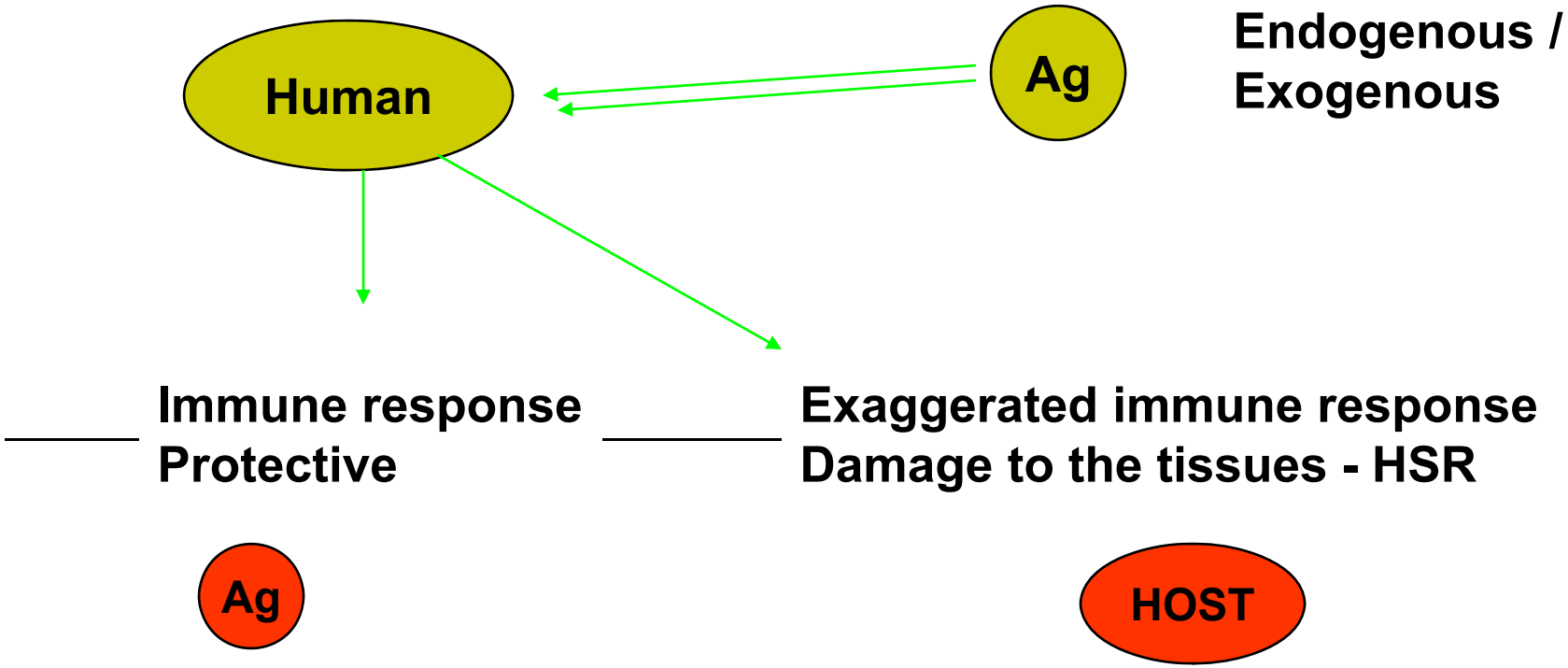

HYPERSENSITIVITY


Something more is harmful
&
Something less is harmful

Disorders of immune system

- Hypersensitivity reactions
- Autoimmune diseases
- Immunologic deficiency syndrome
- Amyloidosis

? What is hypersensitivity reactions (HSR)



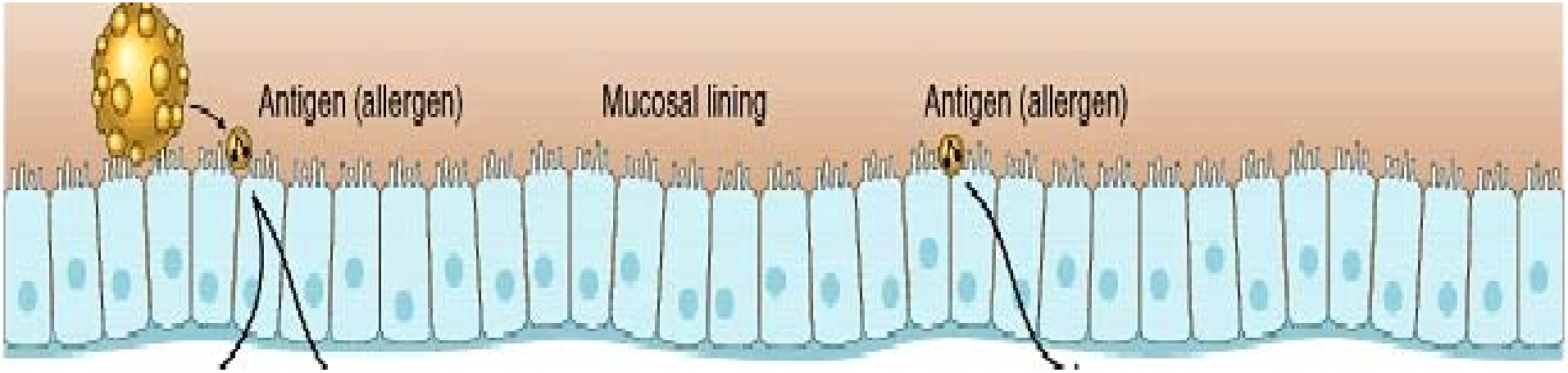
The term hypersensitivity refers to <u>injurious</u> consequences in the <u>sensitized host</u>, following contact with <u>specific antigen.</u>

