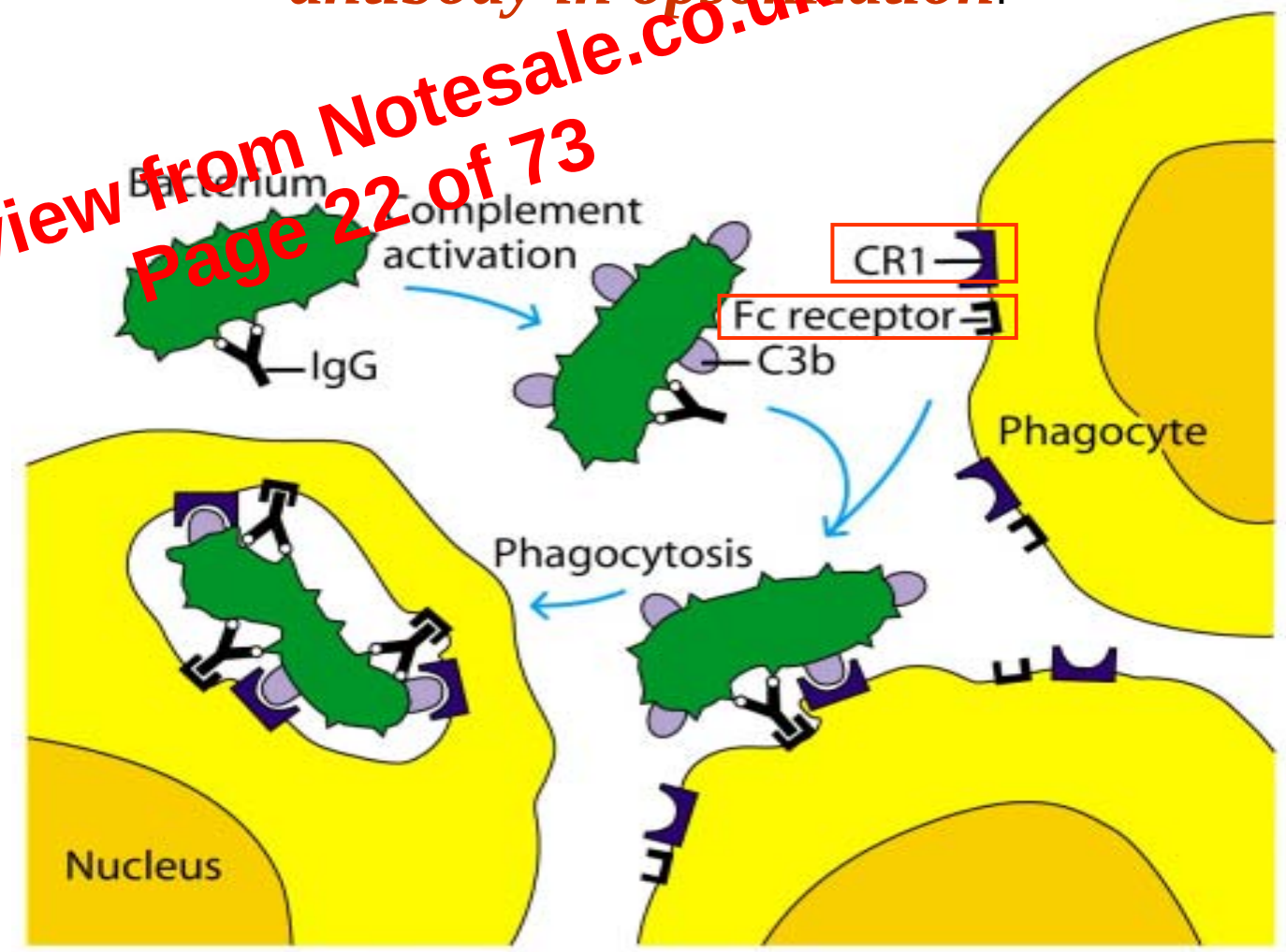
- The Functions of Complement
- The Complement Components
- Complement Activation
- Regulation of the Complement System
- Biological Consequences of Complement Activation
- Complement Deficiencies

