Hypersensibilités allergiques et non allergiques

Audrey Nosbaum, Florence Hacard, Marie Tauber, Frédéric Bérard, Jean-François Nicolas, Marc Vocanson

Département Allergologie et Immunologie Clinique
INSER U1111/CIRI
Université Lyon1

http://allergolyon.fr

Maladies autoimmunes
Maladies allergiques
Maladies inflammatoires chroniques

Département Allergologie et Immunologie Clinique

Clinical Research Unit

INSERM translational research team

Allergology & Clinical Immunology Department

Plan

- Présentation du département Allergologie et Immunologie Clinique Lyon-Sud
- Généralités sur les Maladies Allergiques
- Hypersensibilités allergiques et non allergiques
  - Définition immunologique: type I (IgE); type IV (lymphocytes T)
  - Définition allergologique: type I (mastocyte); type IV (lymphocytes)
- Classification des Hypersensibilités: Gell & Coombs (1975-2024)
  - Type I
  - Type II
  - Type III
  - Type IV
- Nouvelle classification des Hypersensibilités: EAACI (2023)

Plan

- Présentation du département Allergologie et Immunologie Clinique Lyon-Sud
- **Généralités sur les Maladies Allergiques**
- Hypersensibilités allergiques et non allergiques
  - Définition immunologique: type I (IgE); type IV (lymphocytes T)
  - Définition allergologique: type I (mastocyte); type IV (lymphocytes)
- Classification des Hypersensibilités: Gell & Coombs (1975-2024)
  - Type I
  - Type II
  - Type III
  - Type IV
- Nouvelle classification des Hypersensibilités: EAACI (2023)

Physiopathologie de l’allergie

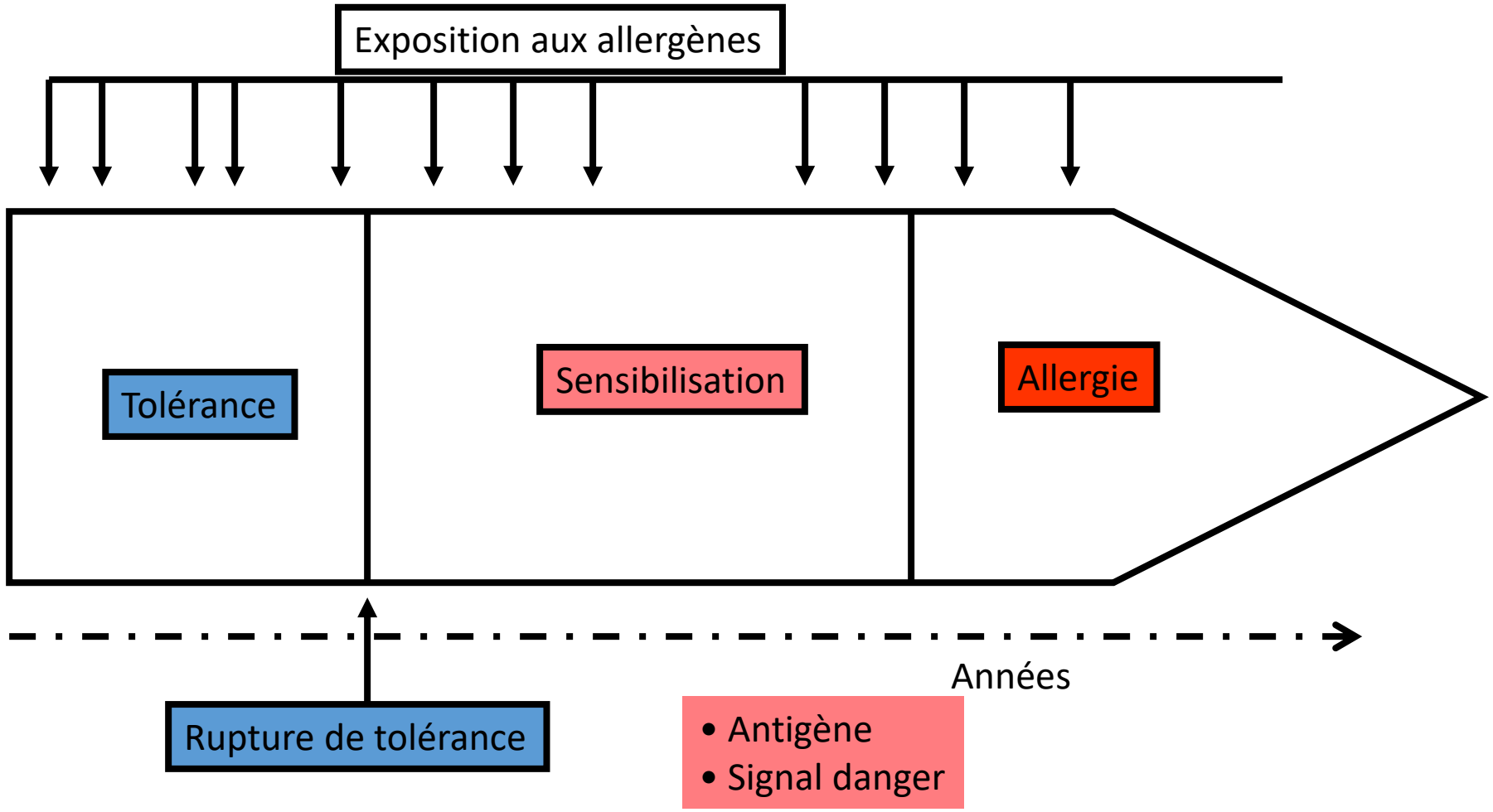
- La mise en place d’une maladie allergique obéit aux mêmes règles que la mise en place d’une réponse immunitaire vis à vis d’agents infectieux
- La physiopathologie des maladies allergiques est donc similaire à celle de la réponse anti-infectieuse

