Immunity to infection

Infection

- Most microorganisms arriving at the **external surfaces** of the body **fail** to establish a **colony**.

- Those which are **able to colonize**, have the **ability to overcome** the physical and physiological barriers which protect the surfaces of the body.

- Even then the **majority** of colonizing organisms **do not penetrate** the body's surface and are called **commensal** bacteria.

- Those organisms which are capable of **both colonizing and invading** are called **pathogens**.

- **Exceptions** are those organisms (almost all are **intestinal** bacteria) that cause disease by secreting **toxins.**

  These **toxins damage the host** without the organisms themselves penetrating the body surface.

The body defense systems

The body defense systems can be divided into:

- -- **Immediate (0-4 hrs)**
- -- **Early (4-96 hrs)**
- -- **Late (4 days onwards)**

The Immediate defence systems

(0-4 hours)

The **immediate defence (first wave)** of the body against an invasion must be in the hands of **preformed** molecules.

Its main players are:

1.Complement

2.Phagocytes

3.Natural Antibody

Complement

- The most important **immediate defender** is the **C3** component of complement.

- The **activated C3** which initiates alternative pathway, is continually generated at a low rate.

- This is called **C3 'tickover'**.

- Normally **activated C3** is short lived but it can **covalently attach** to a protein or carbohydrate surface to increase its life.

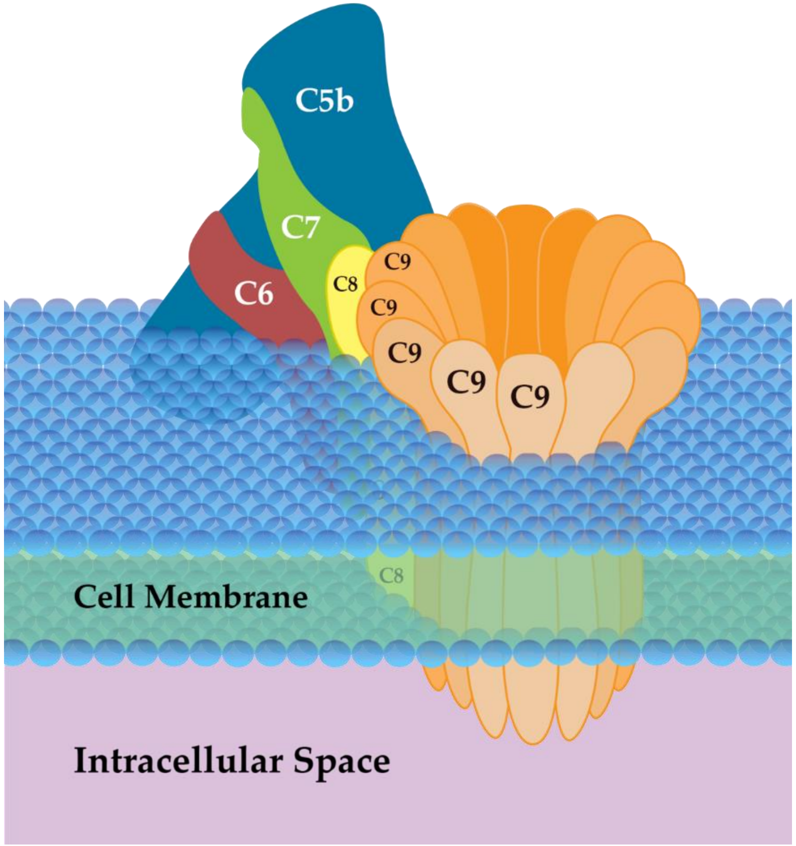
-- Usually it attaches to the **serum factor B** which is a substrate for the **protease factor D**, generating the active **C3 convertase** which splits **C3** into active parts **C3a** and **C3b**.

-- Normally, in a host cell, regulators of the complement system rapidly inactivate the **C3 convertase**.

-- However a pathogen **lacks** the host regulatory proteins and thus does not affect **C3 convertase**.