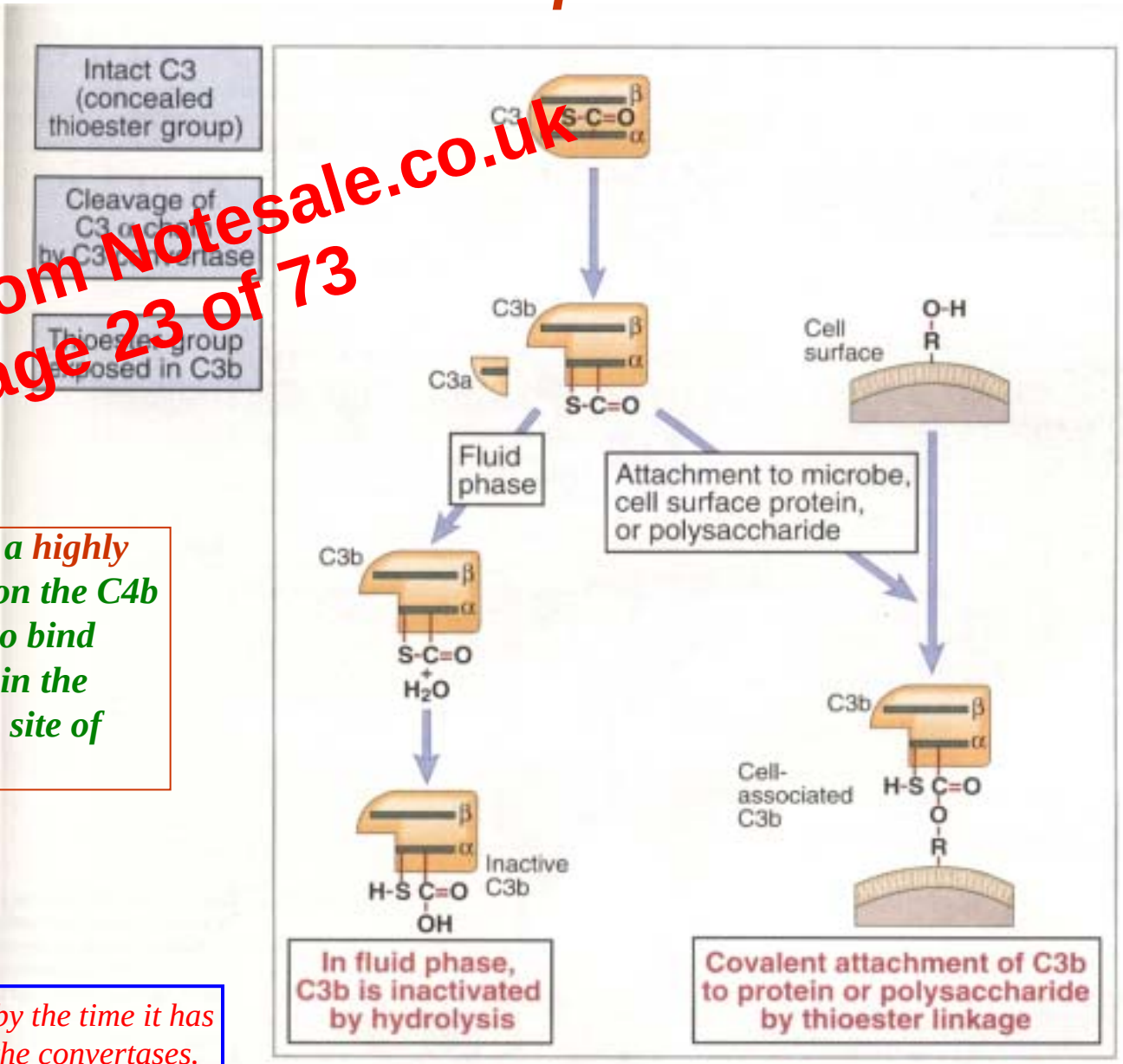
Schematic representation of the roles of C3b and antibody in opsonization.



Kuby J et al., Immunology 2003

Internal thioester bonds of C3 molecules

C3 contains an unstable thioester bond.



Cleavage of C4 exposes a highly reactive thioester bond on the C4b molecule that allows it to bind covalently to molecules in the immediate vicinity of its site of activation.

C3b undergoes hydrolysis by the time it has diffused 40 nm away from the convertases.

Abbas AK & Lichtman AH. Cellular and Molecular Immunology 5th ed. 2003

Biological consequences of complement activation

TABLE 13-3 Summary of biological effects mediated by complement products

Effect	Complement product mediating*
Cell lysis	C5b–9, the membrane-attack complex (MAC)
Inflammatory response	
Degranulation of mast cells and basophils†	C3a, C4a, and C5a (anaphylatoxins)
Degranulation of eosinophil	C3a, **C5a**
Extravasation by chemotaxis of leukocytes at inflammatory site	C3a, **C5a**, C5b67
Aggregation of platelets	C3a, C5a
Inhibition of monocyte/macrophage migration and induction of their spreading	Bb
Release of neutrophils from bone marrow	C3c
Release of hydrolytic enzymes from neutrophils	C5a
Increased expression of complement receptors type 1 and 3 (CR1 and CR3) on neutrophils	C5a
Opsonization of particulate antigens, increasing their phagocytosis	**C3b**, C4b, iC3b
Viral neutralization	C3b, C5b–9 (MAC)
Solubilization and clearance of immune complexes	C3b

*Boldfaced component is most important in mediating indicated effect.