Allergie: rupture de tolérance

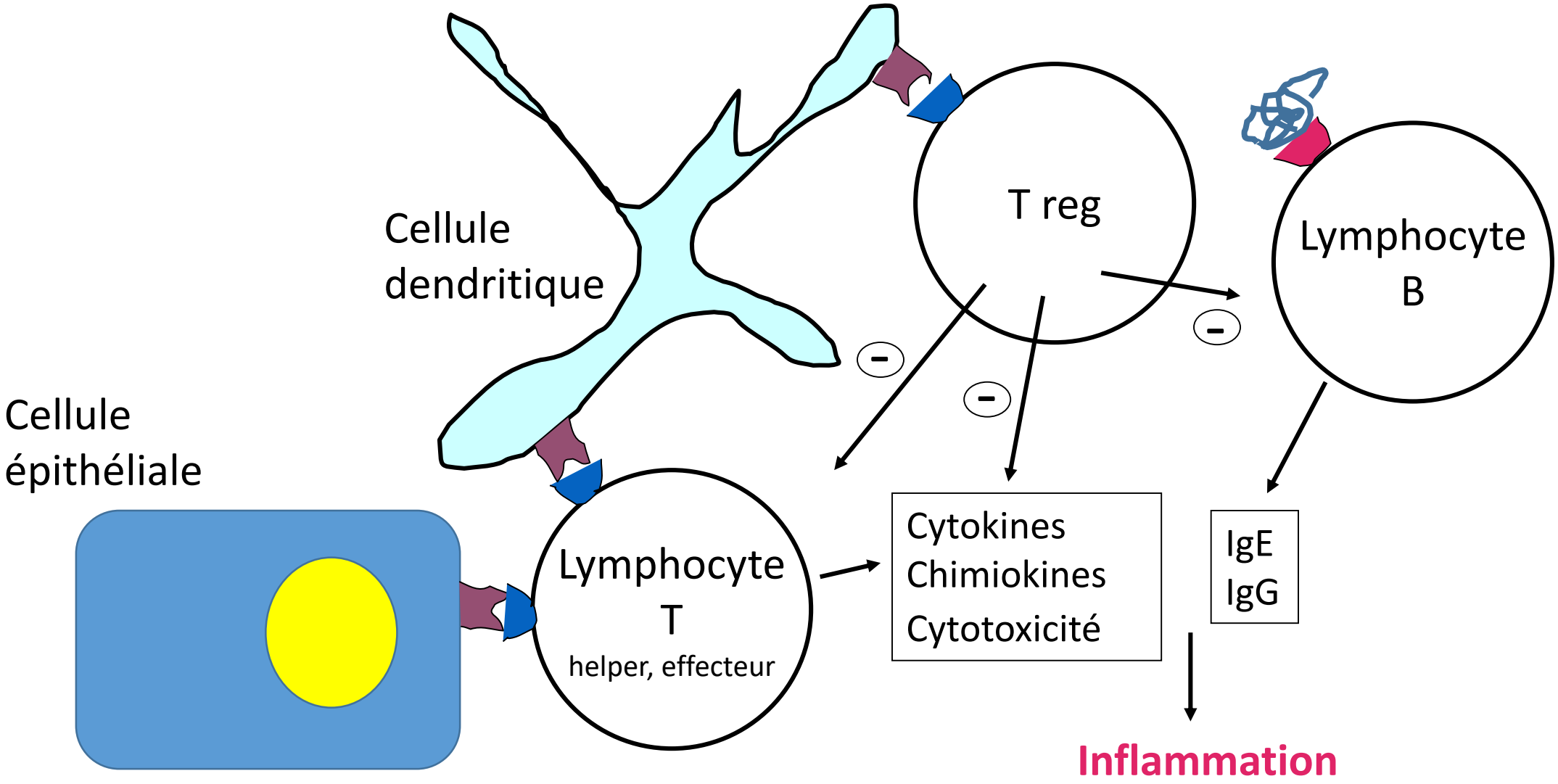
- Nous sommes tous en contact avec notre environnement
- Nous sommes tous sensibilisés vis à vis des antigènes de l'environnement
- Les sujets non allergiques développent une réponse immune tolérogène (régulatrice)
- Les sujets allergiques développent une réponse effectrice

ALLERGIE

Rupture de tolérance aux molécules de l'environnement



Allergie
Sensibilisation versus tolérance



Maladies allergiques

et
et
- *allergène naturel*
- *voie naturelle de contact*
- *sujet génétiquement prédisposé (ATCD familiaux)*

