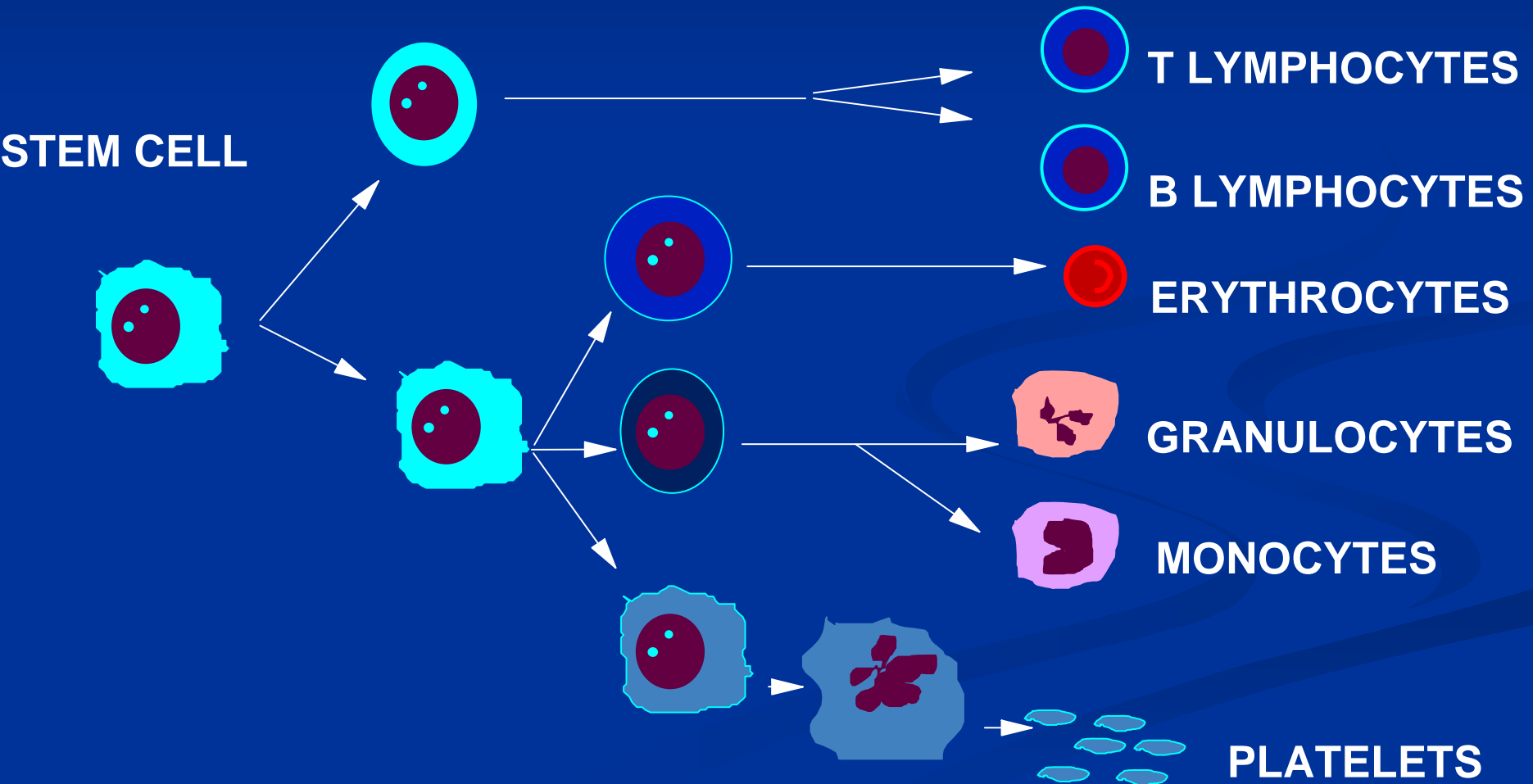
Stem Cells



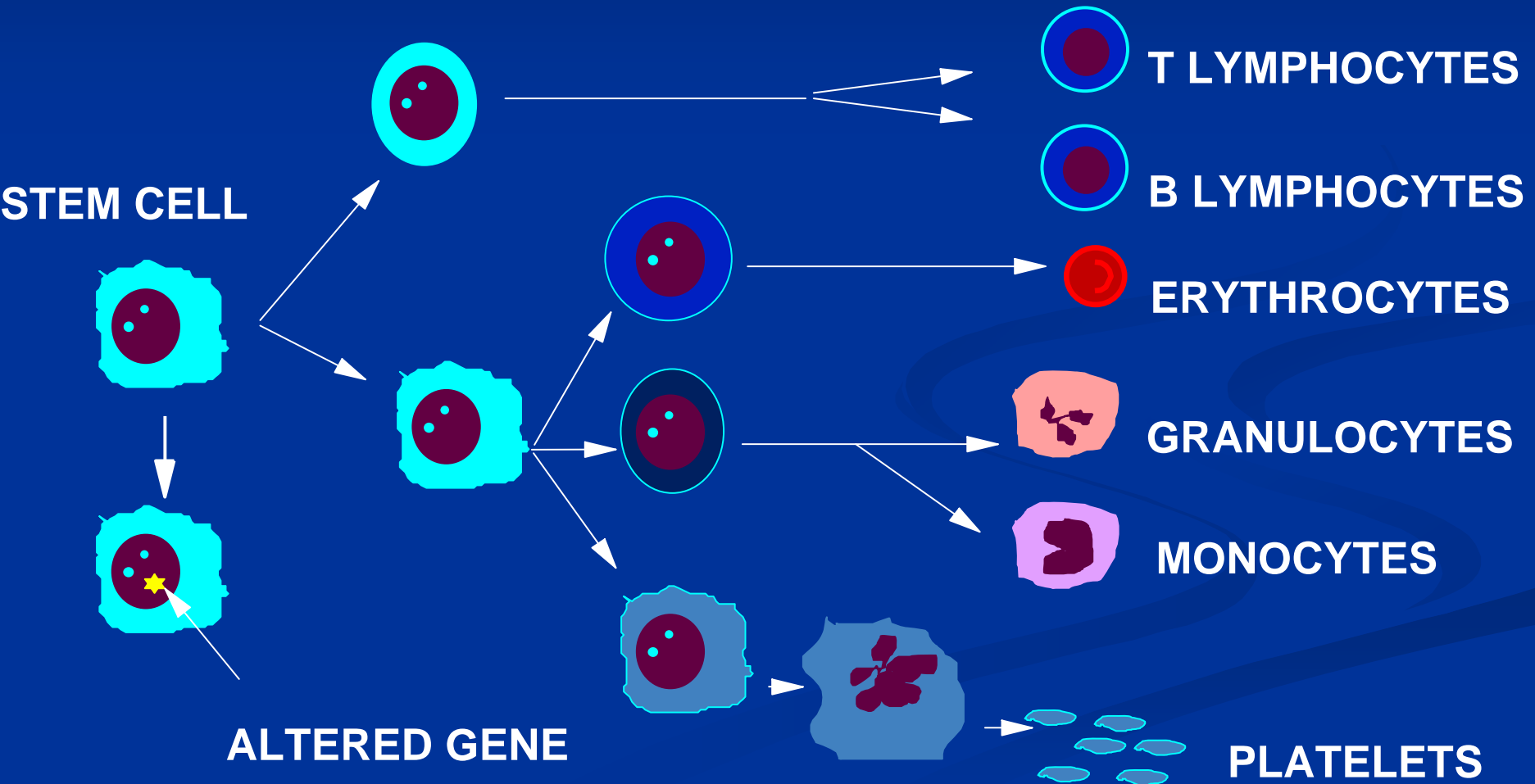
Stem Cells



A Stem Cell Can Give Rise To All The Cells Of The Blood

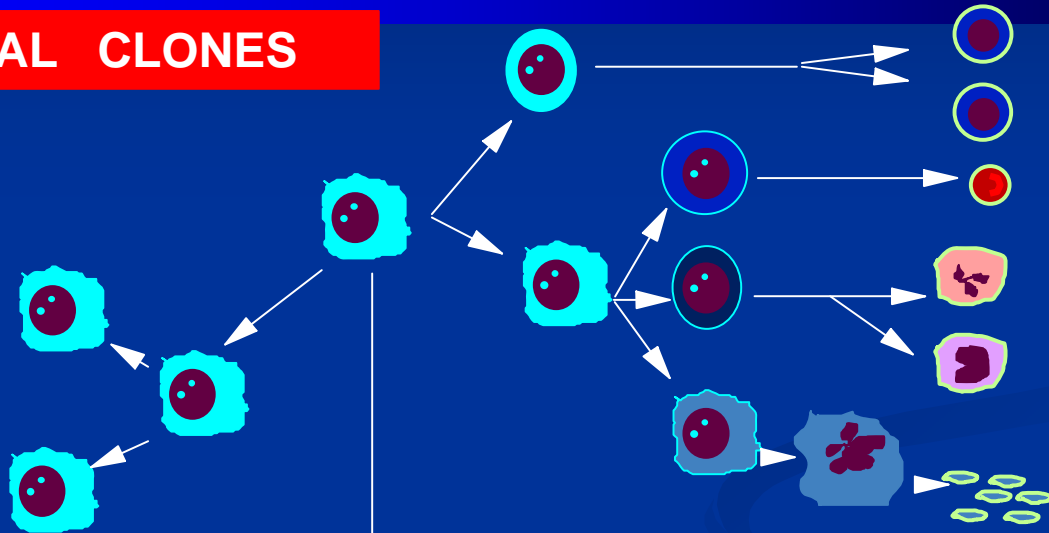


In PNH, a single mutation occurs in one blood stem cell

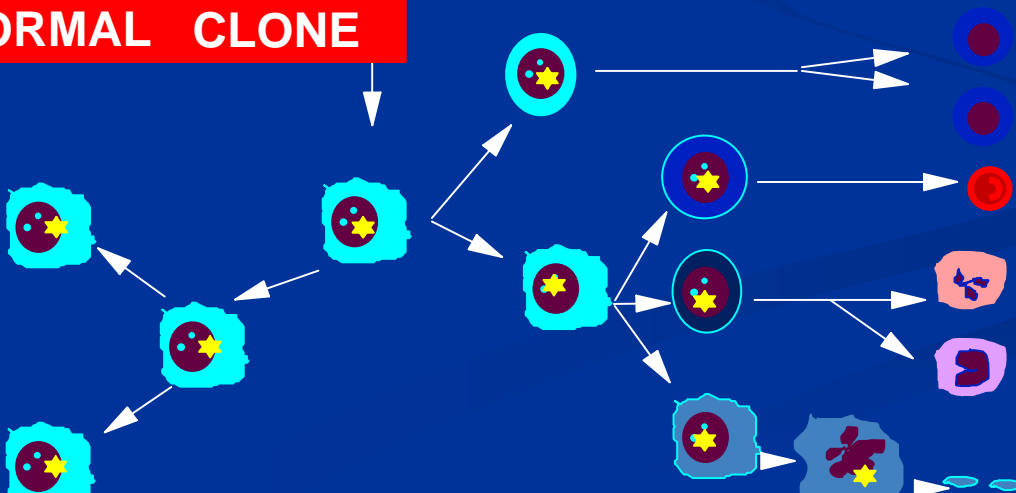


Evolution of PNH in Marrow

NORMAL CLONES



ABNORMAL CLONE

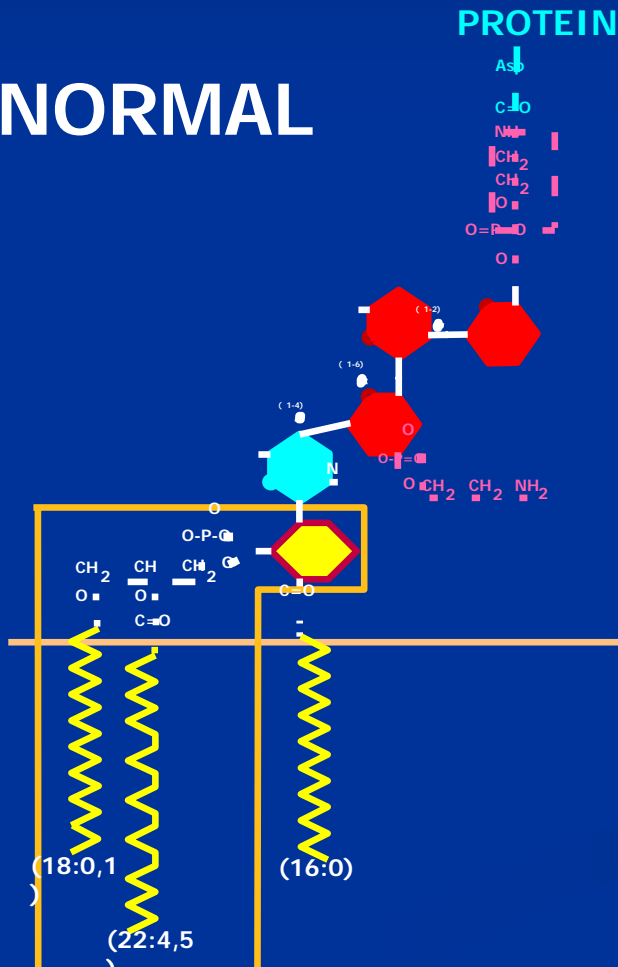


The Beginning of PNH

- The change that occurs in PNH stops the production of an anchor that ties protein molecules to the cell
 - Sometimes the stop is only partial and PNH II cells occur

The GPI Anchor Defect in PNH

NORMAL



PNH



The Beginning of PNH

- The change that occurs in PNH stops the production of an anchor that ties protein molecules to the outside of the cell
 - Sometimes the stop is only partial and PNH II cells occur
- About 25 molecules are not attached but only one plays a major role in causing PNH
 - This is CD59, which protects the cells from complement

How Do These Abnormal Cells Take Over The Bone Marrow?