- **In protective immune response the focus of attention is ANTIGEN, while in hypersensitivity reactions antigens are of little concern & focus of attention is WHAT HAPPENS TO THE HOST as result of immune response**

- **Antigens can be endogenous (transfusion reactions, graft rejection) or exogenous (dust, pollens, food, drugs, microbiologic agents).**

Sensitizing dose

Shocking dose



host should have contact with antigen which sensitize the immune system to stimulate B & T cells

What is sensitizing & shocking dose?

- **For induction of HSR, the host should have contact with antigen which sensitize the immune system to stimulate B & T cells. This is kn. as sensitizing or priming dose.**

- **Subsequent contact with the antigen causes manifestations of HS. This is kn. as shocking dose.**

Classification of HSR

Time required for a sensitized host to develop clinical reactions on exposure to the antigen –

1. **Immediate HSR (B-cell mediated)**
2. **Delayed HSR (T-cell mediated)**

Immediate HSR

(B cell mediated)

- Appears & recedes rapidly
- Induced by Ag or hapten by any route
- Circulating Abs are present & responsible for reaction – Ab mediated
- Passive transfer with serum
- Desensitization easy but short lived

Delayed HSR

(T cell mediated)

- Appears slowly, lasts longer
- Induced by Ag or hapten intradermally or with Freund's adjuvant or by skin contact
- Circulating Abs may be absent, cell mediated
- Passive transfer with lymphocyte or transfer factor
- Desensitization difficult but long-lasting

Coombs & Gell classified HSR into 4 types based on the different mechanism of pathogenesis.

TYPE-I IgE or reagin dependent

- Anaphylaxis
- Atopy

TYPE-II Ab-mediated cell cytotoxicity

TYPE-III Immune complex mediated

- Arthrus reaction
- Serum sickness

TYPE-IV Delayed or cell-mediated

TYPE-V Stimulatory

Type 1 hypersensitivity

- **Anaphylaxis : IgE dependent**
- **Classical Immediate Hypersensitivity**
- Richet (1902) Ana = without, phylaxis = protection
- Sensitization is most effective when Ag is introduced parenterally.
- Ag as well as hapten can induce anaphylaxis.

- There should be interval of 2- 3 weeks between sensitizing dose and shocking dose.
- Shocking dose is most effective intravenously, less effective intraperitoneally/subcutaneously & least intradermally.
- Shocking antigen must be identical or immunologically closely related to sensitizing Ag.

- Clinical feature of Anaphylaxis are the same with any Ag but vary between species.

- Clinical features are due to smooth muscle contraction and increased vascular permeability.

- Organ affected vary with species : Target tissue or shock organs
- Guinea pigs are highly susceptible, Rats are resistant. Rabbits, dogs and men are intermediate

Clinical features in human beings

- S/s of anaphylactic shock begins with itching of scalp and tongue, flushing of the skin over the whole body and difficulty in breathing due to bronchial spasm.
- May be nausea, vomiting, abdominal pain and diarrhoea.
- Acute hypotension, loss of consciousness and death follow.

- heterologous serum therapy
- antibiotic injections in humans.
- hormones, enzymes
- insect stings

- Treatment with adrenaline can be life saving.