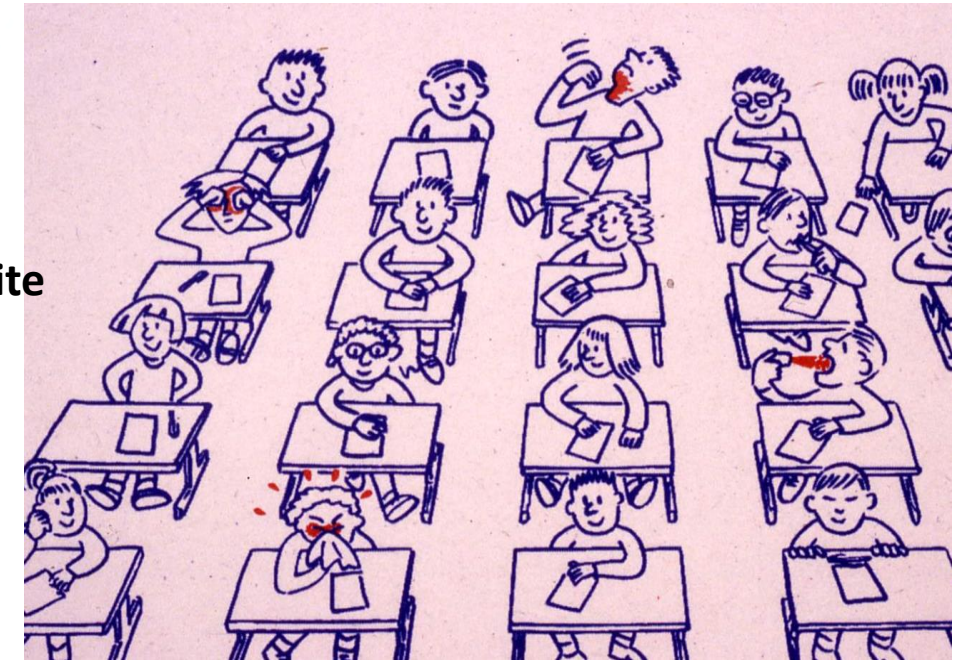
et/ou
et/ou
- *allergène chimique*
- *voie non naturelle de contact*
- *sujet non génétiquement prédisposé (ATCD familiaux)*

Allergènes

- Pneumallergènes
- Trophallergènes
- Injectables
- Contact cutané

maladie atopique

- **asthme**
- **rhinite**
- **conjonctivite**
- **eczéma**
- **aliments**
- **urticaire**



maladie non atopique

Venins guêpe
Médicaments
- **choc anaphylactique**
- **œdème de Quincke**

Allergènes cutanés
- **eczéma contact**

Plan

- Présentation du département Allergologie et Immunologie Clinique Lyon-Sud
- Généralités sur les Maladies Allergiques
- **Hypersensibilités allergiques et non allergiques**
  - Définition immunologique: type I (IgE); type IV (lymphocytes T)
  - Définition allergologique: type I (**mastocyte**); type IV (**lymphocyte**)
- Classification des Hypersensibilités: Gell & Coombs (1975-2024)
  - Type I
  - Type II
  - Type III
  - Type IV
- Nouvelle classification des Hypersensibilités: EAACI (2023)

Les Hypersensibilités

Etiopathogénie (cause)
Physiopathologie (mécanisme)

1. Définition immunologique

Maladies dues à des effecteurs de l'immunité spécifique (Ac et/ou LT)

- M allergiques
- M autoimmunes
- M inflammatoires chroniques

2. Définition allergologique

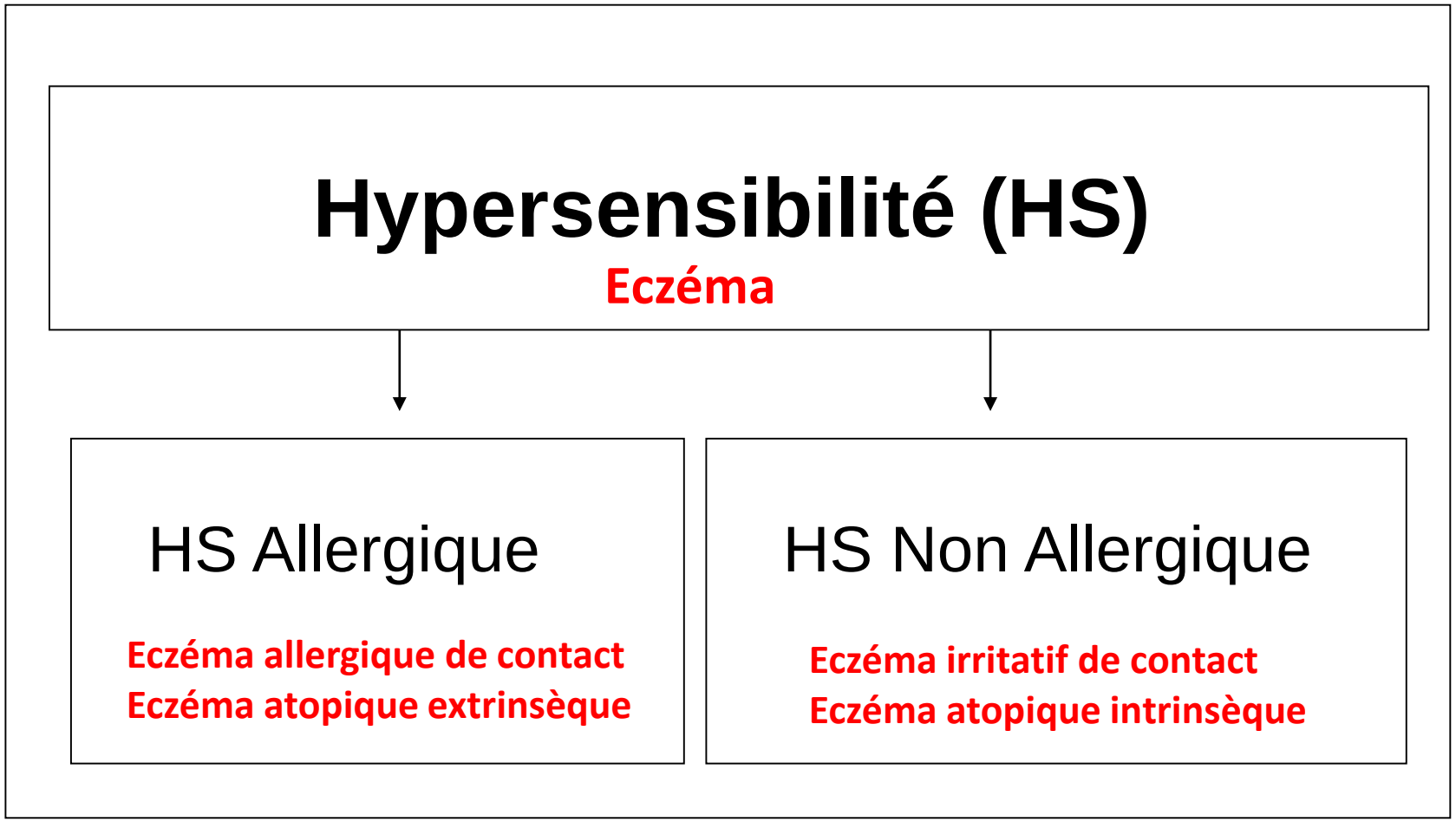
HS allergique: immunité spécifique (Ac et/ou LT)