-- Conversely, some microbes catalyse the binding of another serum component, **P (properdin)** which significantly **stabilizes** the **C3 convertase** and prevents its' inactivation by the soluble inhibitor **factor H**.

- **Complement alone** is able to destroy some pathogens, primarily **Gram -ve bacteria** by activation of the terminal complement components and assembly of the **membrane attack complex.**



- Complement also serves to **activate** the **acute inflammatory** response.
- The **C5a** fragment is a potent **chemoattractant** for neutrophils and activates vascular endothelium directly.
- **C5a** also **activates mast cells** which amplify the inflammatory signals by releasing their preformed vasoactive mediators.

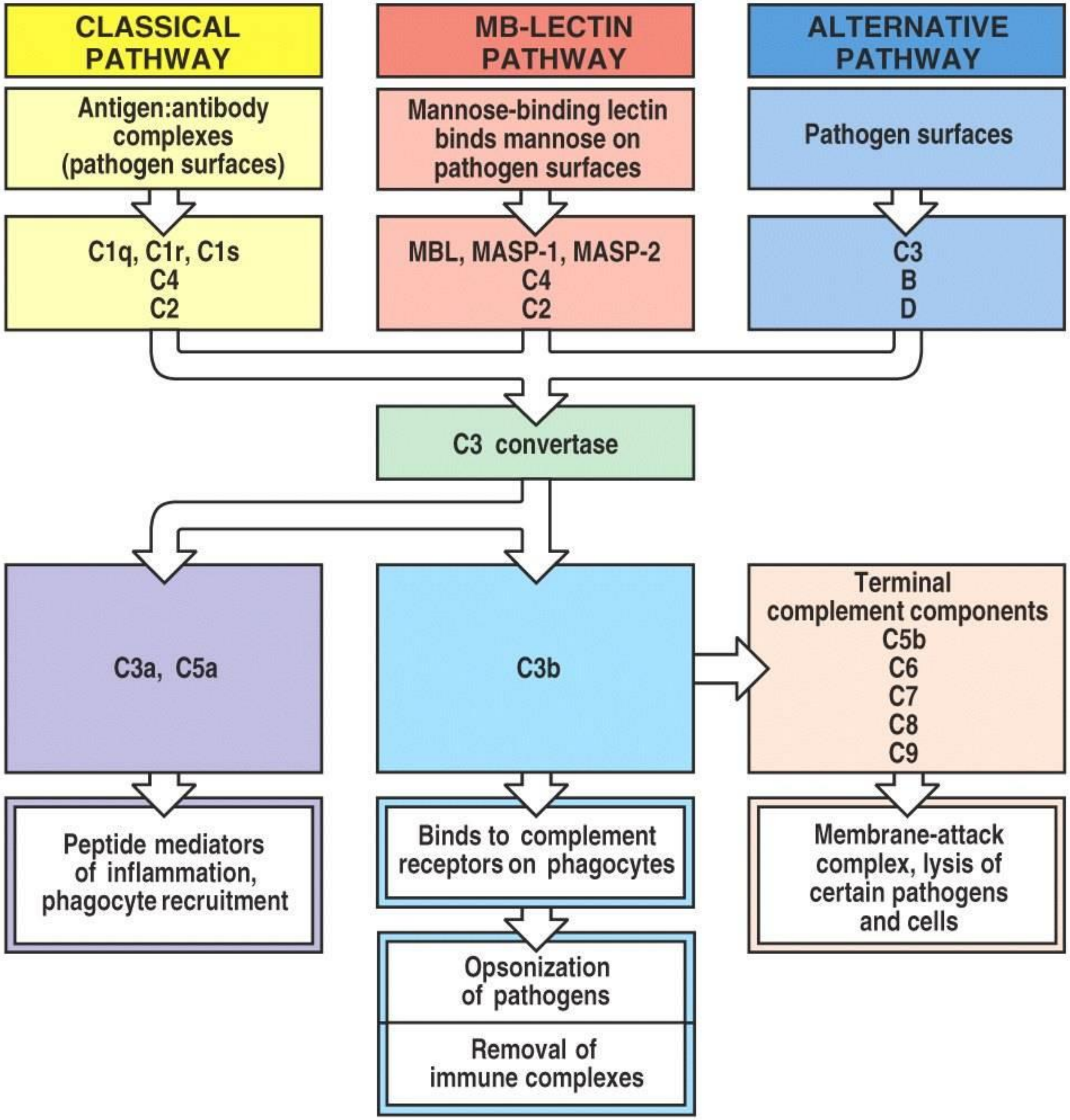


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

Phagocytes

- **Macrophages** are resident in almost **all tissues** and are found in particularly large numbers in mucosal tissues.

- **Neutrophils** are present in the blood in **very large numbers**, they can be rapidly recruited to any site which activates complement.

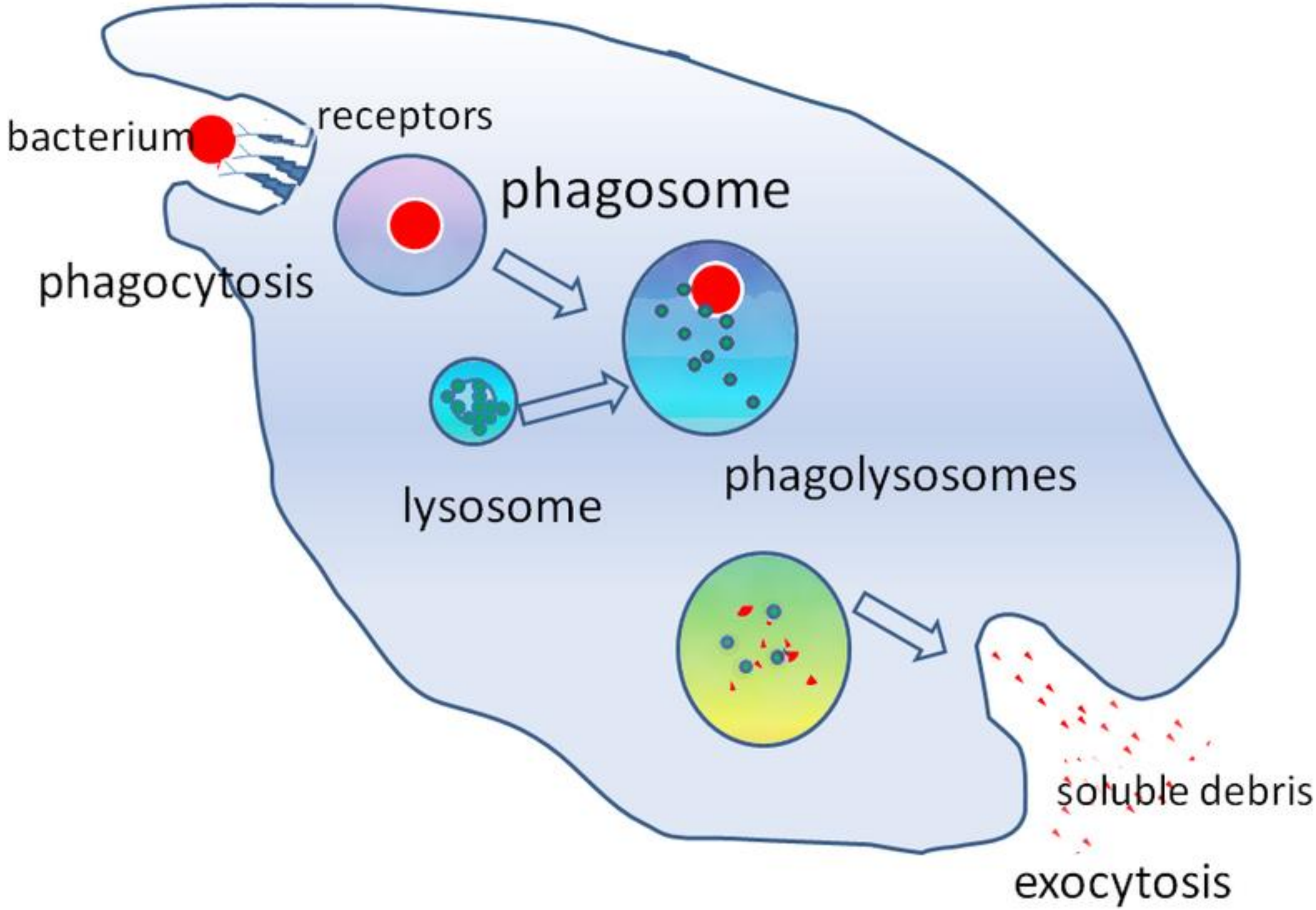
- Both types of phagocytes possess **receptors** which enable them to bind and phagocytose microbial organisms.