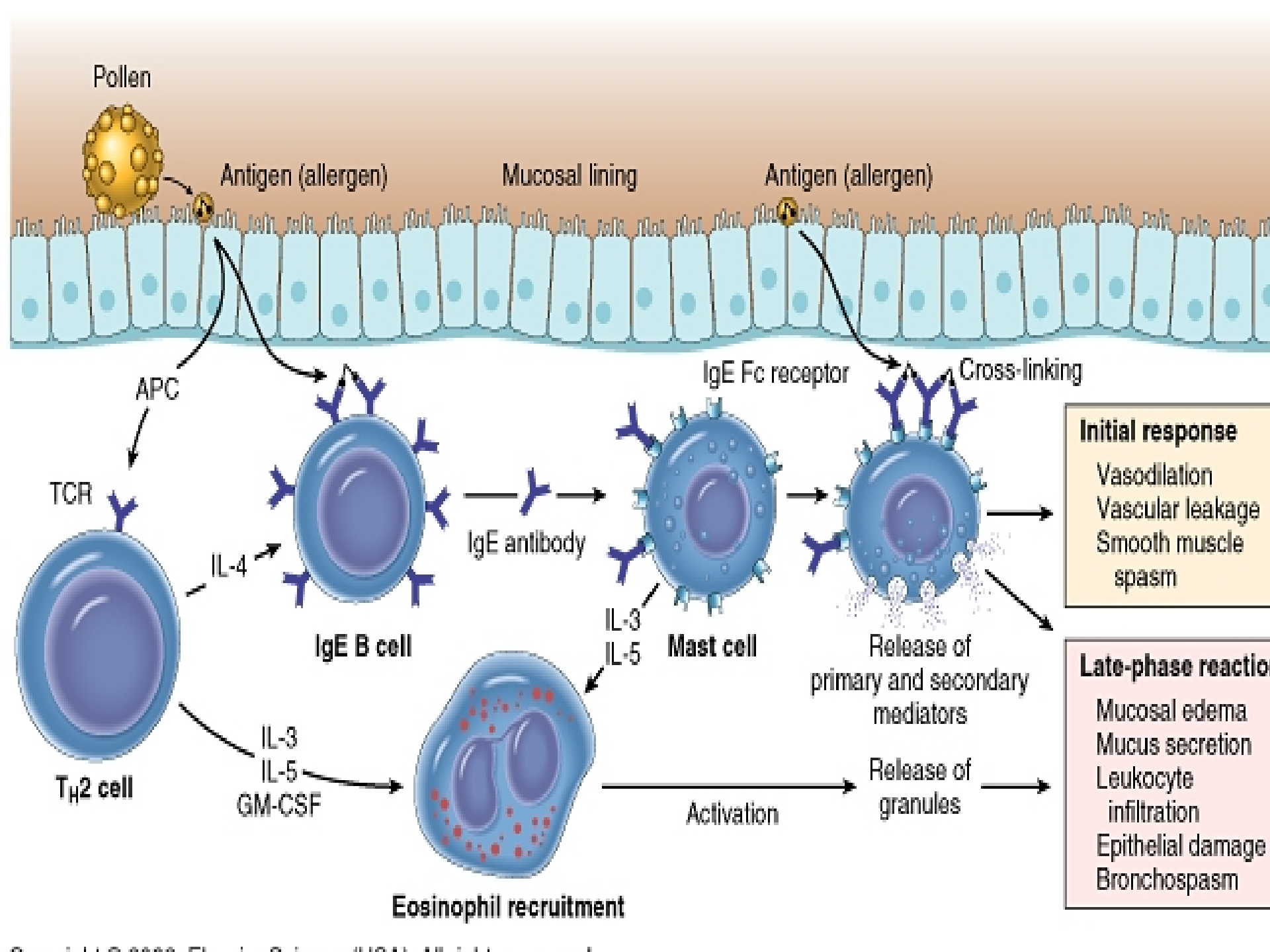
Mechanism of anaphylaxis

- IgE is the major antibody responsible for anaphylaxis.
- Caused by cell bound IgE Ab, not by free circulating IgE Ab

- IgE molecules are bound to surface receptors (FcER) on mast cells in tissue and basophils in circulation.

Contd.

- Following exposure to the shocking dose ,the antigen molecules combine with the cell bound IgE bridging the gap between the adjacent antibody molecules.
- This cross linking increases the permeability of the cells to calcium ions and lead to degranulation with release of biologically active substances contained in the granules.
- The manifestation of anaphylaxis are due to the pharmacologically active mediators – Primary & Secondary.


Pollen
Antigen (allergen)
Mucosal lining
Antigen (allergen)
APC
TCR
IL-4
IgE B cell
IgE antibody
IgE Fc receptor
Cross-linking
IL-3
IL-5
Mast cell
Release of primary and secondary mediators
Initial response
Vasodilation
Vascular leakage
Smooth muscle spasm
IL-3
IL-5
GM-CSF
TH2 cell
Eosinophil recruitment
Activation
Release of granules
Late-phase reactio
Mucosal edema
Mucus secretion
Leukocyte infiltration
Epithelial damage
Bronchospasm

Primary mediators

Preformed content of mast cell and basophil granules e.g. histamine, serotonin, chemotactic factor.

1. Histamine – vasoactive amine

   Decarboxylation of Histidine

   Released in skin, stimulates sensory nerves – burning & itching sensation

   Vasodilatation & hyperemia

   Smooth muscle cont.

   Stimulates secretions

2. Serotonin –

Decarboxylation of tryptophan

Smooth muscle cont.