- Many normal people have blood stem cells with the abnormality characteristic of PNH in very small numbers (perhaps 6 per 1,000,000 bone marrow cells)
- In PNH, something allows the abnormal cells to become a major population in the marrow and blood (anywhere from 1% to over 90%)
 - This “something” may be related to aplastic anemia, a disease of poor production of blood from the marrow

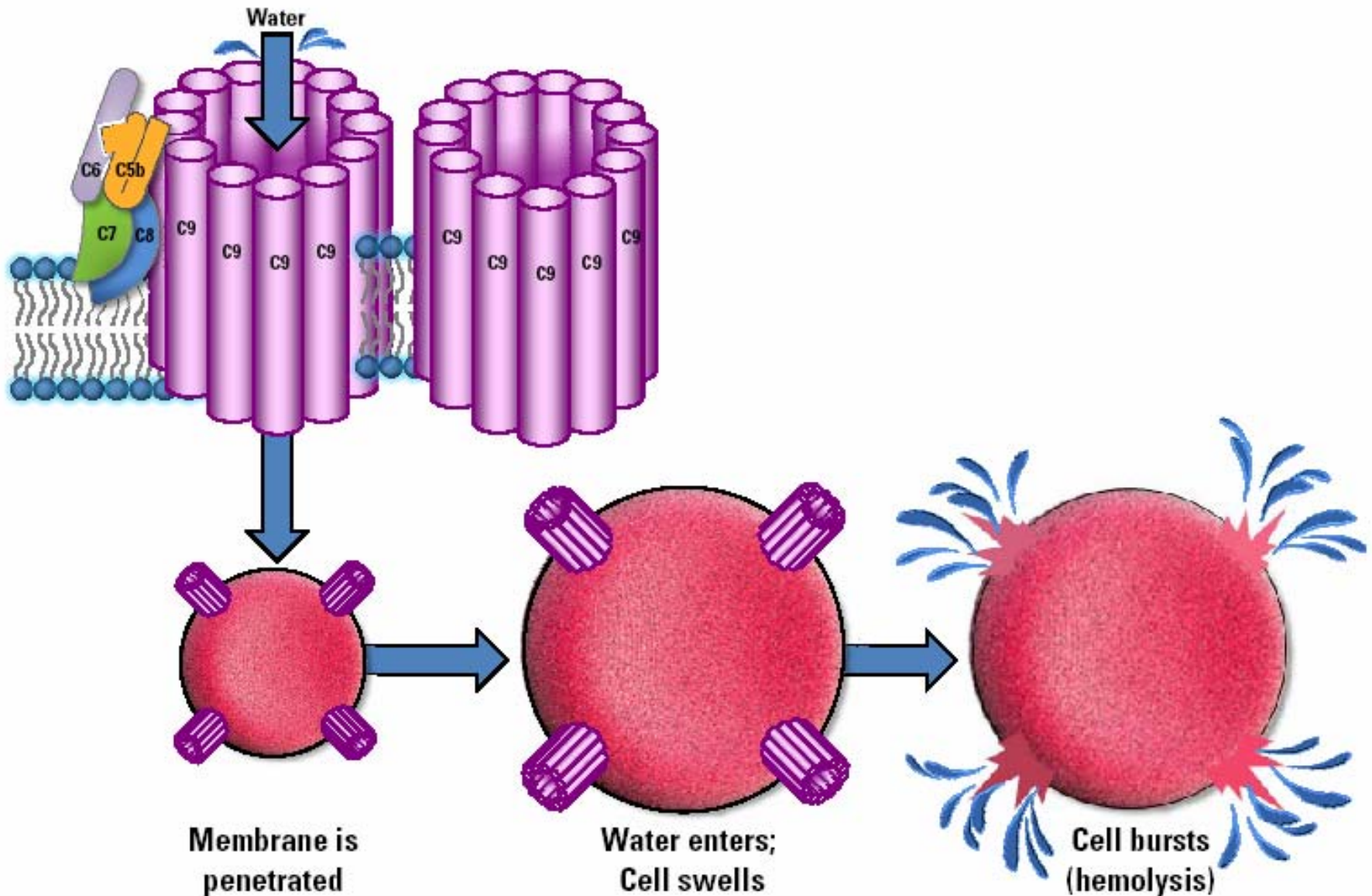
What Does PNH Have To Do With Aplastic Anemia

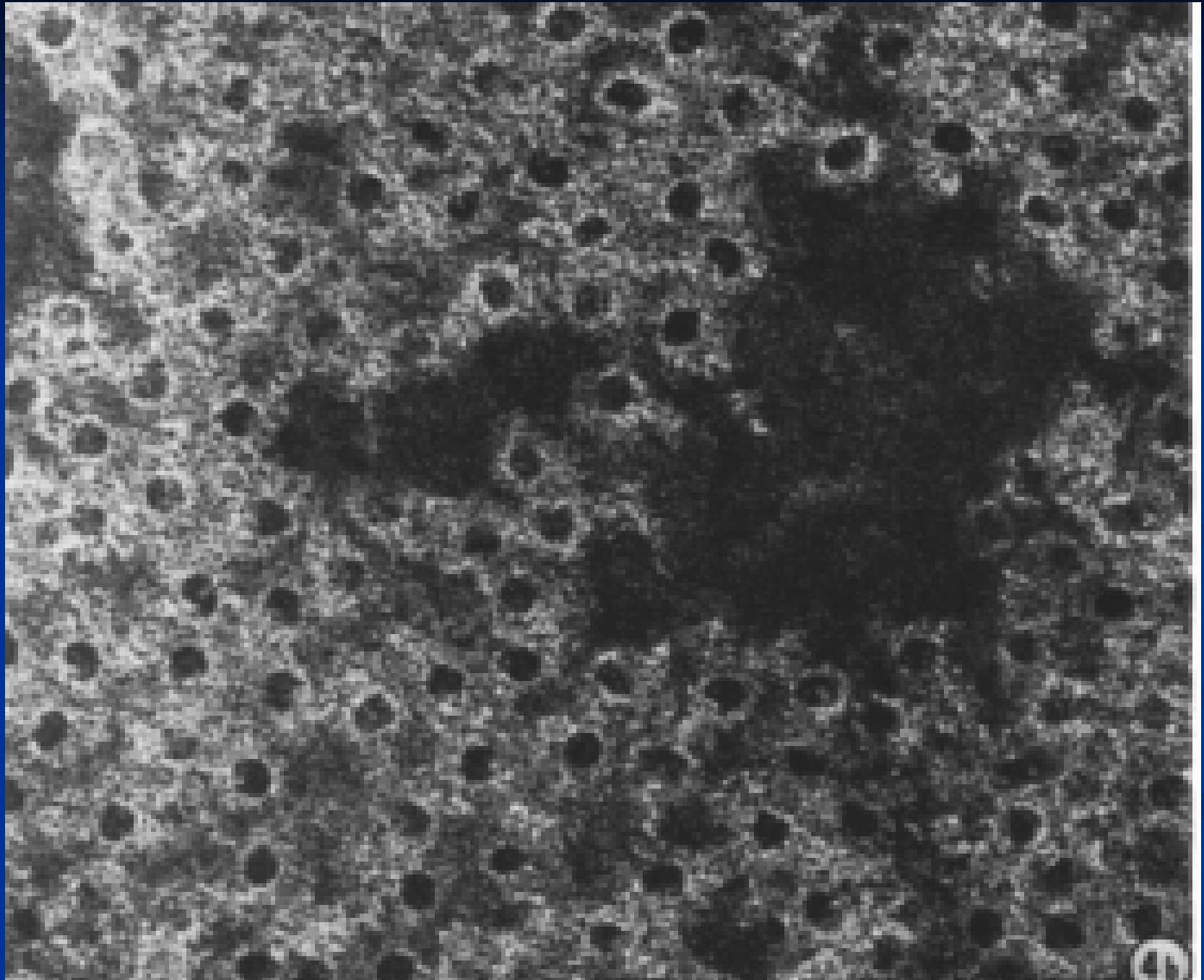
- Many PNH patients have aplastic anemia or a history of aplastic anemia
- Many PNH patients show signs of inadequate blood cell formation
 - Low granulocyte (white cell) and low platelet counts are such signs
- All patients have evidence of a “lazy” bone marrow
- Therefore, whatever causes aplastic anemia (immune suppression?) may allow PNH to develop