- These receptors recognize **carbohydrate structures (**which are **not present** on host cells) including certain mannose linkages and lipopolysaccharide on **Gram -ve bacteria.**

- Both types of phagocytes also possess receptors for **iC3b** which potently **stimulate phagocytosis**.

- **iC3b** is produced when **complement factor I** cleaves **C3b**.

- Once organisms are **engulfed**, they are subject to a battery of **chemical and enzymatic attacks** which in many cases destroy them.


bacterium
receptors
phagosome
phagocytosis
lysosome
phagolysosomes
soluble debris
exocytosis

'Natural' antibody

- Even when an organism is encountered for the **first time** there may be some **IgM** antibody which may **bind to its' surface structures.**

- This is called **'natural'** antibody and is produced by **B1** cells.

- Even very low affinity reactions with **IgM** can produce binding and classical pathway complement **activation.**

Early Immune responses (4-96 hrs)

The **second** wave of defence is primarily triggered by the ***de novo*** **synthesis of cytokines**.

Its main players are:

1. **Macrophages**

2. **Natural Killer Cells**

3. **Interferon**

Macrophages

-- The **secondary effects** of recognition of microbial pathogens via either the innate carbohydrate receptors or the complement receptors is to **activate macrophages to synthesize cytokines.**

-- In particular **TNFα, IL12** and **IL1** play an important role in the second phase response.

-- **TNFα** is critical in activating local vascular endothelium.

-- This results in **increased vascular permeability** leading to supply of complement (and other serum effector proteins when present) and **increased fluid drainage** to the lymph node.

- It is followed by **recruiting of polymorphs and macrophages** which in turn promotes **platelet activation** and **clotting**.

- The effect of local vessel **clotting** is important to **prevent spread** of the pathogen into the blood stream.

- **TNFα** also **'primes' neutrophils**, causing them to activate oxygen-dependent intracellular killing mechanisms and making them more effective.

- In synergy with **IL1, TNF** stimulates the **acute phase response** which triggers massive increases in the serum concentration of **Mannose Binding Protein** and **C-Reactive protein.**

- These molecules provide **additional means** to recognize the invaders.

- Both bind simple chemical structures on **microbial cells**.

- Both have **specific receptors on phagocytes** and both are capable of **activating the complement system** mimicking **C1q** and **IgM** respectively.