Vasoconstriction

Increased capillary permeability

3. Chemotactic factors -

ECF

NCF

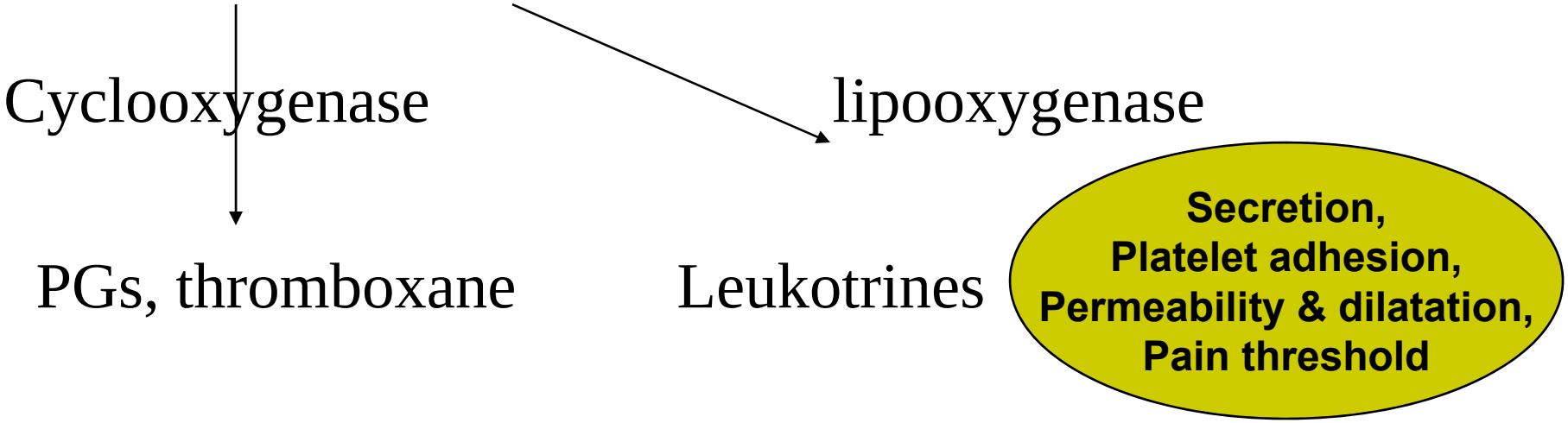
4. Heparin – acidic mucopolysaccharides

Secondary mediators

Newly formed upon stimulation by mast cell, basophil and other leukocytes

1. Prostaglandins & leukotrines

Arachidonic acid



2. Platelet activating factors

Anaphylactoid reaction

- Type of reaction that clinically resembles anaphylactic shock
- I/V inj. Of peptone, trypsin & other substances provokes
- Chemical mediators – same
- No immunologic basis
- Nonspecific mechanism involving the activation of complement & release of anaphylotoxins

Passive Cutaneous Anaphylaxis

- Ovary in 1952
- In vivo method to detect antibodies
- Used to detect human IgG Ab (heterocytotropic)

Cutaneous Anaphylaxis

- When a small shocking dose of Ag is administered intradermally, to a sensitized host, there will a local wheal and flare reaction (local anaphylaxis).
- Wheal is a pale central area of puffiness due to edema which is surrounded by a flare caused by hyperemia and subsequent erythema.
- Used to test hypersensitivity & to identify the allergen.

Anaphylaxis in vitro

- **Schultz-Dale phenomenon**

  Isolated tissues, such as intestinal or uterine muscle strips from sensitized guinea pig, held in bath of Ringer's solution will contract vigorously on addition of the specific Ag to the bath.

Atopy

- Cocca (1923)
- Atopy = out of place or strangeness
- Refers to naturally occurring familial hypersensitivity of human beings, typified by hay fever and asthma.
- Commonly involved antigens are characteristically inhalants (e.g.pollen.house dust) or ingestants (e.g. eggs, milk) or contact allergens
- Difficult to induce artificially
- Genetically determined, probably linked to MHC genotype.
- Runs in families

Mechanism

- What is inherited is not sensitivity to a particular antigen but tendency to produce IgE Abs in unusually large quantities
- This often associated with deficiency of IgA.
- In normal individual the inhalants and ingestants antigen are dealt with the IgA lining the respiratory and intestinal mucosa.
- When IgA is deficient, the antigen cause massive stimulation of IgE forming cells, leading to overproduction of reagin.