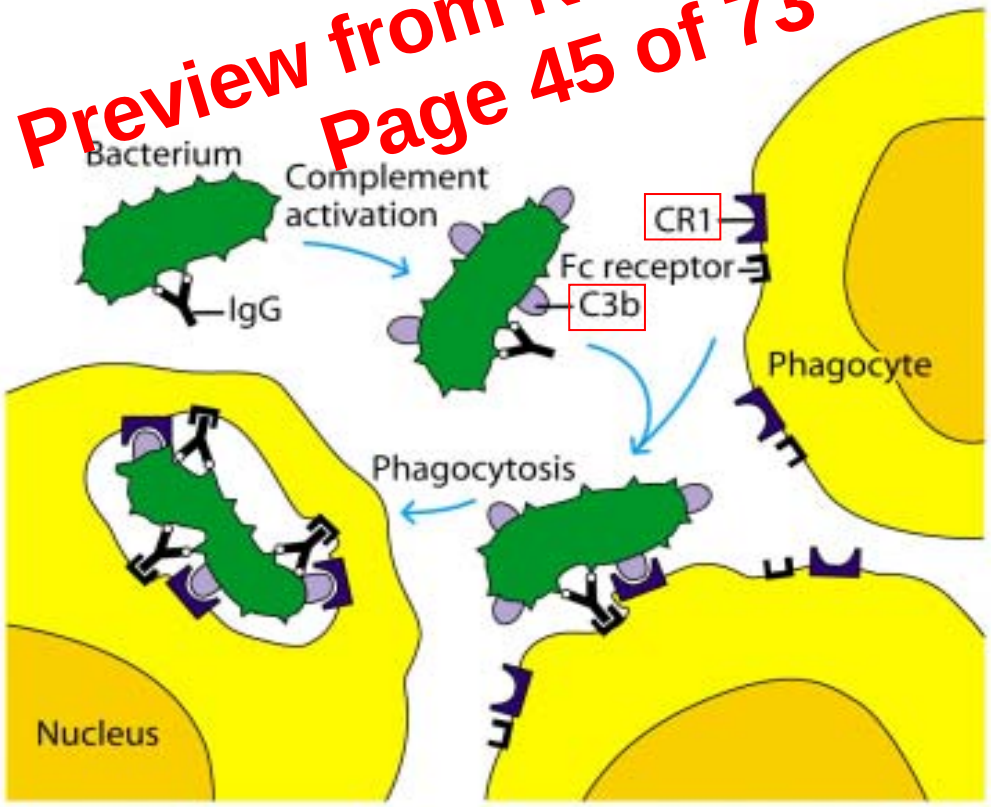
†Degranulation leads to release of histamine and other mediators that induce contraction of smooth muscle and increased permeability of vessels.

Kuby J et al., Immunology 2003

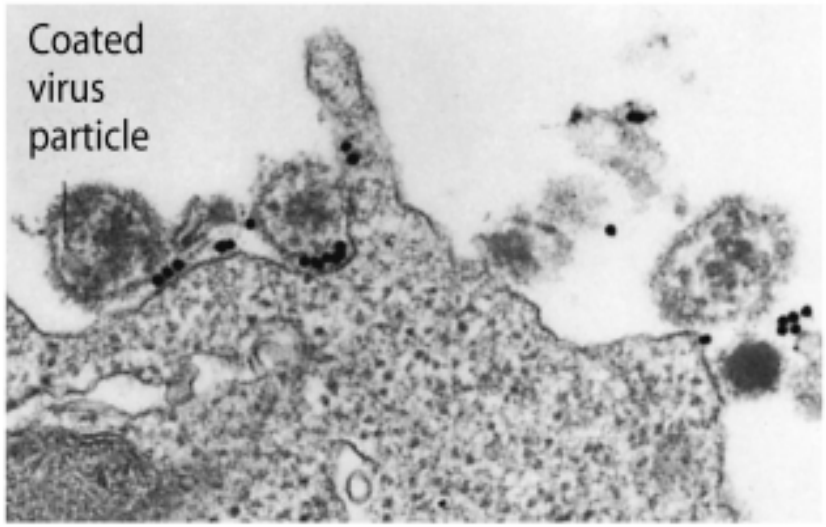
Schematic representation of the roles of C3b and antibody in opsonization.

