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Course: blood transfusion
Level: Senior Stage / Medical Laboratory tec

Lecture 4 : The Rhesus (Rh) Blood Group System

Introduction

- The Rh blood group system is named after the Rhesus monkey (Macaca mulatta), which was used in early immunization experiments.
- When Rhesus monkey red blood cells (RBCs) were injected into rabbits and guinea pigs, the animals produced antibodies that also agglutinated human RBCs.
- This cross-reactivity led to the discovery of the so-called “Rh factor.”

🔻 The Rh system is the second most important blood group system in transfusion medicine — after the ABO system.The Rh system contains over 50 antigens, but five are clinically significant: D, C, c, E, and e. No “d” antigen exists — “d” simply indicates the absence of D antigen.

Key Antigen: D

- The D antigen (Rh factor) is the most immunogenic and clinically significant.
- Rh positive (Rh^+) → D antigen present
- Rh negative (Rh^-) → D antigen absent
- Example:
  - A^+ → A antigen + D antigen
  - A^- → A antigen only without D antigen

Clinical Importance of this system : Rh antibodies are clinically significant because they can cause:

1. Hemolytic Transfusion Reactions (HTR)
2. Hemolytic Disease of the Newborn (HDN) due to maternal anti-D crossing the placenta.

Rh Nomenclature Systems

There are two main systems used to describe Rh antigens:

System	Basis	Example	Usage
Fisher–Race	Each antigen (D, C, E) controlled by a separate gene	Dce, DCe	Most widely used
Wiener	One gene controls multiple antigens (D,C,E)	R_0, R_1, R_2, r	more complex and less commonly used.

Equivalence Table

Fisher–Race (CDE)	Wiener
Dce	**R_0**
DCe	**R_1**
DcE	**R_2**
DCE	**Rz**
dce	**r**
dCe	**r′**
dcE	**r″**
dCE	**ry**

Molecular and Genetic Basis of system

Genes of this system Located on chromosome 1:

- RHD gene → D antigen
- RHCE gene → C, c, E, and e antigens
  - The RHAG gene (chromosome 6) encodes Rh-associated glycoprotein (RhAG), which forms a complex stabilizing the Rh proteins on the RBC membrane.

Inheritance Pattern : this system Follows Mendelian dominance:

- Rh^+ → DD or Dd : Rh^- → dd

Example (Punnett Square):

- Two heterozygous Rh^+ parents (Dd × Dd) produce:
  - 25% DD (Rh^+) , 50% Dd (Rh^+) , 25% dd (Rh^-)
- Two Rh^- parents (dd × dd) → all Rh^- offspring.

Rh Antibodies

Feature	Description
Type of Ig	IgG (immune, not naturally occurring) some IgM
Produced After	Pregnancy or transfusion with Rh^+ blood
Most Immunogenic Antigen	D antigen
Alloimmunization Rate	~80% of Rh^- individuals exposed to one Rh^+ unit
Dosage Effect:	All Rh antibodies except anti-D show a dosage effect that meaning they react more strongly with RBCs homozygous for a particular antigen than heterozygous cells. Example: EE cells → stronger reaction than Ee cells.

Rh Phenotypic Variants

A. Weak D (formerly D^u)

Feature	Description
Mechanism	Quantitative decease in D antigen expression
Serology	Negative at immediate spin; positive at AHG phase
Causes	Altered D protein, C in trans effect (e.g., Dce/dCe)
Donor Status	Treated as D^+ (Rh+)
Recipient Status	Usually safe to receive D^+ blood (Rh+)

B. Partial D Phenotype

Feature	Description
Mechanism	Qualitative alteration — some D epitopes missing
D Antigen Level	Normal, but altered structure
Alloimmunization Risk	Can form anti-D upon exposure to complete D antigen
Donor Classification	D^+ (Rh+)
Recipient Classification	Must receive D^- blood (Rh-)

C. Rh null Phenotype ("Golden Blood")

Feature	Description
Definition	RBCs lack all Rh antigens (Rh and RhAG)
RBC Morphology	Stomatocytosis → mild hemolytic anemia
Clinical Value	Vital for transfusion compatibility and research

9. Summary Table: Comparison of Rh Variants

Type	Cause	Effect on D Antigen	Clinical Concern
Weak D	Quantitative decrease	Fewer D sites	Usually safe to receive D^+ blood
Partial D	Qualitative change	Altered epitopes	May produce anti-D → must get D^- blood
Rh null	Absence of Rh complex	No Rh antigens	Mild anemia

Clinical Implications of Rh system

1. Transfusion Compatibility:
   Rh typing is essential to prevent hemolytic reactions.
   Rh^- individuals must not receive Rh^+ blood (except specific weak D scenarios).
2. Hemolytic Disease of the Newborn (HDN):
   Caused when Rh^- mother carries Rh^+ fetus, leading to anti-D formation that attacks fetal RBCs in subsequent pregnancies.
   Prevention: Rho(D) immune globulin (RhoGAM).