Symptoms –

contact with allergen with cell-bound IgE in the bronchial tree, the nasal mucosa, the conjuctival tissue, intestine or skin, releases of pharmacologically active mediators & produce symptoms of

- Asthma
- Hay fever
- Conjunctivitis
- GI symptoms
- Dermatitis
- Urticaria in persons allergic to food such as strawberry

- Specific desensitization - treatment

Characteristics of IgE

- Cannot be demonstrated by conventional serological reactions
- Detected by RAST (radioallergosorbent assay), ELISA, PAT
- Hemocytotropic
- Heat sensitive
- Prausnitz–Kustner (PK) reaction

- to find out atopic antibody (IgE)

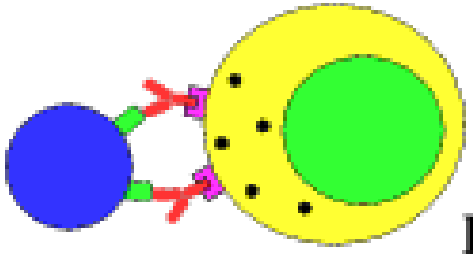
Type II reaction: Cytolytic and Cytotoxic

- Antigenic determinants may be intrinsic to the cell membrane or may be an exogenous antigen absorbed on the cell surface.
- Antibodies directed towards these antigens
- Mechanism – complement mediated
  - Antibody dependent (IgG, rarely IgM)

Examples

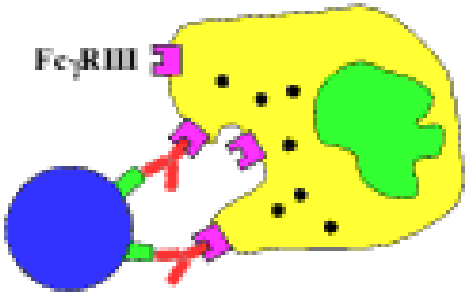
- Transfusion reactions
- Erythroblastosis foetalis
- Autoimmune hemolytic anemia
- Agranulocytosis, Thrombocytopenia
- Pemphigus vulgaris

