PATHOGENESIS AND MECHANISMS OF IMMUNE HEMOLYTIC ANEMIA

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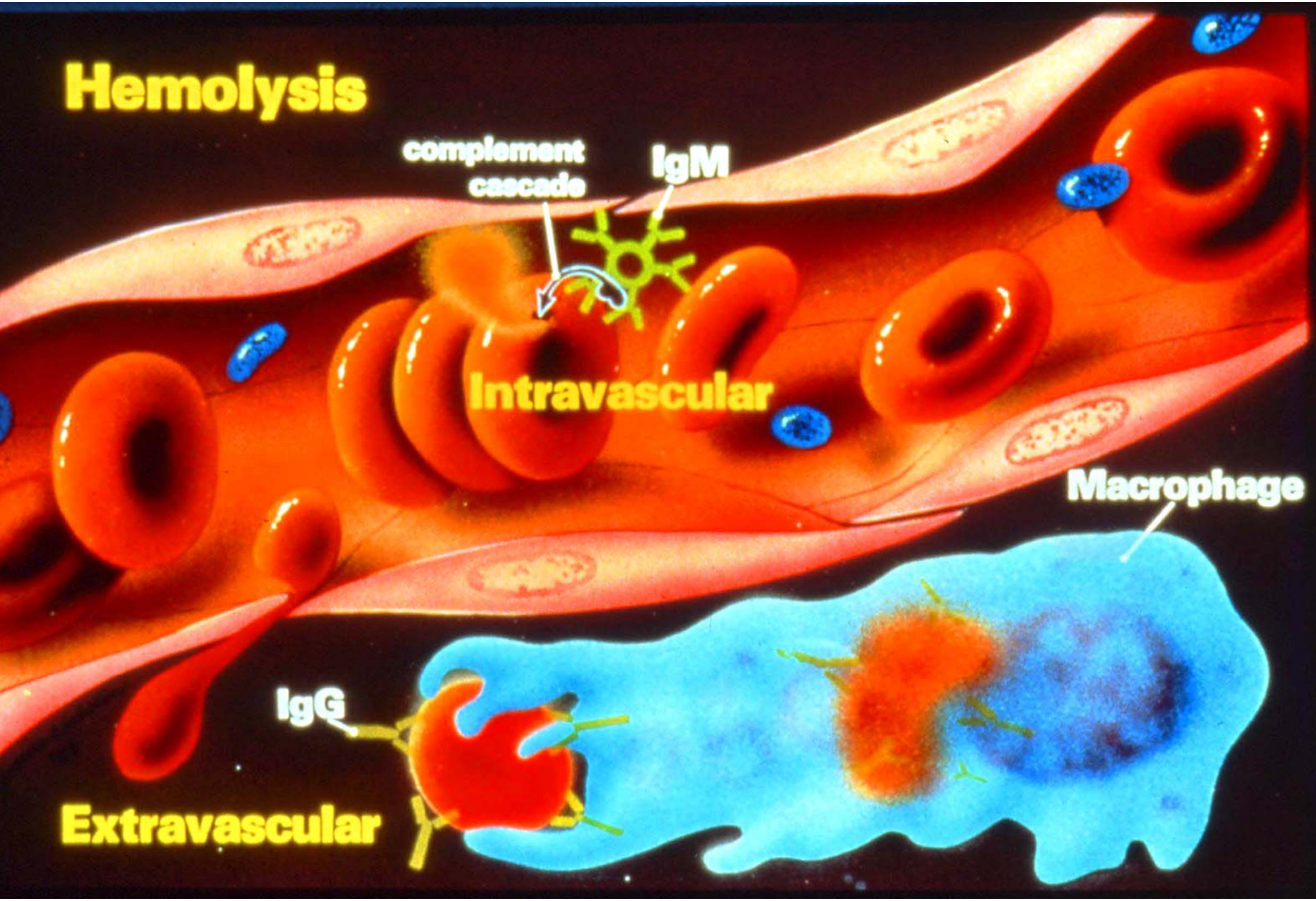
IMMUNE DESTRUCTION OF CIRCULATING BLOOD CELLS