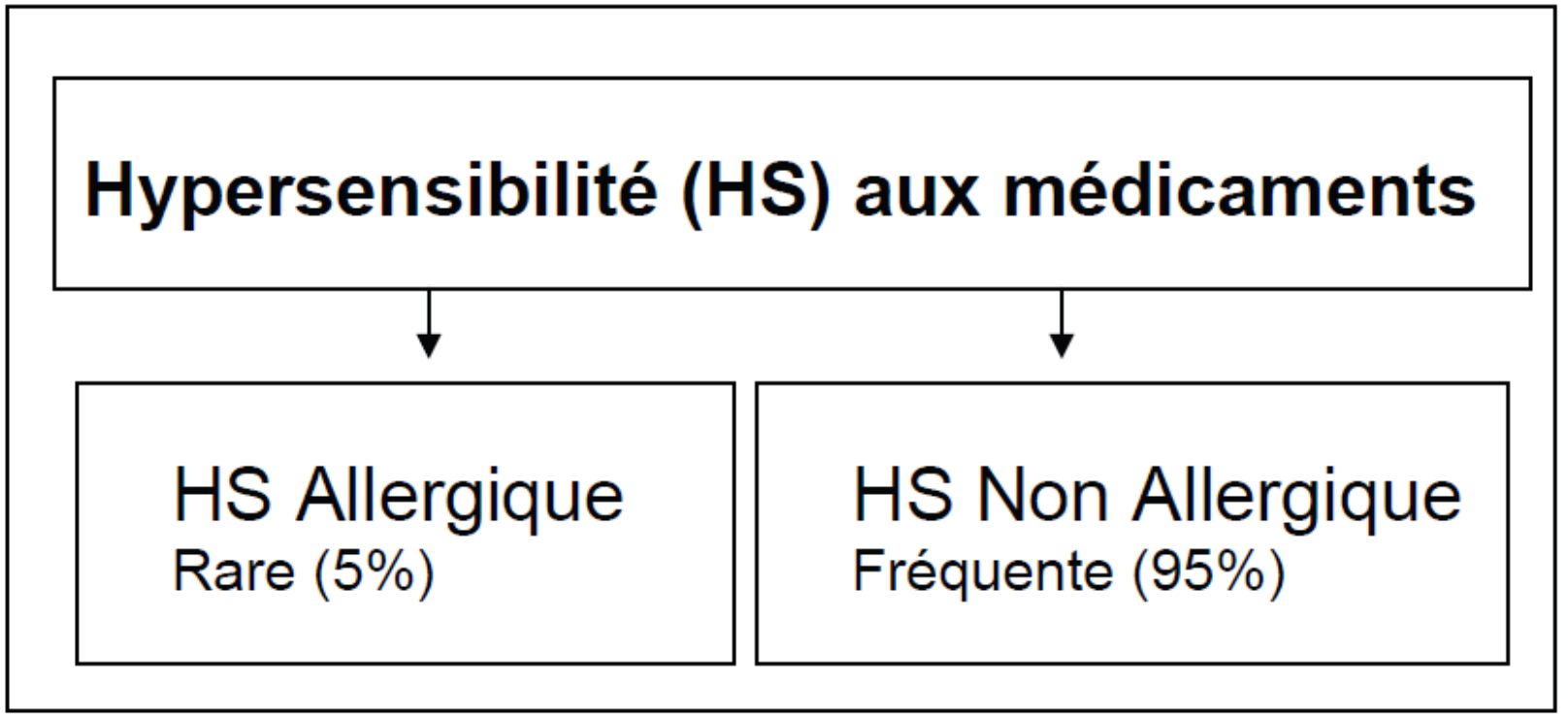
HS non allergique: immunité innée

Terminologie

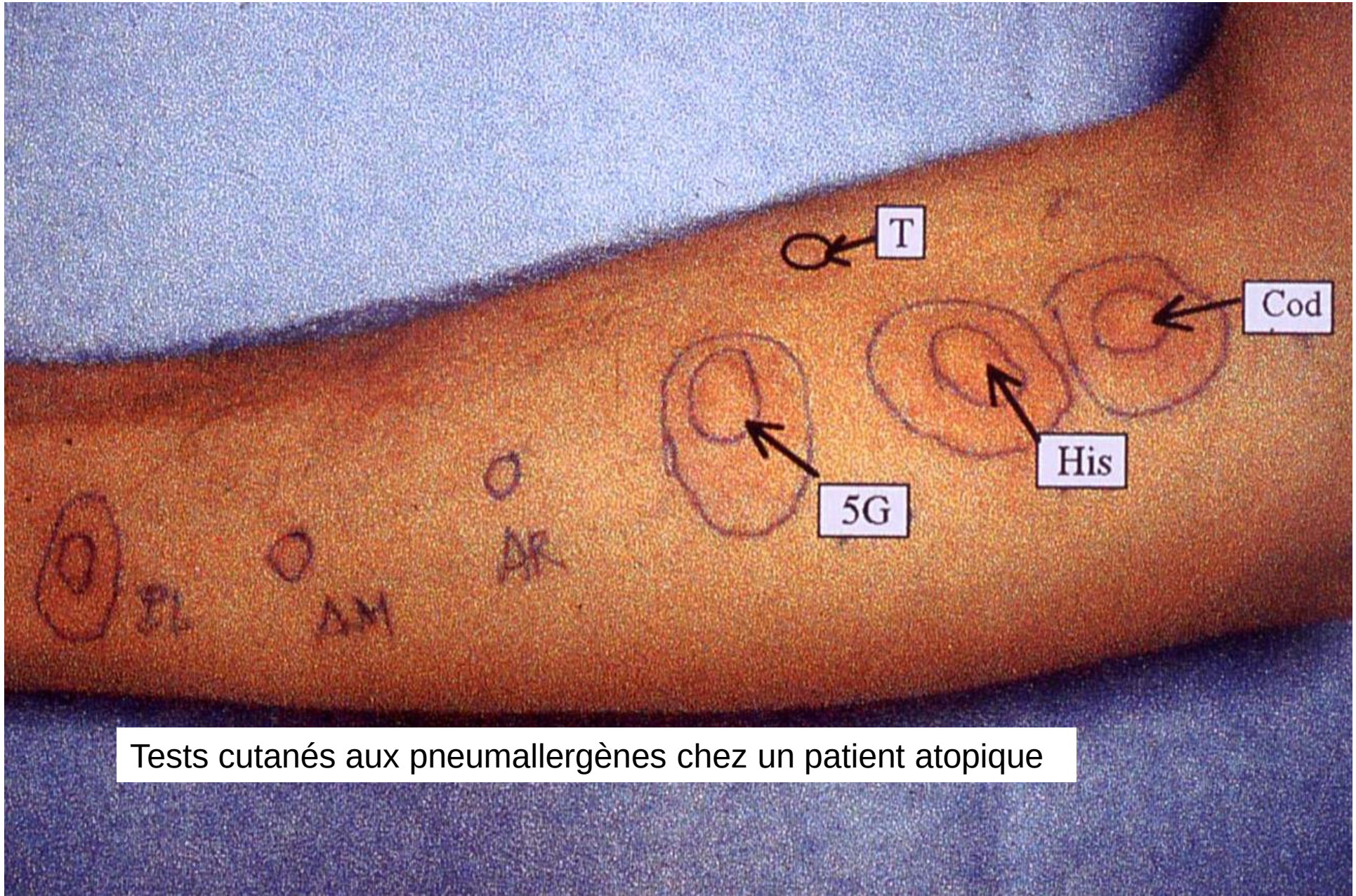
- **Allergie** (gell et coombs: immunité adaptative; immunité spécifique)
  - Type I / hypersensibilité immédiate:IgE
  - Type II: IgG
  - Type III:CIC
  - Type IV / hypersensibilité retardée: lymphocytes T
- **Hypersensibilité** (immunité innée et adaptative)
  - HS allergique = Allergie
  - HS non allergique (immunité innée)

  (intolérance, pseudo-allergie, anaphylactoide, fausse allergie)
    - **HS immédiate: MASTOCYTES**
    - **HS retardée: LYMPHOCYTES**


Hypersensibilité (HS)
Eczéma
HS Allergique
Eczéma allergique de contact
Eczéma atopique extrinsèque
HS Non Allergique
Eczéma irritatif de contact
Eczéma atopique intrinsèque


Hypersensibilité (HS) aux médicaments
HS Allergique
Rare (5%)
HS Non Allergique
Fréquente (95%)
sévère
bénigne

HSI allergique et non allergique



Tests cutanés aux pneumallergènes chez un patient atopique

[redacted] Danièle

7 Côte Carmagnac

69 [redacted]

tel

le 11 Mai 2003

Docteur Nicolas,

Mon fils Yves a rendez-vous le 25 Juin pour des tests. Il est né le 8 janvier 1983, et a fait un urticaire géant au Clamoxyl en 1986, donc on a évité cet antibiotique. Le 22 Décembre dernier, il a fait un oedème de Quincke, après avoir passé un gel "erythrogel" 4 % sur ses boutons d'acné. Le 23 Mars dernier, il