Type II Hypersensitivity



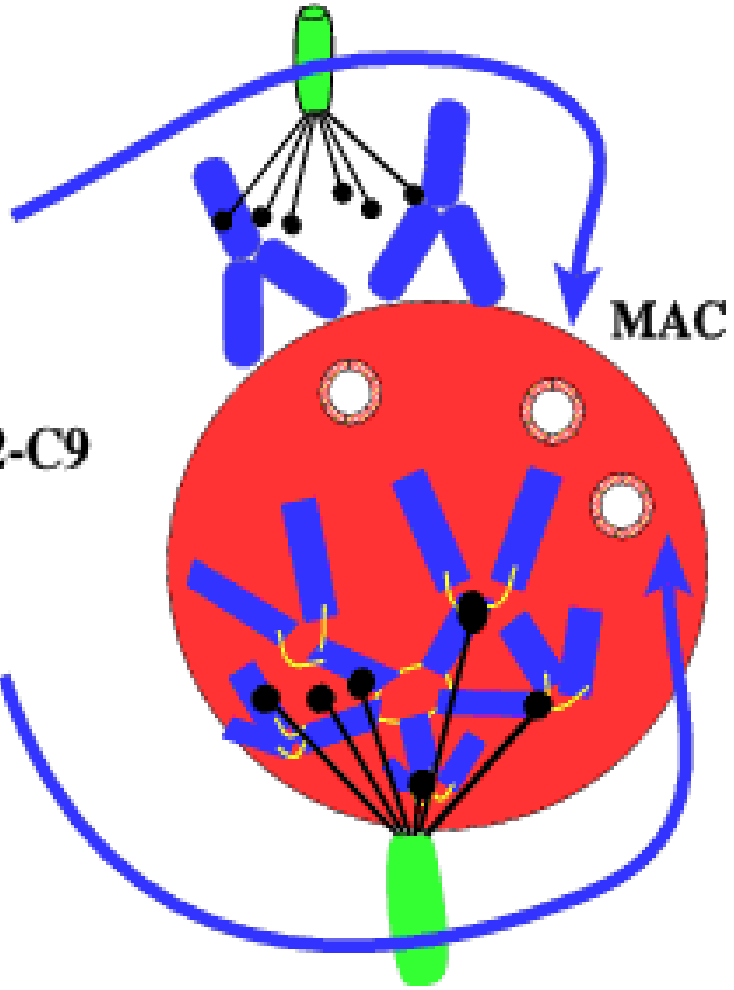
K cell

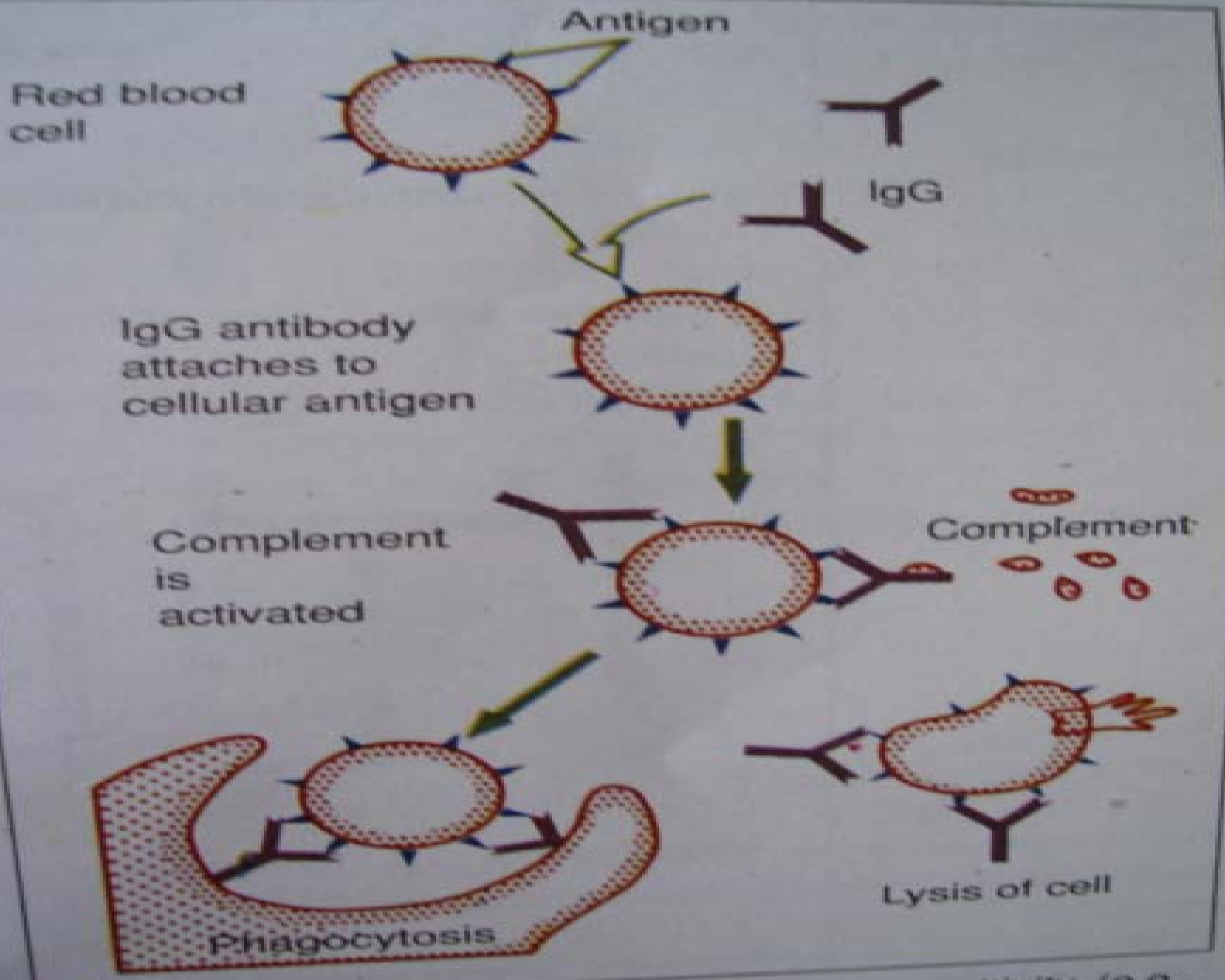
Antibody dependent cell cytotoxicity



macrophage

classical pathway complement activation




Antigen
Red blood cell
IgG
IgG antibody attaches to cellular antigen
Complement is activated
Complement
Phagocytosis
Lysis of cell

Type III reaction : Immune complex disease

- Induced by antigen antibody complexes that produce damage as a result of their capacity to activate the complement system.
- Antigens