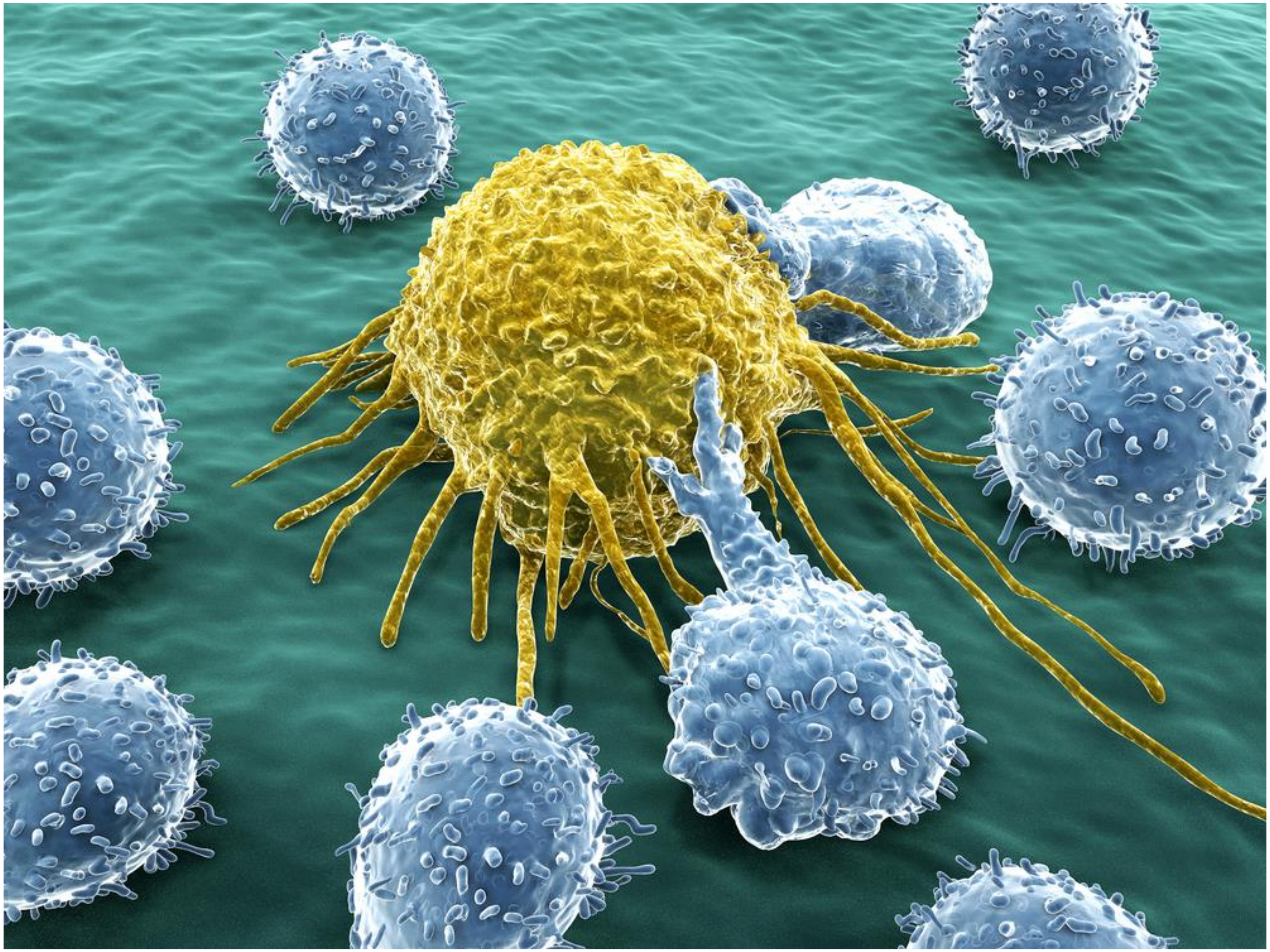
Natural Killer (NK) cells

- These lymphocytes **lack the antigen specific receptors** of T and B cells.

- NK cells **directly** attack the infected cells.

- They are part of the **innate immune system** and they play an important role in **viral infections**.