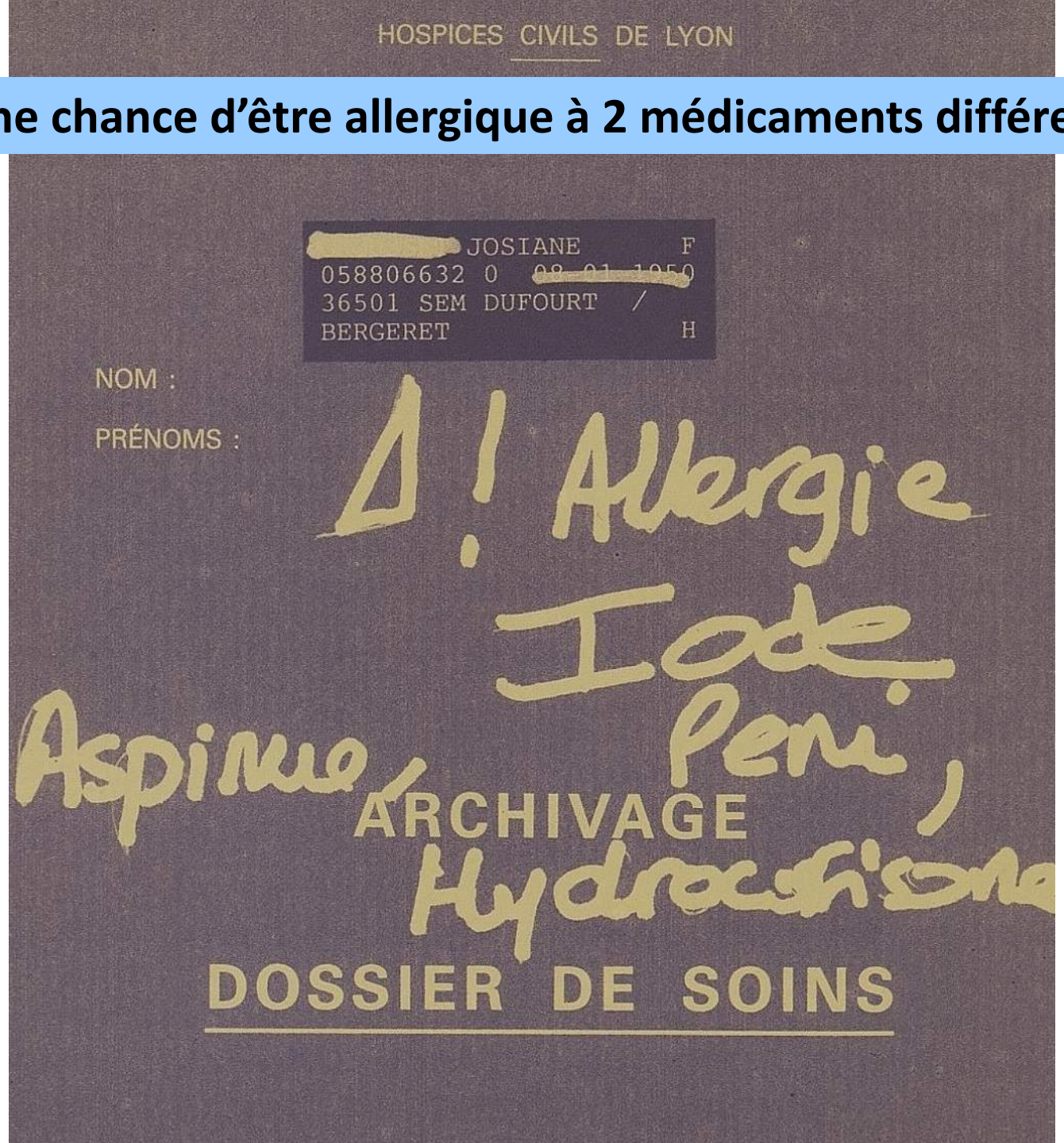
Quand on est allergique à tout, on est allergique à rien

ni aucun médicament, et il a refait un oédème de Quincke. J'ai donc noté qu'il avait mangé = du nougat chinois, concombres, tomates, betteraves, magret de Canard, sauce au poivre vert, mangues, litchis, comté et pâtes.

Il y avait aussi un très gros bouquet de tulipes posé près de lui, avec des jonquilles.

Désolé d'avoir dû changer le rendez-

Aucune chance d'être allergique à 2 médicaments différents

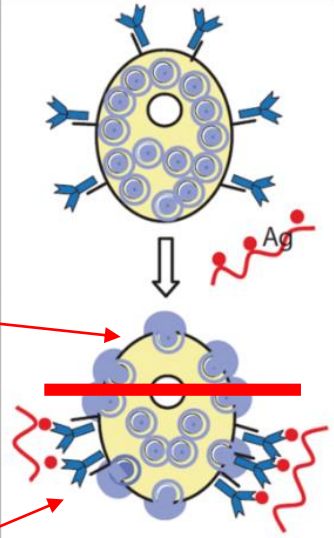
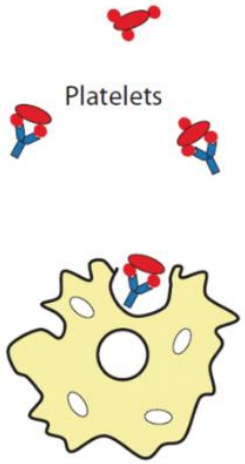
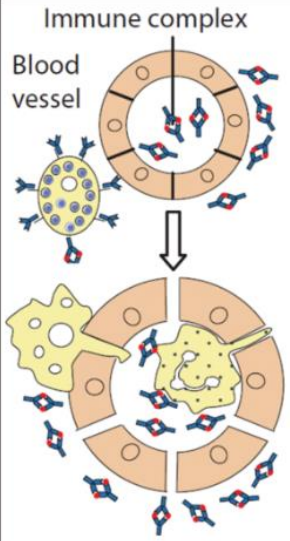
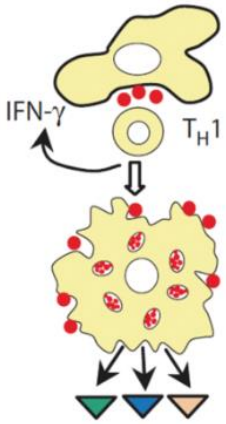
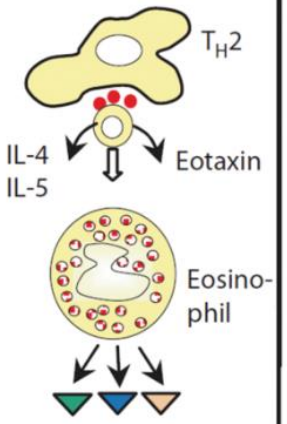
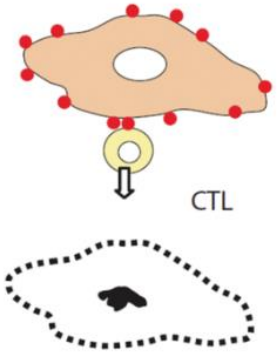
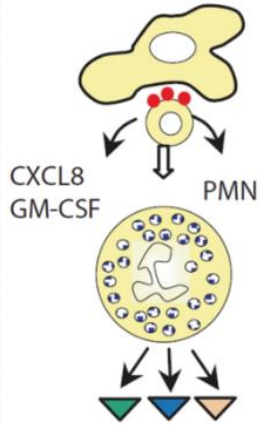