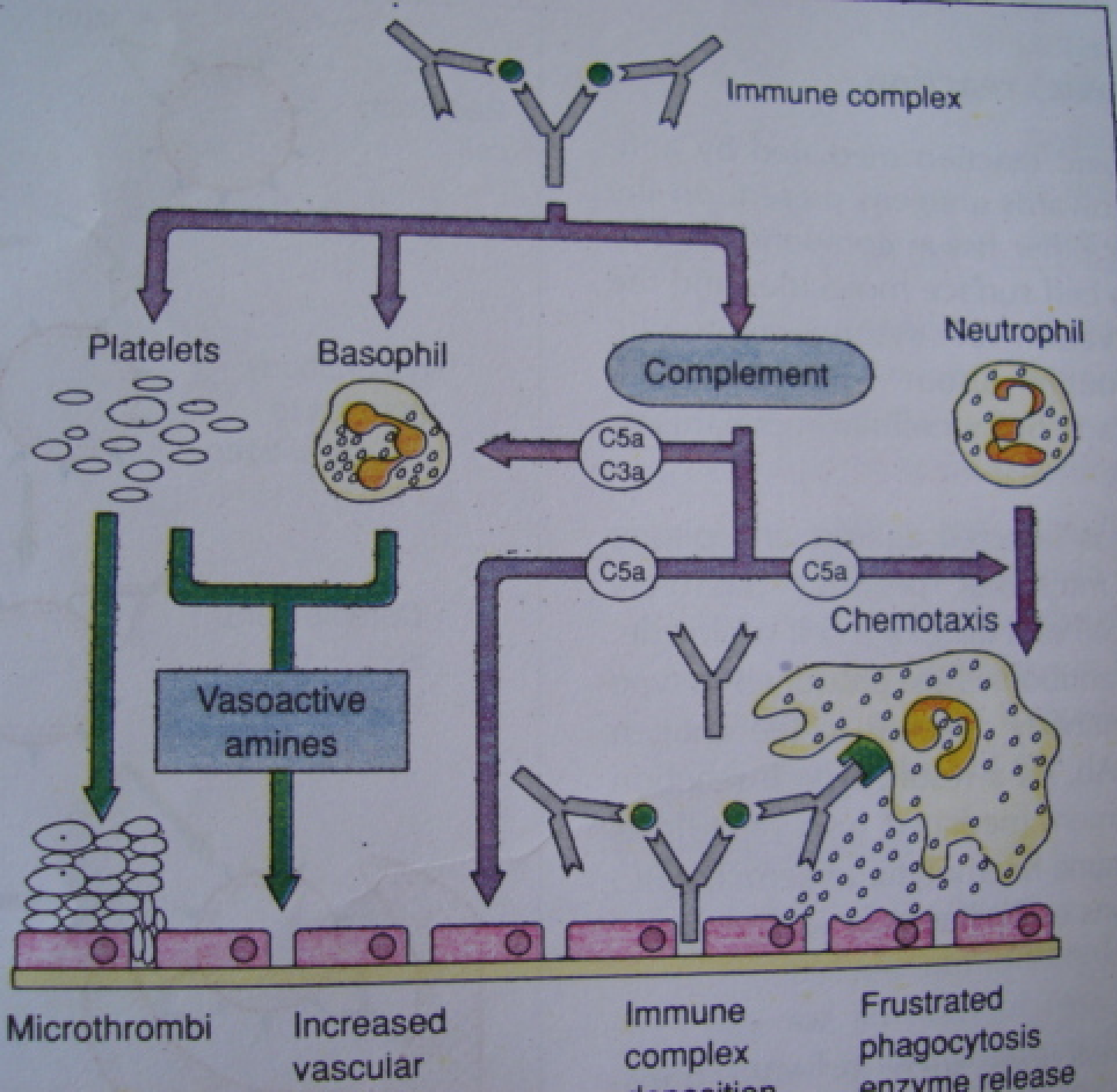
Exogenous – Bacteria, viruses, parasites, fungi or drugs or chemicals

Endogenous – nuclear antigens (SLE), Ig (RA), tumor antigens (GN)

- Diseases – generalised (I.C. formed in circulation)
  - localised (I.C. localised to particular organ)

Arthus reaction (Arthus 1903)

- Local inflammatory reaction with particular involvement of blood vessels.
- Occurs following inj. of Ag (horse serum) subcutaneously in hyper immunized animals (animal which has received several inj. of horse serum & developed high level of Abs-IgG).
- Reaction present as an erythema, oedema, indurations and hemorrhagic necrosis.
- It is a local manifestation of generalized hypersensitivity.


Immune complex
Platelets
Basophil
Complement
Neutrophil
C5a
C3a
C5a
C5a
Chemotaxis
Vasoactive amines
Microthrombi
Increased vascular
Immune complex
Frustrated phagocytosis
enzyme release

Serum sickness

- Systemic form of type III hypersensitivity.
- Von Pirquet & Schick (1905)
- The syndrome is currently more common following injections of penicillin or other antibiotics or diphtheria antitoxin.
- A single injection can serve both as the sensitizing dose and shocking dose.
- Symptoms appear after 7-14 day

  - fever, lymphadenopathy, splenomegaly, arthritis, glomerulonephritis, endocarditis, vasculitis, urticaria, abdominal pain, nausea, vomiting

- Pathogenesis – formation of I.C. which get deposited to endothelial lining of blood vessels in various parts of the body

- Plasma complement level decreases

- Self limited (I.C. are removed by phagocytosis & immune elimination)

- Immune complexes occur in many diseases, including bacterial (PSGN), viral (HBV) and parasitic infections (malaria), disseminated malignancies and autoimmune conditions

Diseases associated with ICs

- Autoimmune diseases- SLE, RA, Goodpasture's syndrom
- Drug reactions- allergies to penicillin and suphonamides
- Infectious diseases

Bacterial	Viral	Parasitic
SGPN,LL	DHF	Malaria
Secondary syphillis	HBV, CMV	Toxoplasmosis
Endocaditis	IM	Filariasis
Shunts in paed.	Panencephalitis	Schistosomiasis

Type IV reactions : Delayed hypersensitivity

- Cell mediated HSR, initiated by specifically sensitized T lymphocytes
- Not induced by circulating antibodies
- The antigens activates specifically sensitized T lymphocytes, leading to the secretion of lymphokines.
- Cutaneous reactivity, which becomes visible after 24-48 hours after introduction of Ag

- Inflammatory & indurated type involving lymphocytes & macrophages & NOT wheal & flare type as seen in anaphylaxis
- Passively transfer by lymphocytes or by transfer factor
- Two types - Tuberculin (Infection Type)

  - Contact dermatitis type

- Tuberculin type
  When a small dose of tuberculin is injected intradermally in an individual sensitized to tuberculoprotein by prior infection or immunization, an indurated inflammatory reaction occurs at the site within 48 – 72 hours.