- Intravascular complement-mediated destruction usually initiated by antibody
- Extravascular macrophage-mediated destruction: antibody (IgG, IgA), complement (C3b, iC3b), antibody + complement


Hemolysis
complement cascade
IgM
Intravascular
Macrophage
IgG
Extravascular

MAXIMUM RATE OF RBC DESTRUCTION (Mollison et al 1997, pg 341)

Extravascular

0.25 ml RBCs/kg/hr

∴ 70 kg patient = 17.5 ml RBCs/hr

= 420 ml RBCs/24 hr

Intravascular

e.g., anti-A/B can destroy 200 ml RBCs in 1 hr

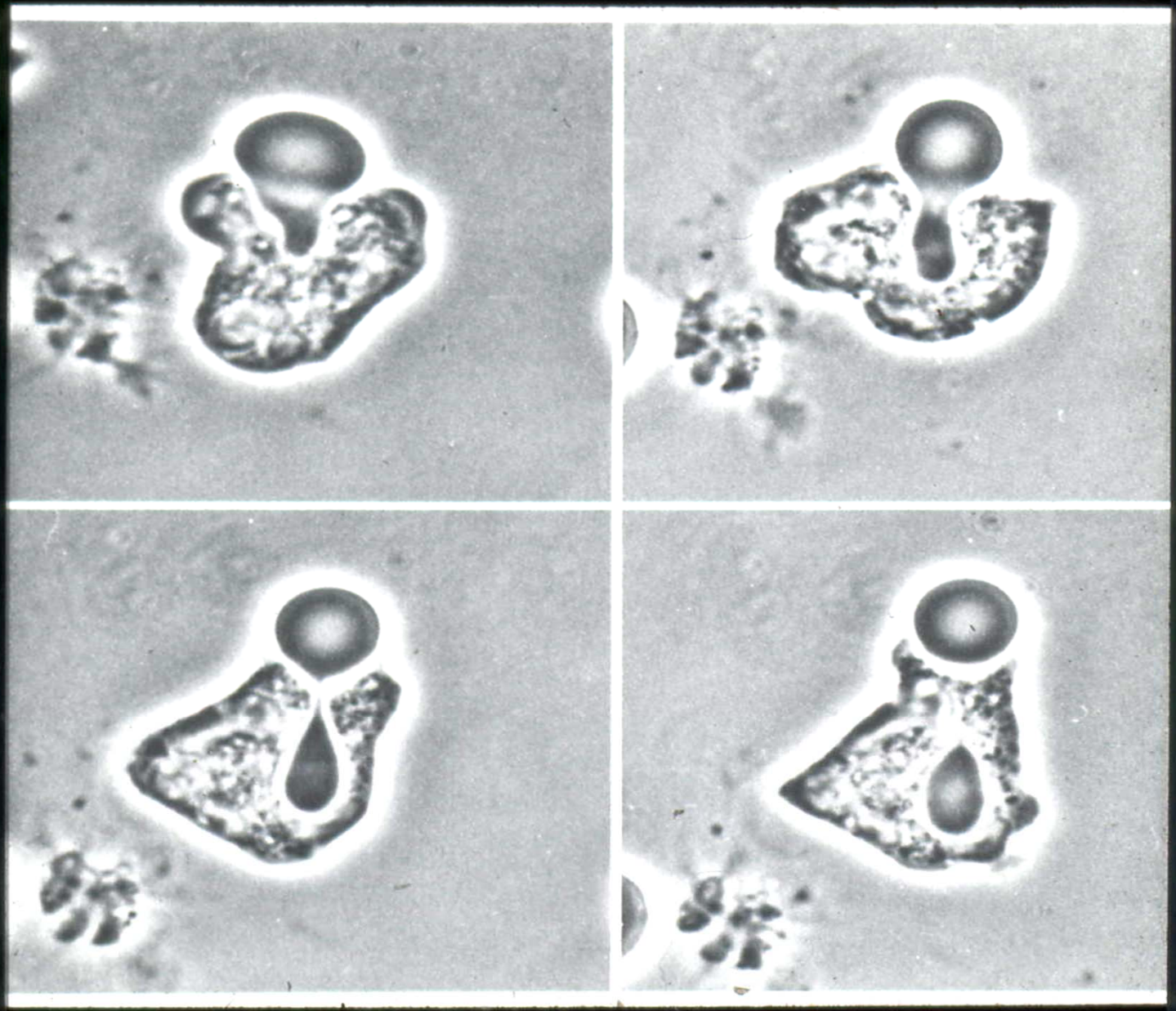
RECEPTORS ON MACROPHAGES AND MONOCYTES

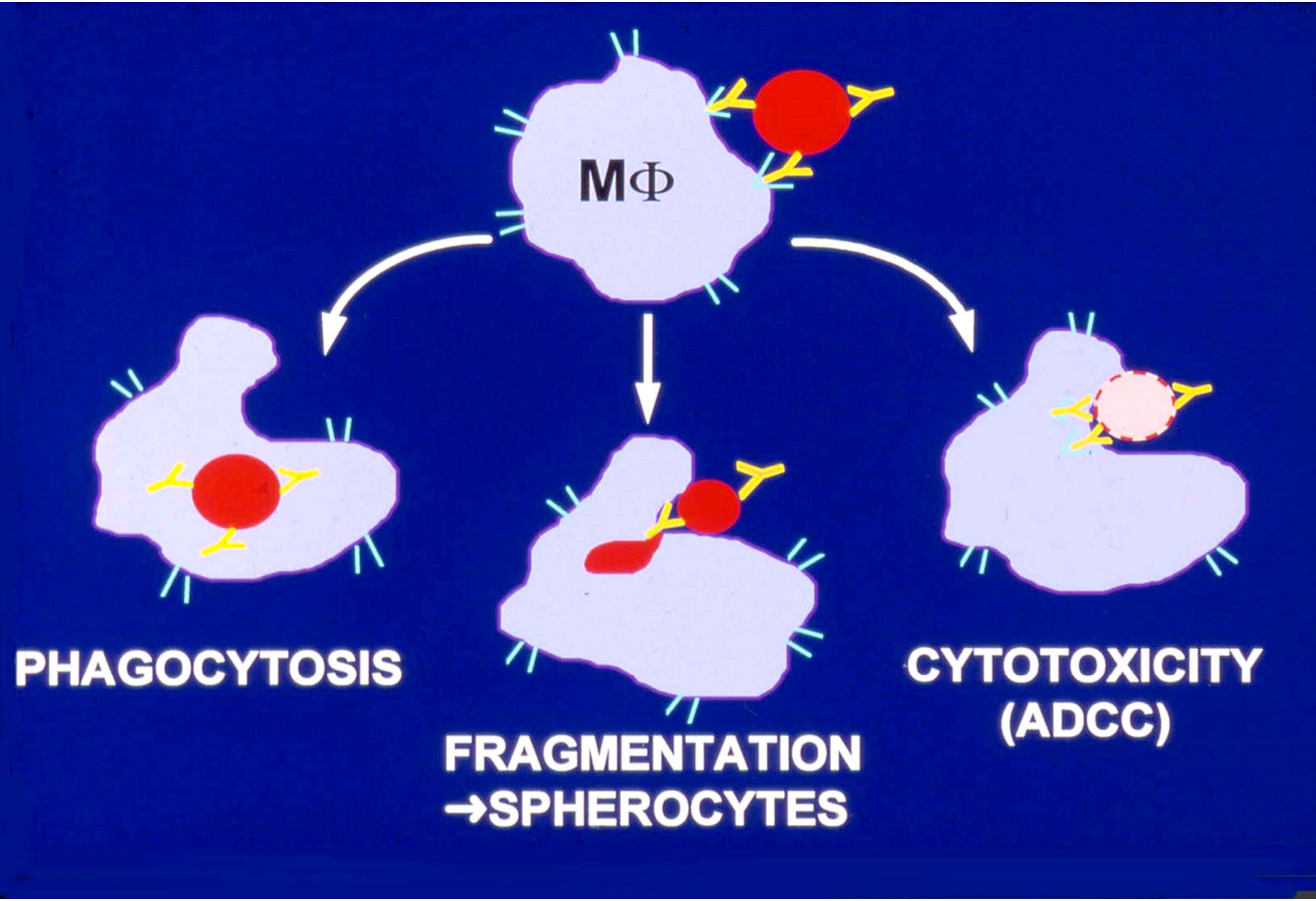
Fc: IgG1, IgG3, (IgG2), IgA

CR1: C3b, iC3b

CR3: iC3b

CR4: iC3b (C3dg, C3d)




MΦ
PHAGOCYTOSIS
FRAGMENTATION
→SPHEROCYTES
CYTOTOXICITY
(ADCC)

FACTORS THAT INFLUENCE THE PATHOGENICITY OF RBC ANTIBODIES