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

Lysis Of Red Blood Cell By C5b-9





What is Complement?

Complement circulates in an inactive form

- It is activated spontaneously and by a variety of events (infections, trauma, etc.)
 - 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

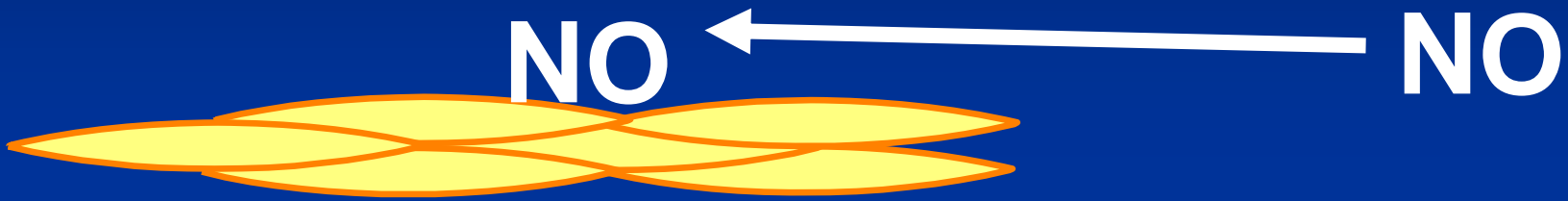
What Happens in PNH When Complement Is Activated?

- Complement successfully attacks the red cells and they break up (hemolysis)
 - This releases hemoglobin (the red pigment in red cells) into the plasma (the fluid part of the blood)"
- The red cells are destroyed, resulting in anemia

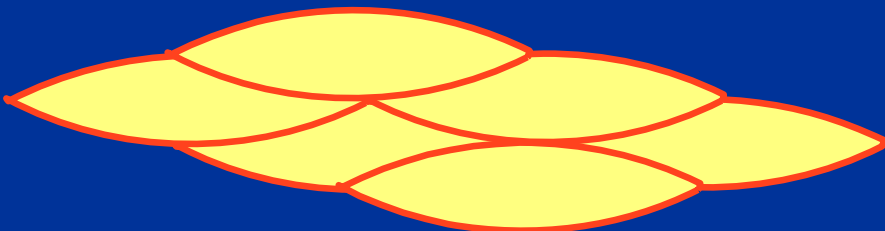
What Are The Effects of Releasing Hemoglobin?

- Some of the hemoglobin passes through the kidneys and into the urine, causing red to dark brown urine
 - This causes a marked loss of iron from the body
 - In the long run, this damages the kidney
- Free hemoglobin binds nitric oxide

Action of Nitric Oxide (NO)