Electron micrograph of EB virus coated with antibody and C3b and bound to the Fc and C3b receptor (CR1) on a B lymphocyte

(a)



(b)

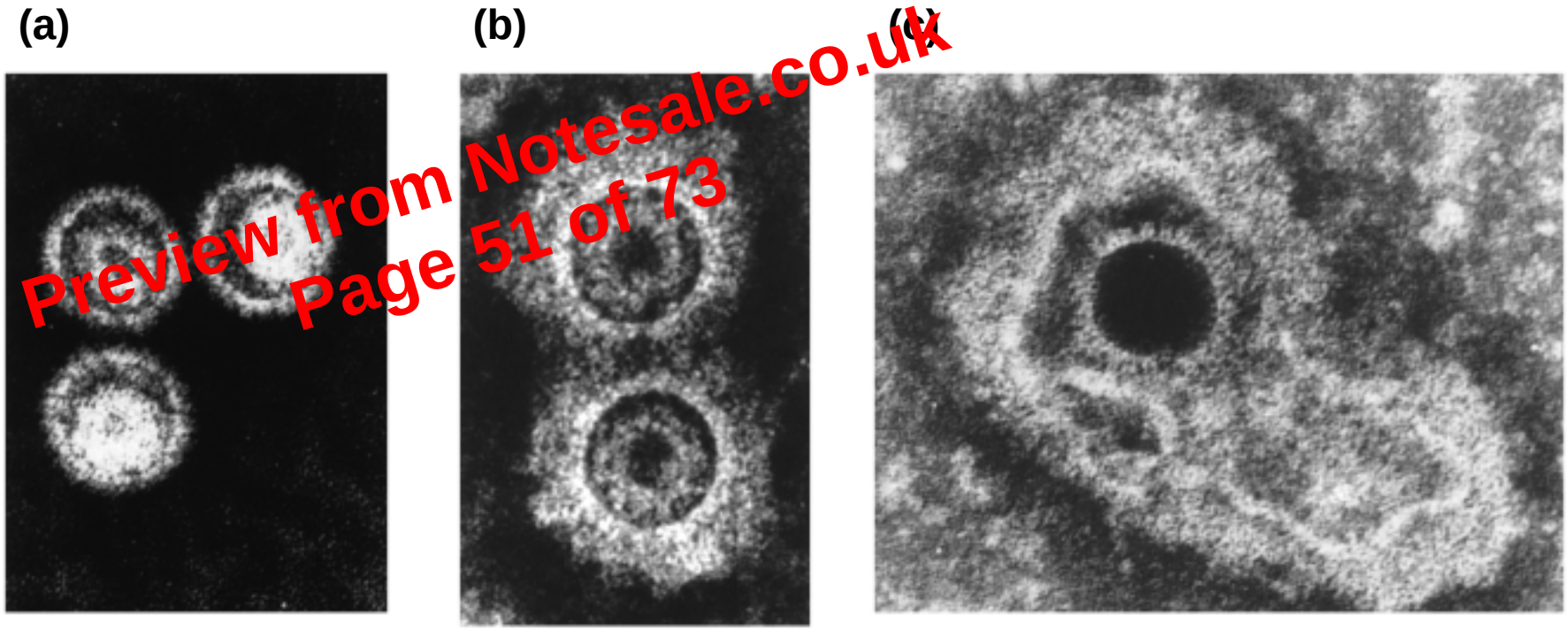


Kuby J et al., Immunology 2003

Opsonins: C3b, C4b, iC3b

CR1: 5,000/resting phagocytes
50,000/activated cells

Electron micrographs of negatively stained preparations of EB virus



Control without antibody

Antibody-coated particles

Particles coated with antibody and complement

Kuby J et al., Immunology 2003

Complement deficiencies

- immune-complex diseases (genetic deficiencies)
- recurrent infection
- C3 deficiencies:
  - with the most severe clinical manifestations
- hereditary angioedema:
  - deficiency of C1Inh
  - localized edema of the tissue
- paroxymal nocturnal hemoglobinuria (PNH)
  - defect in cell-surface DAF and MIRL
- studies using knock-out mice