- Characteristics of antibody
- Quantity of RBC-bound IgG/complement
- Characteristics of target antigen
- Type of complement present on RBCs
- Activity of reticuloendothelial system

CHARACTERISTICS OF ANTIBODY THAT INFLUENCE PATHOGENICITY OF RBC ANTIBODIES

- Class
- Subclass
- Specificity
- Thermal range
- Complement activating efficiency
- Affinity

CHARACTERISTICS OF ANTIGEN THAT INFLUENCE PATHOGENICITY OF RBC ANTIBODIES

- Chemistry of target antigen
- Quantity of antigen on membrane
- Distribution of antigen on membrane
- Antigen in tissues and/or body fluids (competition)

SIGNIFICANCE OF RBC-BOUND COMPLEMENT COMPONENTS

- Intravascular lysis
- Sequestration in reticuloendothelial system with subsequent phagocytosis
- Temporary sequestration with normal or shortened RBC survival
- Essentially normal survival

ABNORMAL MACROPHAGE ACTIVITY

HYPERACTIVE

- Infection
- AIHA, SCD, thalassemia
- cytokines (INFy, IL6)

HYPOACTIVE

- Fc receptors blocked with:
  immune complexes (e.g., SLE)
  maternal anti-HLA (fetal MPs)
- ? Drugs (e.g., methyldopa)

A RETROSPECTIVE ANALYSIS OF THE VALUE OF MONOCYTE MONOLAYER ASSAY RESULTS FOR PREDICTING THE CLINICAL SIGNIFICANCE OF BLOOD GROUP ALLOANTIBODIES.

Arndt PA, Garratty G.

Transfusion 2004;44:1273-81

DELAYED HEMOLYTIC TRANSFUSION REACTIONS (DHTRs) VS. DELAYED SEROLOGICAL TRANSFUSION REACTIONS (DSTRs) AT MAYO CLINIC (1980-1998)

Specificity	DHTR	DSTR
E	47	137
Jk^a	45	50
Fy^a	26	36
c	18	36
K	16	46
Jk^b	12	15
C	8	14
Fy^b	4	8
S	4	3
e	3	9
C^w	3	2
A_1, Yt^a, Kp^a, Lu^a, Lu^b, D	6	1
M, Js^a, V, G, P_1, Co^b	0	9
TOTAL	182 (33%)	366 (67%)