Questions

Q: Explain the origin of the name "Rhesus (Rh)" blood group system and describe how the Rh factor was first discovered.
Answer:
The Rh blood group system is named after the Rhesus monkey (Macaca mulatta), which was used in early immunization experiments. When Rhesus monkey RBCs were injected into rabbits and guinea pigs, the animals produced antibodies that agglutinated both monkey and most human red cells. This cross-reactivity led to the discovery of the "Rh factor."

Q: List the five principal antigens of the Rh system and explain the meaning of "d."
Answer:
The five main Rh antigens are D, C, c, E, and e.
There is no actual "d" antigen; "d" simply indicates the absence of the D antigen.

- $Rh^+ \rightarrow$ D antigen is present
- $Rh^- \rightarrow$ D antigen is absent

Q: Why is the D antigen considered the most clinically significant antigen in the Rh system? Give examples of Rh^+ and Rh^- blood types.
Answer:
The D antigen is the most immunogenic of all non-ABO blood group antigens — it readily stimulates antibody production after exposure through transfusion or pregnancy.

- Example: A^+ = A antigen + D antigen; while A^- = A antigen only (no D antigen).
  Because of its strong immunogenicity, anti-D can cause severe hemolytic transfusion reactions and hemolytic disease of the newborn (HDN).

Q: Describe two major clinical conditions associated with Rh antibodies and briefly explain their mechanisms.
Answer:

1. Hemolytic Transfusion Reaction (HTR):
   Occurs when Rh^- recipients receive Rh^+ blood, leading to anti-D–mediated destruction of donor RBCs.
2. Hemolytic Disease of the Newborn (HDN):
   Happens when an Rh^- mother produces anti-D antibodies after carrying an Rh^+ fetus; these antibodies cross the placenta in later pregnancies and destroy fetal RBCs.

Q: Differentiate between the Fisher–Race and Wiener systems and provide an example showing equivalence.
Answer:

System	Basis	Example	Notes
Fisher–Race	Each antigen (D, C, E) controlled by separate genes	DCe	Most widely used
Wiener	One gene produces multiple antigen factors	R_1	Historical system

Example of equivalence:
Fisher–Race **DCe** = Wiener **R_1**

Q: Identify the main genes responsible for the Rh antigens, their chromosomal locations, and the role of the RHAG gene.
Answer:

- RHD gene (chromosome 1): Encodes the D antigen.
- RHCE gene (chromosome 1): Encodes C, c, E, and e antigens.
- RHAG gene (chromosome 6): Encodes the Rh-associated glycoprotein (RhAG), which stabilizes Rh proteins and is required for expression of the Rh complex on the RBC membrane.

Q: Using the Punnett square principle, explain how two heterozygous Rh^+ parents (Dd × Dd) can produce Rh^+ and Rh^- offspring.
Answer:
Inheritance of the D antigen follows Mendelian dominance:

- DD or Dd → Rh^+ phenotype
- dd → Rh^- phenotype

Punnett square outcome (Dd × Dd): 25% DD (Rh^+) : 50% Dd (Rh^+) : 25% dd (Rh^-)
Thus, there is a 75% chance of Rh^+ and 25% chance of Rh^- offspring.

Q: Discuss the immunologic characteristics of Rh antibodies with respect to antibody class, method of formation, and dosage effect.
Answer:

- Type: Usually IgG (occasionally IgM).
- Formation: Produced after immune exposure (pregnancy or transfusion with Rh^+ blood); not naturally occurring.
- Dosage effect: All Rh antibodies except anti-D react more strongly with homozygous cells (e.g., EE) than with heterozygous cells (e.g., Ee).
- Anti-D is the most immunogenic and clinically significant.

Q: Compare the Weak D, Partial D, and Rhnull phenotypes in terms of cause, antigen expression, and transfusion significance.
Answer:

Variant	Cause	D Antigen Expression	Clinical Concern
Weak D	Quantitative ↓ in D antigen (altered expression)	Fewer D sites	Usually safe to receive Rh^+ blood
Partial D	Qualitative defect — missing epitopes	Normal quantity, altered structure	May form anti-D → must receive Rh^- blood
Rhnull	Complete absence of Rh complex (Rh & RhAG)	No Rh antigens	Mild hemolytic anemia; very rare ("golden blood")

Q: Explain how Rh incompatibility can lead to HDN and state the preventive measure used.
Answer:
If an Rh^- mother carries an Rh^+ fetus, fetal D-positive RBCs may enter the maternal circulation during delivery or trauma. The mother forms anti-D antibodies, which in subsequent pregnancies cross the placenta and destroy fetal Rh^+ RBCs, causing hemolytic disease of the newborn (HDN).

Prevention: Administer **Rho (D) immune globulin (RhoGAM)** to Rh^- mothers during and after pregnancy to prevent sensitization.

Q: why Rh null blood is called **"Golden Blood"?**
because it lacks all Rh antigens and is compatible with any Rh phenotype. It is extremely rare — about 1 in 6 million people — and highly valuable for transfusion and research.