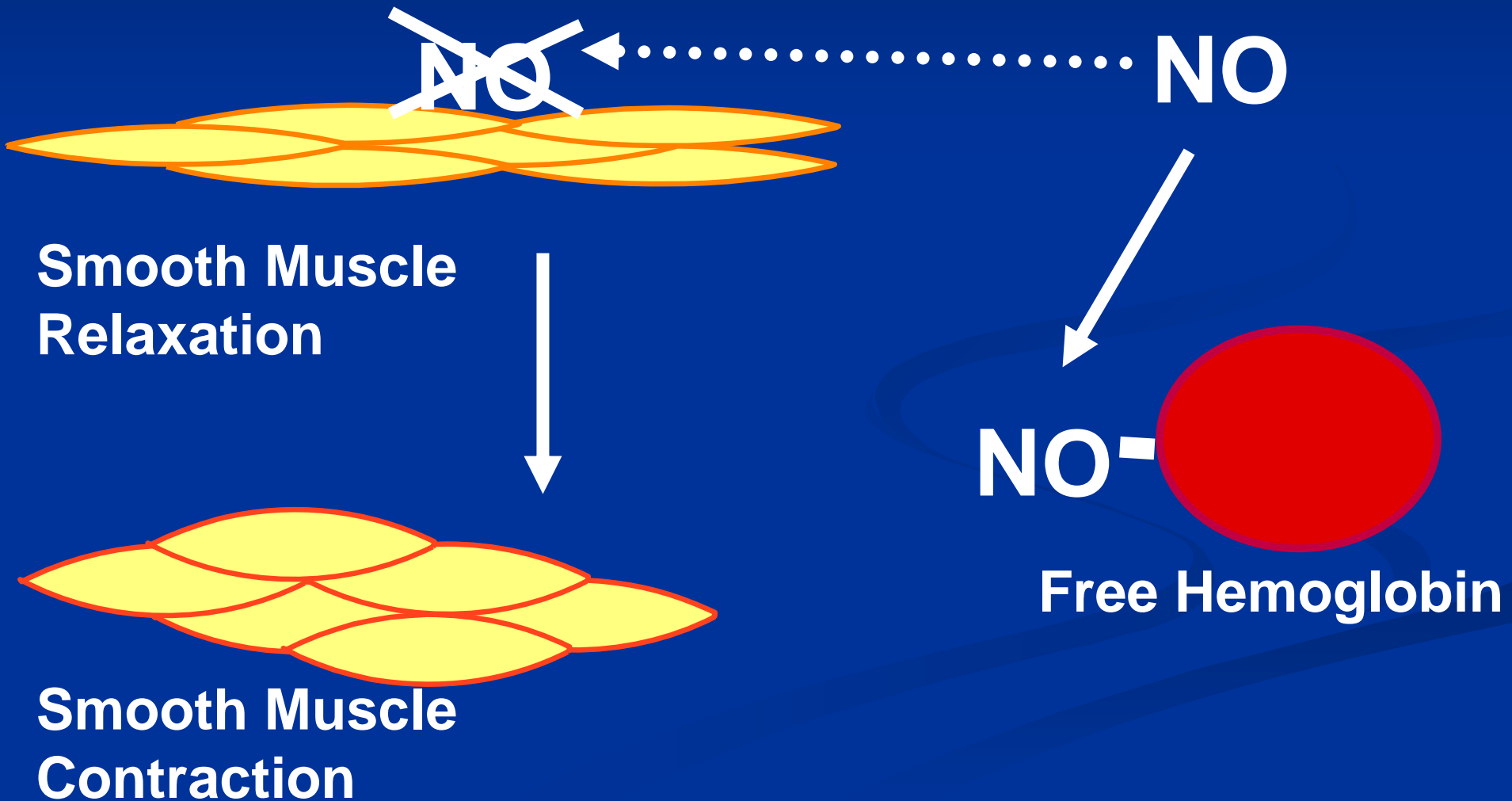


Smooth Muscle
Relaxation



Smooth Muscle
Contraction

Free Hemoglobin Binds NO



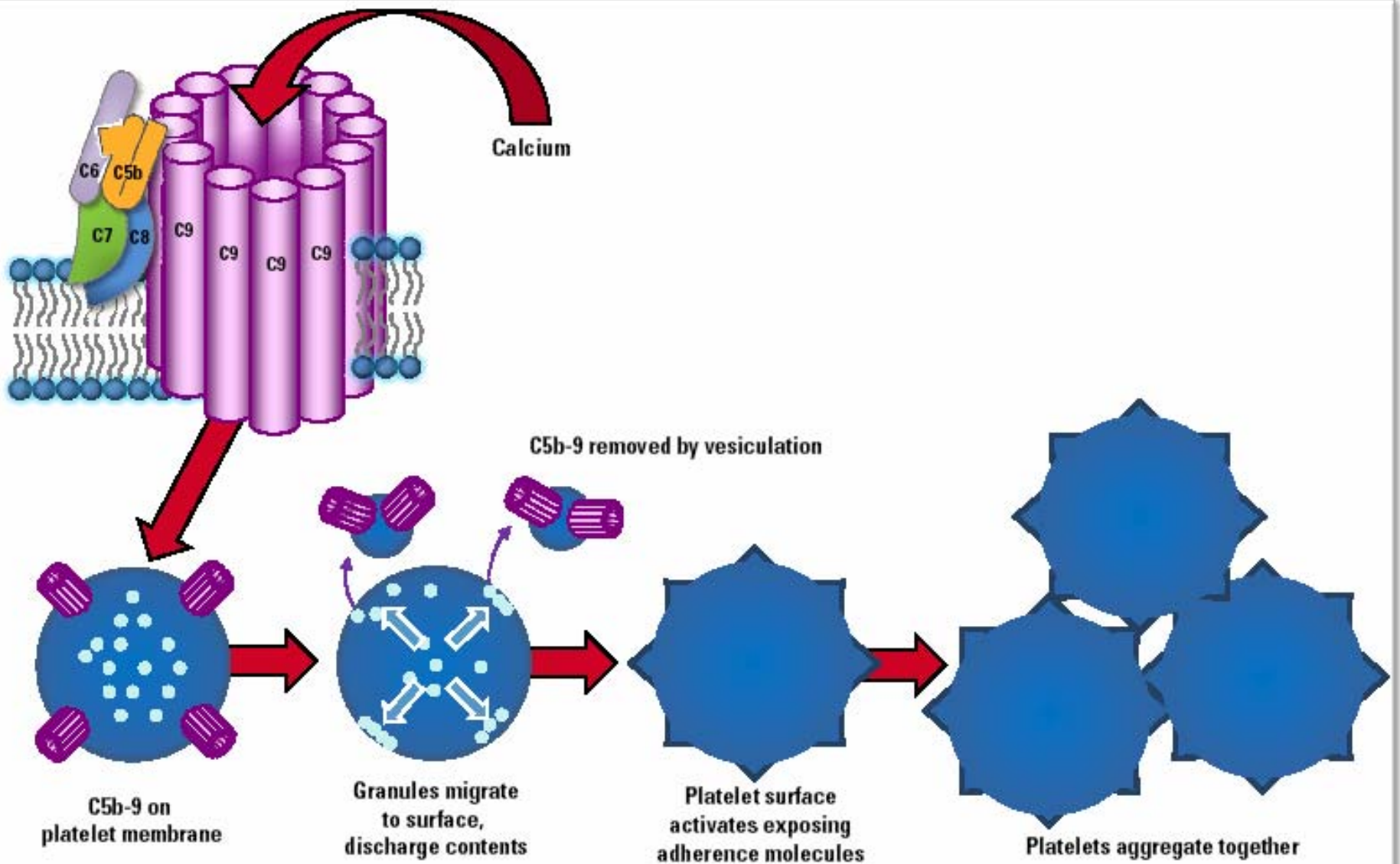
What Are The Effects of Nitric Oxide Trapping by Hemoglobin

- Spasm of the esophagus
- Abdominal pain
- Erectile dysfunction
- Other symptoms such as “fatigue”

What Happens in PNH When Complement Is Activated?

- Platelets are attacked and become "activated"
 - They stick together and form clots

Activation Of Platelets By C5b-9



What Happens in PNH When Complement Is Activated?

- Platelets are attacked and become "activated"
 - They stick together and form clots
- These clots are often in unusual places
 - Liver veins ("Budd-Chiari syndrome")
 - Other abdominal veins
 - Veins covering the brain

The Clinical Picture in PNH

- Hemolytic anemia due to complement activation
 - Hemoglobinuria and, eventually, kidney damage
 - Anemia to a variable degree
 - Effects of NO trapping
- Thrombosis due to complement activation
 - Often in unusual places (liver veins, abdominal veins, etc)
- “Lazy” bone marrow (not related to complement activation)

What Can Be Done For PNH?