PATIENTS RECEIVING ABO INCOMPATIBLE BLOOD MEANT FOR ANOTHER PATIENT

- Linden et al: Transfusion errors in New York State: an analysis of 10 years' experience. Transfusion 2000;40:1207
  - 47% of 237 patients reported as “no adverse effect”
- Robillard et al: Trends in red cell-associated ABO mistransfusions, acute and delayed serologic transfusion reactions in the Quebec Hemovigilance System: 2000-2003. Transfusion 2004;44:17A (abstr)
  - 46% of 24 patients reported as “asymptomatic”

CLINICAL OUTCOMES OF ABO-INCOMPATIBLE TRANSFUSIONS (Janatpour et al, Am J Clin Pathol 2008;129:276)

	≤50 mL	>50 mL
No. of Patients	12	36
Survived	12	30
Died	0	6 (20%)
Patients without signs or symptoms	9 (75%)	13 (36%)
Patients with signs or symptoms	3	23
Acute hemolytic transfusion reaction	3	16
Renal failure	0	10 (28%)
Shock	1	3
Disseminated intravascular coagulopathy	0	3

THE JAMES BLUNDELL AWARD LECTURE 2007: DO WE REALLY UNDERSTAND IMMUNE RED CELL DESTRUCTION?

Garratty G. Transfus Med Rev 2008;18:321-34

QUESTIONS STILL TO BE ANSWERED

- Why do circulating RBCs die after 110 – 120 days ? [autoantibody; sialic acid; phosphatidylserine; apoptosis (eryptosis)]
- Why do RBCs strongly coated with IgG1 or IgG3 sometimes survive normally?
- Why do ABO incompatible transfusions sometimes not cause severe reactions?

QUESTIONS STILL TO BE ANSWERED

- Why are some auto and alloantibodies causing severe immune hemolytic anemia not detected by routine techniques?
- Can T (cytotoxic) lymphocytes, NK cells, granulocytes, dendritic cells participate in immune hemolysis?
- Do differences in clinical severity and response to treatment relate to relative efficiency of macrophage-induced phagocytosis versus cytotoxicity?

QUESTIONS STILL TO BE ANSWERED

- Why do hyperhemolytic HTRs occur in sickle cell disease?
- Can antibodies cause IHA without activating complement or interaction with macrophage Fc/receptors?
- How do we predict the clinical significance of a RBC antibody?
- How should we define "clinical significance"?

POSSIBLE NOVEL MECHANISMS FOR IMMUNE DESTRUCTION OF RBCs AND PLATELETS

- Bystander / reactive lysis
- Immune complexes
- "Armed" macrophages
- Antibody independent cell-mediated cytotoxicity (NK cells)
- Antibody activation of platelets can lead to RBC lysis
- Antibody generated ozone /H_2O_2 → lysis

POSSIBLE NOVEL MECHANISMS FOR IMMUNE DESTRUCTION OF RBCs AND PLATELETS

- Antibodies to antigens on GPA can change the RBC membrane → channels allowing Ca^{2+} to enter RBCs plus appearance of phosphatidylserine on membrane
- Agglutinins can sometimes sequester in spleen/liver → HA without Fc or complement involvement

- Baudino et al. IgM and IgA anti-erythrocyte autoantibodies induce anemia in a mouse model through multivalency-dependent hemagglutination but not through complement activation. Blood 2007;109:5355-62.
- Liepkalns et al. Biphasic clearance of incompatible red blood cells through a novel mechanism requiring neither complement nor Fc gamma receptors in a murine model. Transfusion 2012;52:2631-45.

- Chadebech et al. IgA-mediated human autoimmune hemolytic anemia as a result of hemagglutination in the spleen, but independent of complement activation and FcαR1. Blood 2010;116:4141-7.

PERSONAL OPINIONS

- Most HTRs associated with IVIG are due to ABO alloantibodies
- Although reducing the titer of anti-A and anti-B will help lower the number of cases with HA there will still be a few cases associated with low titer antibodies
- The only way to stop the HTRs is to have no anti-A/-B in products