- Seen in many infections with bacteria, fungi, viruses and parasites, when the infection is chronic and pathogen is intracellular.

Contact dermatitis type

- Delayed type HSR as a result of contact of skin with a variety of sub. such as
  - drugs like topical penicillin, sulfonamides
  - metal like nickel, cobalt, etc.
  - chemical e.g. hair dyes, picryl chloride.
- These sub. are not Ag but act as hapten & combine with skin proteins & become antigenic
- Hypersensitivity is detected by patch test.

Type V Stimulatory type reaction

- It is a modification of type II hypersensitivity.
- Certain IgG Abs have ability to stimulate (functional activity) their target cell rather than to kill or inhibit them
- Examples - Grave's disease in which thyroid hormones are produced in excess amount - thyrotoxicosis.

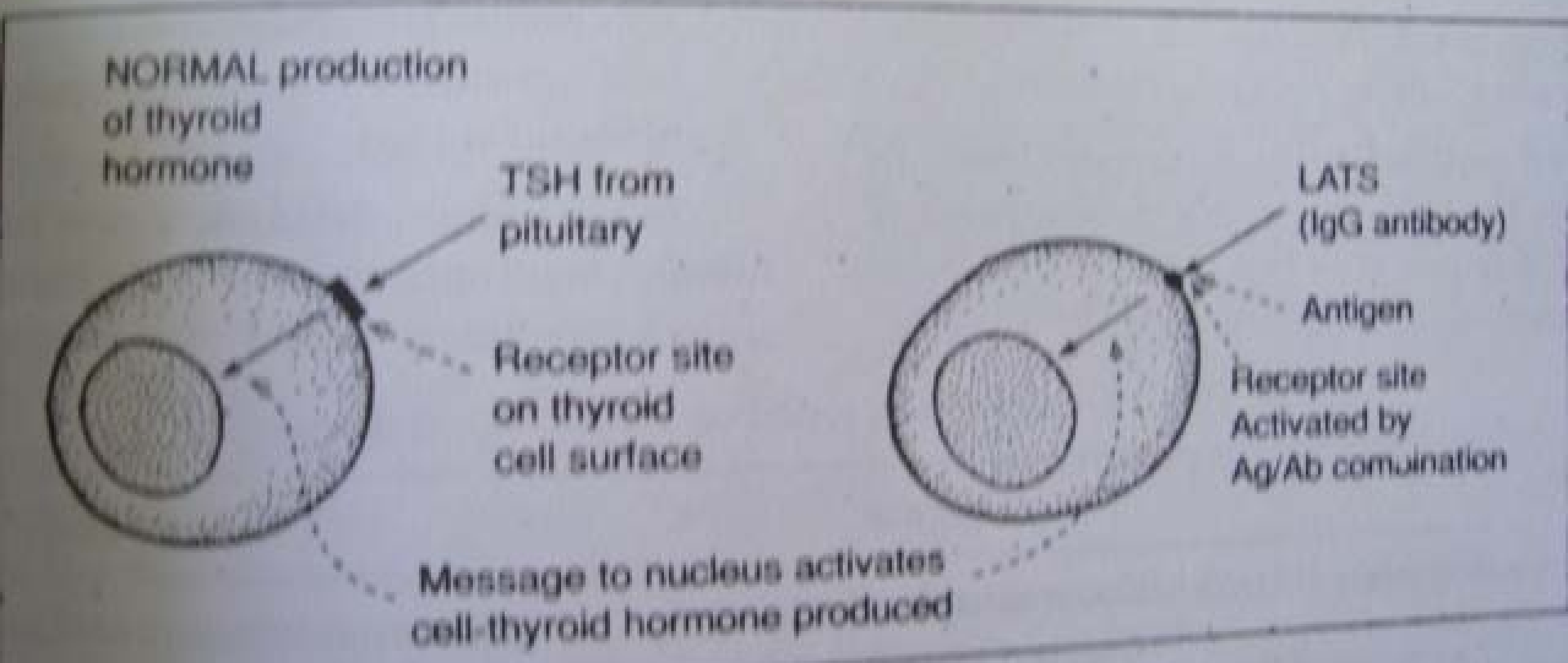


Fig. 19.6 : Mechanism of Gave's disease

mann Phenomenon

The phenomenon of *self toleran*
originally described by Paul Ehrlich i

Remember

"too much" of anything is bad.

'Excess' is not Excellence.

"too less" of anything is bad.

"Deficiency" can not ensure "efficiency"