Plan

- Présentation du département Allergologie et Immunologie Clinique Lyon-Sud
- Généralités sur les Maladies Allergiques
- Hypersensibilités allergiques et non allergiques
  - Définition immunologique: type I (IgE); type IV (lymphocytes T)
  - Définition allergologique: type I (mastocyte); type IV (lymphocytes)
- **Classification des Hypersensibilités: Gell & Coombs (1975-2024)**
  - Type I
  - Type II
  - Type III
  - Type IV
- Nouvelle classification des Hypersensibilités: EAACI (2023)

Hypersensibilités
Classification de Gell & Coombs

Antibody → T cells

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	IIFN-γ, TNF-α (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ granzyme B (CTL)	IL-17, IL-22 (Th17)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators

HSI non allergique

HSI allergique

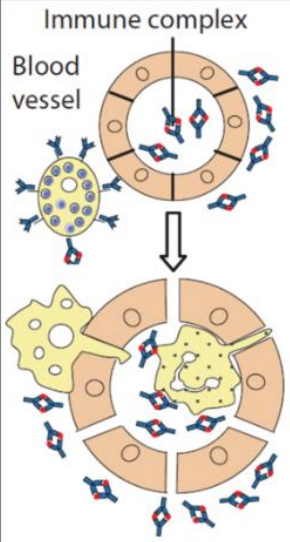
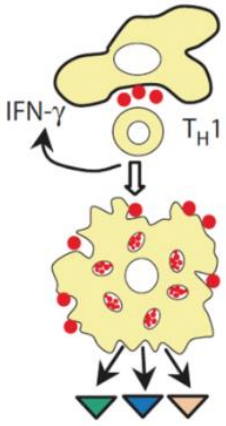
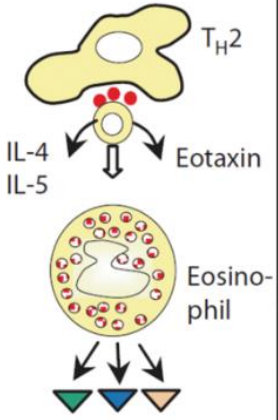
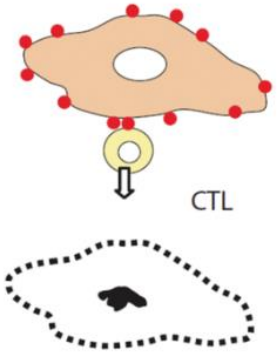
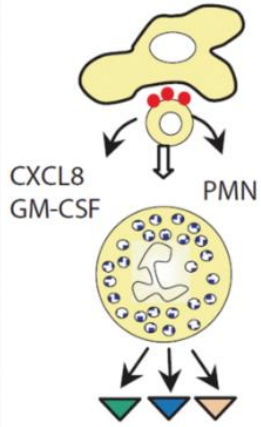
Hypersensibilités
Classification de Gell & Coombs

Antibody → T cells

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	IIFN-γ, TNF-α (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ granzyme B (CTL)	IL-17, IL-22 (Th17)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
Maladies autoimmunes, allergiques et HS	**Anaphylaxie Rhinite Asthme**	Platelets	Immune complex; Blood vessel	IFN-γ; T_H1; Chemokines, cytokines, cytotoxins	T_H2; IL-4 IL-5; Eotaxin; Eosino-phil; Cytokines, inflammatory mediators	CTL	CXCL8 GM-CSF; PMN; Cytokines, inflammatory mediators
Dermatoses autoimmunes, allergiques et HS	**Urticaire SAMa**						
Allergie et HS médicaments	**Choc anaphylactique Urticaire aux médicaments**						

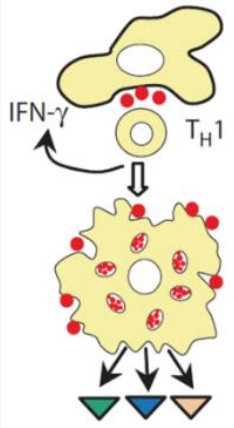
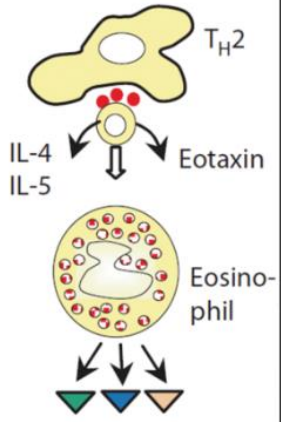
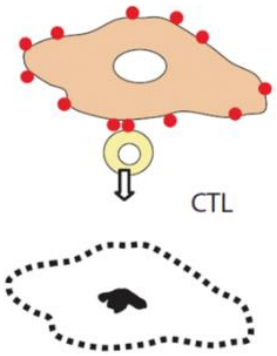
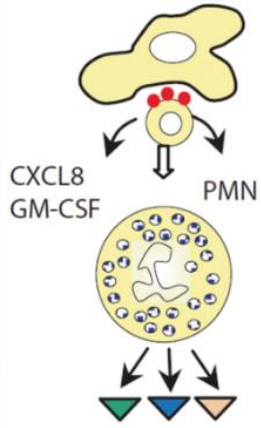
Hypersensibilités
Classification de Gell & Coombs