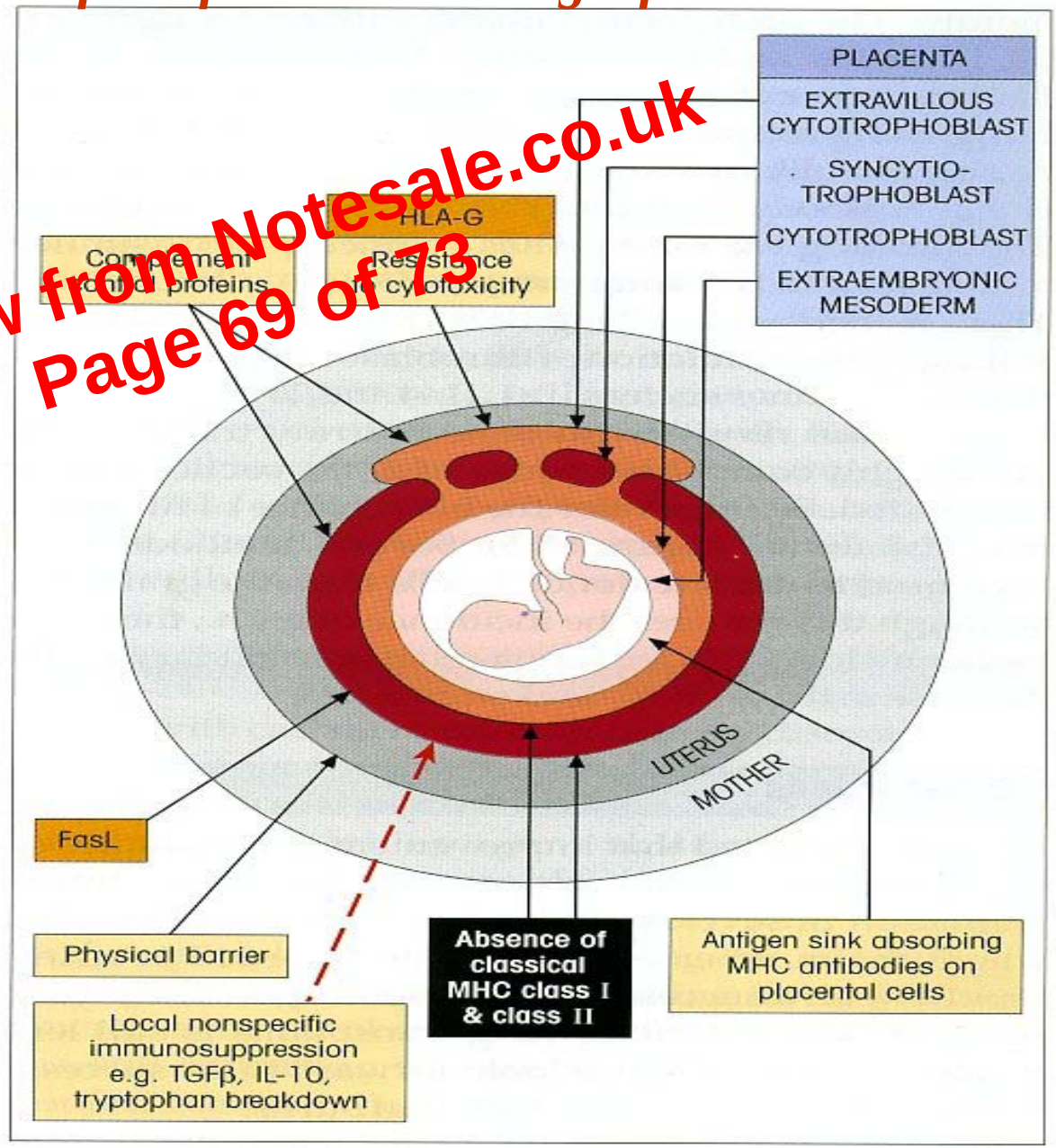
Paroxysmal nocturnal hemoglobinuria (PNH) - A defect in regulation of complement lysis

- The defect lies in a posttranslational modification of the peptide anchor (glycolipid GPI anchor) that binds DAF and MIRL to the cell membrane.

- The defect identified in PNH lies early in the path to formation of a GPI anchor and residues in the *pig-a* gene.

  * X-linked *pig-a* gene
  (phosphatidylinositol glycan complementation class A gene)

Mechanisms postulated to account for the survival of the fetus as an allograft in the mother



Complement inhibitor

- Trophoblast and decidua may also be relatively resistant to complement-mediated damage because they express high levels of a C3 and C4 inhibitor called Crry.

- Crry may block maternal alloantibody-mediated damage through the classical pathway of complement activation.

- Crry-deficient embryos die before birth and show evidence of complement activation on trophoblast cells.

8. Because of its ability to damage the host organism, the complement system requires complex passive and active regulatory mechanisms.

9. Clinical consequences of inherited complement deficiencies range from increases in susceptibility to infection to tissue damage caused by immune complexes.