- They are activated by the cytokines **IL12** and **IFN α/β.**



NK cell attacking an infected cell

Interferon

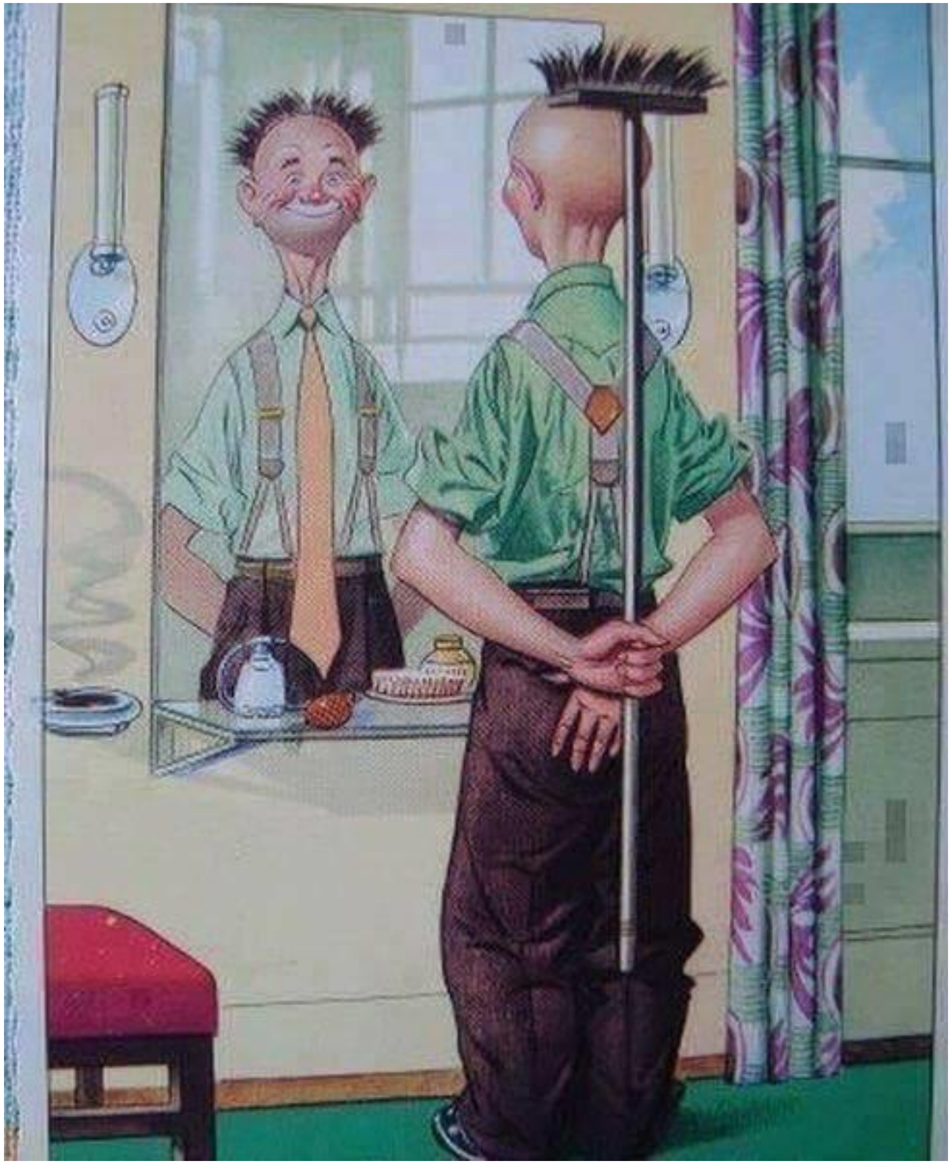
- **Interferon α/β** are produced by a variety of cells in response to viral infection. They have an important role in limiting viral infection in the **early phase**.

- They do this **both directly and indirectly**.

- They **directly** act on a wide variety of cell types to induce the synthesis of a series of proteins which **interfere with viral replication** both by **degrading RNA** and by **inhibiting protein synthesis.**

- **Indirectly**, they also potently activate **NK cells**.

"The biggest obstacle to happiness is undervaluing what you have and overvaluing what others have"



Dil ke khush rakhne ko Ghalib ye khayal achha hey

The horizontal line on the eyes means that the animal is "prey", able to see the ground widely and find a place to escape or hide.

The vertical line in the eyes means that the animal is a "hunter" to precisely find the target.


Thank You!