- Symptomatic treatment
 - Iron supplementation
 - Folic acid
 - Transfusion

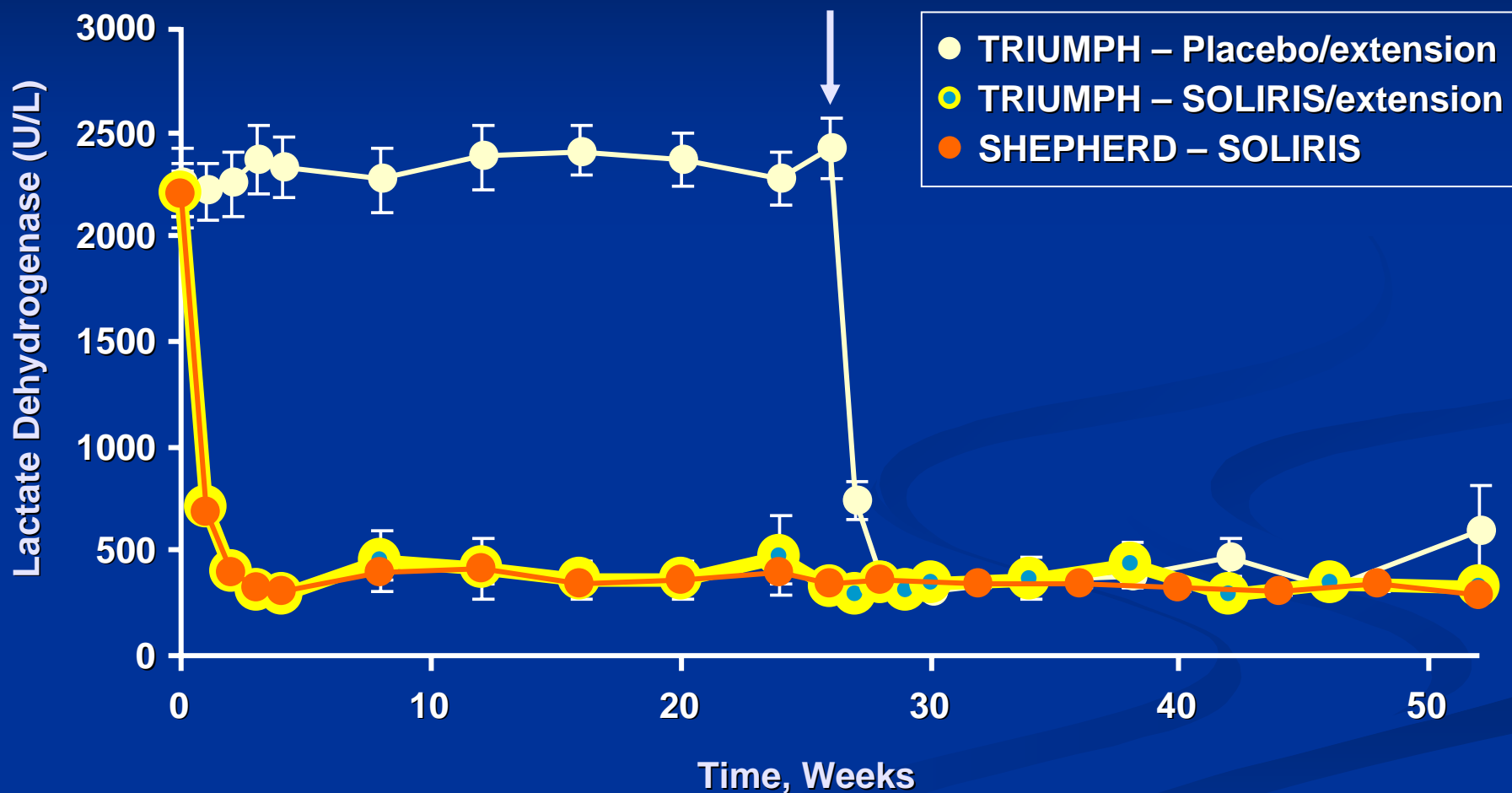
What Can Be Done For PNH?

- Treatment of thrombosis
 - Prevention by coumadin
 - Acute treatment by clot busters
 - Use of coumadin or heparin
- Stopping the effect of complement activation
 - Prednisone
 - Eculizumab (Soliris®), an antibody that inactivates one of the components of complement (C5)

What Does Soliris® Do?

- Quickly and markedly reduces hemolysis
 - Stops hemoglobinuria
 - Increases hematocrit and hemoglobin level
 - Reduces transfusions
 - Hematocrit may not be quite normal

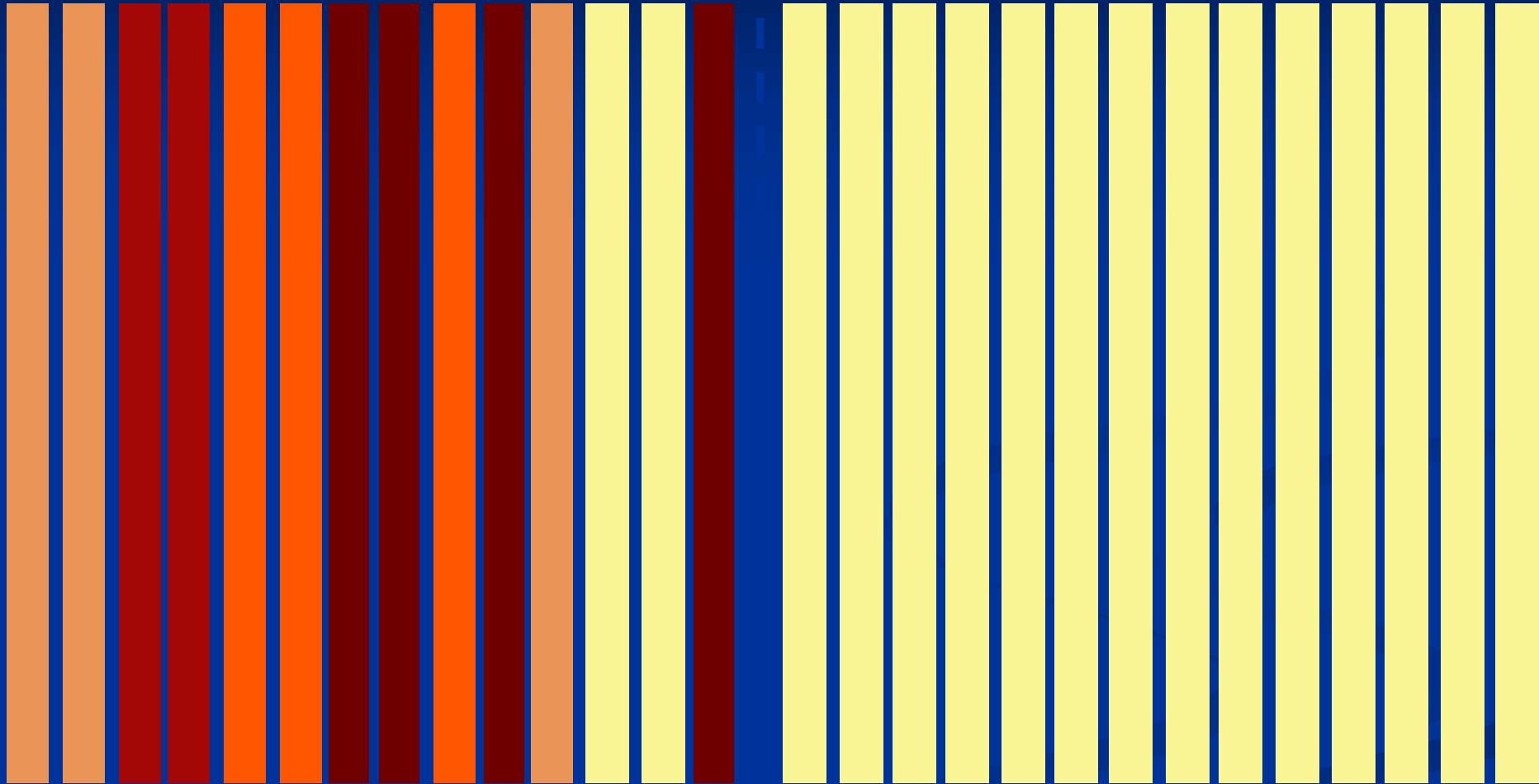
Reduction in LDH During Soliris® Treatment in TRIUMPH and SHEPHERD



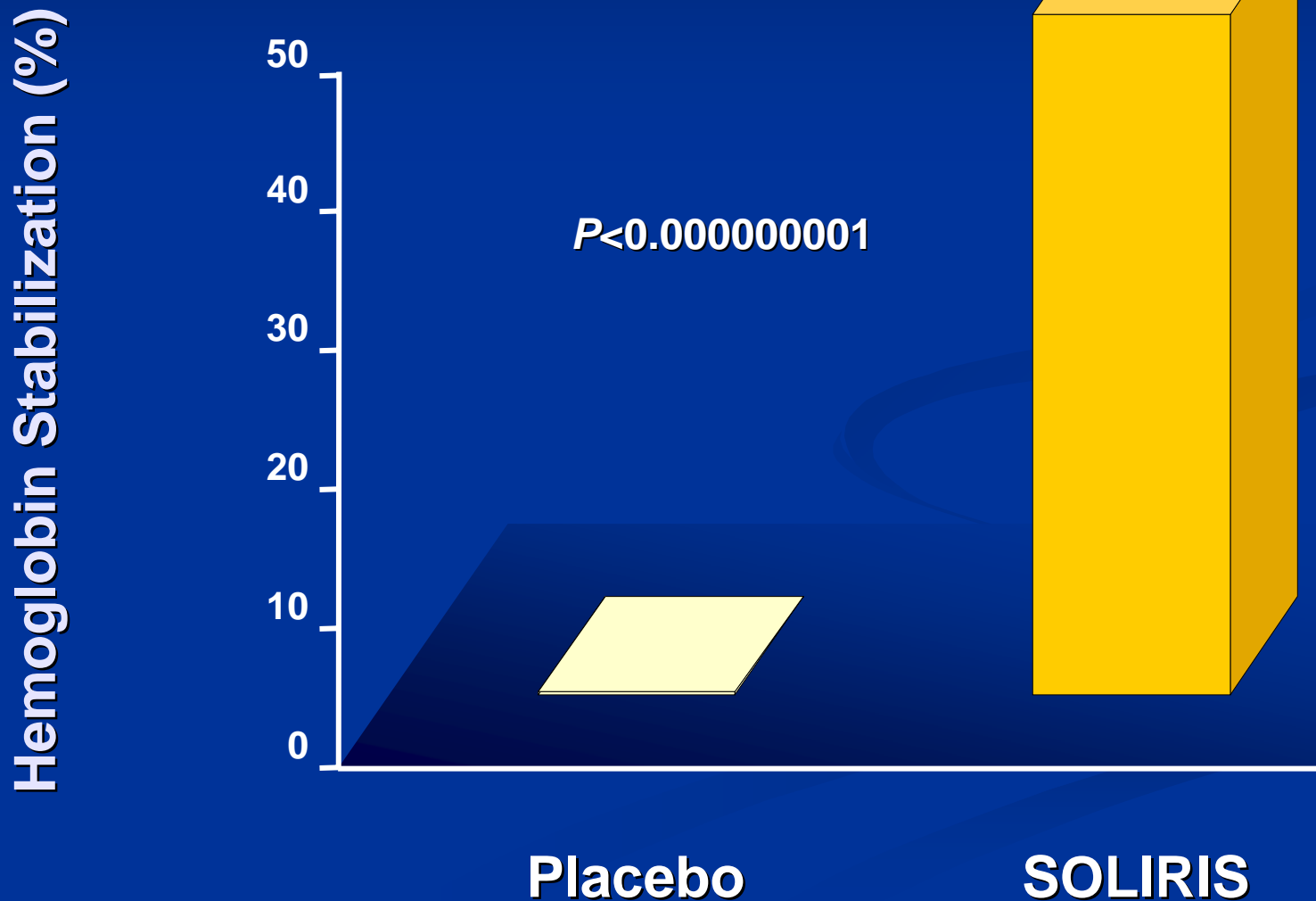
PI: All patients sustained a reduction in intravascular hemolysis over a total SOLIRIS exposure time ranging from 10 to 54 months.

TRIUMPH placebo patients switched to SOLIRIS after week 26. All TRIUMPH patients entered the long term extension study.

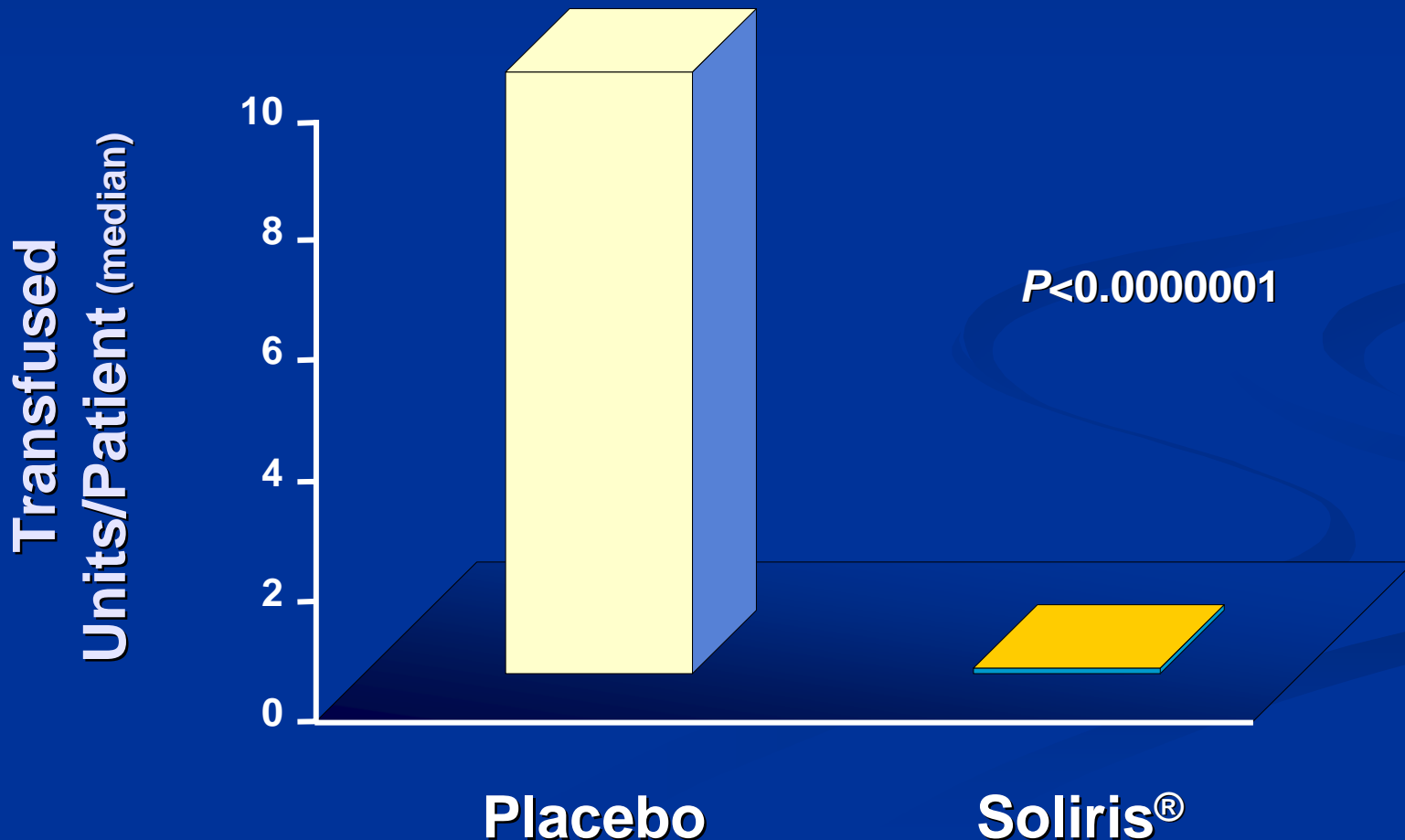
D.T., urine score 2 weeks before & after Eculizumab



Effect of Soliris[®] on Ability to Maintain a Good Hemoglobin



Effect of Soliris® on Transfusion in PNH



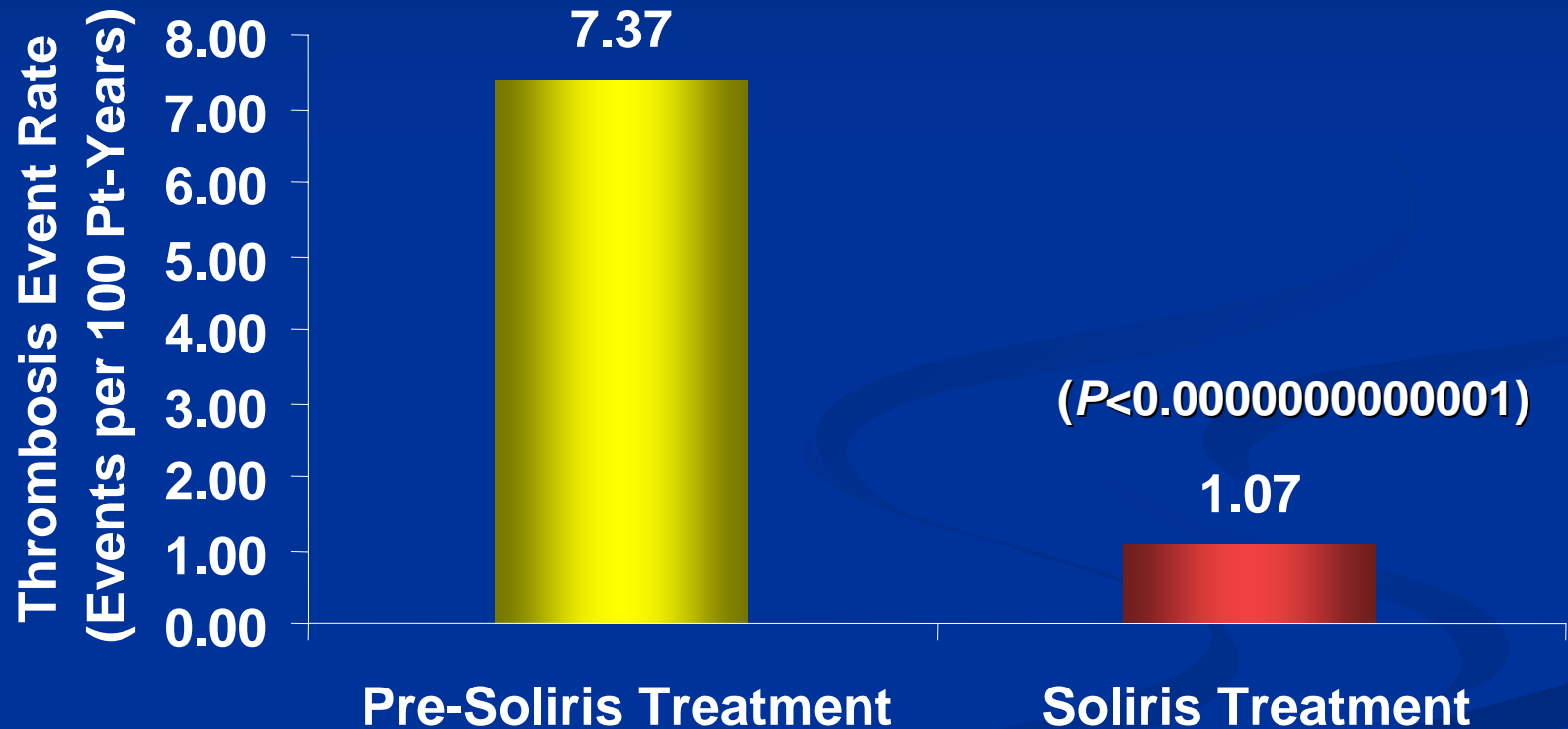
What Does Soliris® Do?

- Stops the symptoms associated with hemolysis
 - "Fatigue"
 - Esophageal and abdominal spasm
 - Erectile dysfunction
 - Improves sense of well being

What Does Soliris® Do?

- Appears to reduce thrombosis
 - May change role of chronic blood thinning

Clots in Patients With and Without Soliris™



Hillmn P, et al. *Blood*. First Edition Papr, prepublished online August 16, 2007.

What Does Soliris® Do?

Improves kidney function

- May in part be due to reduced hemoglobinuria
- May in part be due to availability of nitric oxide
- Improves hypertension

What Does Soliris® NOT Do?

- Does not appear to improve impaired hematopoiesis (lazy bone marrow)
 - Low white count or low platelet count will persist
 - Other treatments may be indicated
 - Bone marrow transplantation
 - ATG and other immunosuppressives

Downside of Soliris® Treatment

- Susceptibility to sepsis by meningococcal organism
 - All patients must be vaccinated
 - All patients must know to seek medical help at once when fever happens
 - All patients must carry cards describing this complication
- Cost
- Inconvenience
 - Must be given every 12-14 days by vein

Who Should Get Soliris®?

- Patients with significant anemia, especially those requiring transfusion
- Patients with clots or a history of clots, especially of the abdomen or brain
- Patients incapacitated by symptoms of PNH

In all cases, the decision should be made by doctors and patients that understand PNH and its treatment

The End

Any Questions?