Antibody → T cells

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	IIFN-γ, TNF-α (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ granzyme B (CTL)	IL-17, IL-22 (Th17)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
Maladies autoimmunes, allergiques et HS	**Anaphylaxie Rhinite Asthme**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**		 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
Dermatoses autoimmunes, allergiques et HS	**Urticaire SAMa**	**Pemphigus Pemphigoide Urticaire chroni.**					
Allergie et HS médicaments	**Choc anaphylactique Urticaire aux médicaments**	**Cytopénies medic.**					

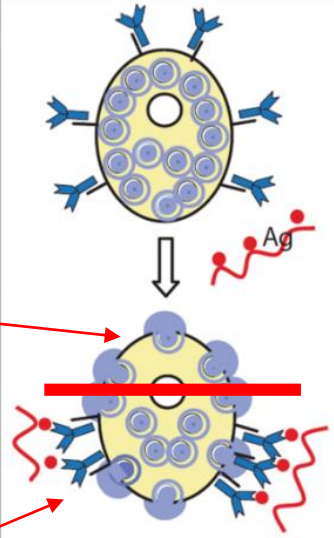
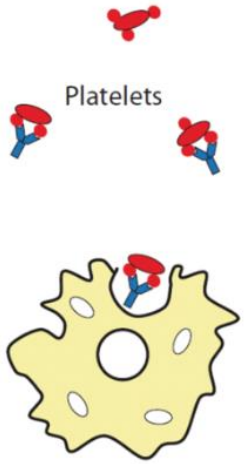
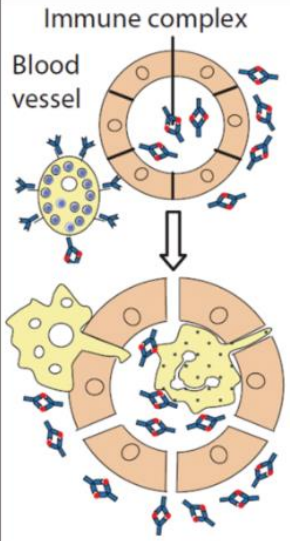
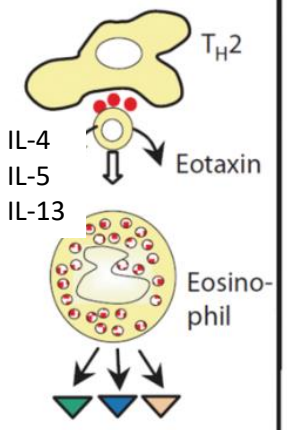
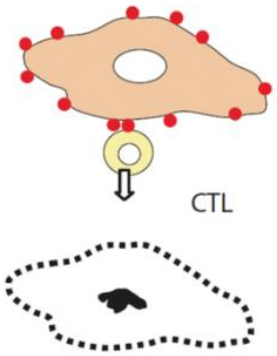
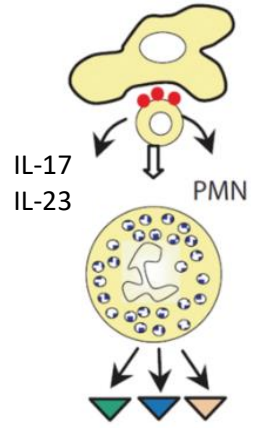
Hypersensibilités
Classification de Gell & Coombs

Antibody → T cells

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	IIFN-γ, TNF-α (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ granzyme B (CTL)	IL-17, IL-22 (Th17)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
Maladies autoimmunes, allergiques et HS	**Anaphylaxie Rhinite Asthme**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
Dermatoses autoimmunes, allergiques et HS	**Urticaire SAMa**	**Pemphigus Pemphigoide Urticaire chroni.**	**Vascularites**				
Allergie et HS médicaments	**Choc anaphylactique Urticaire aux médicaments**	**Cytopénies medic.**	**Vascularites immuno-allerg.**				

Hypersensibilités
Classification de Gell & Coombs

Antibody → ← Lymphocytes

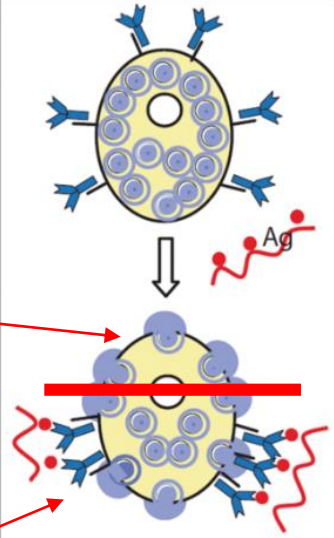
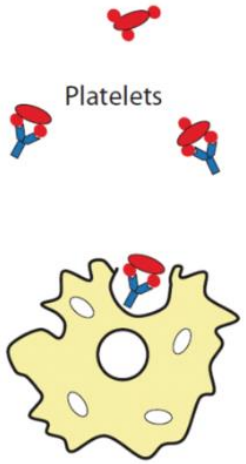
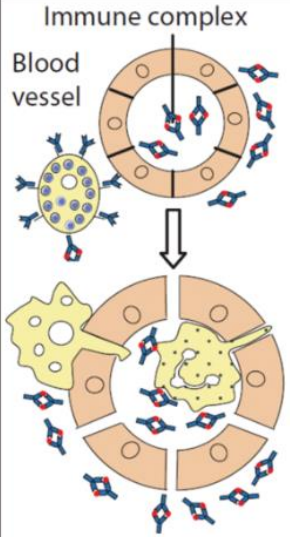
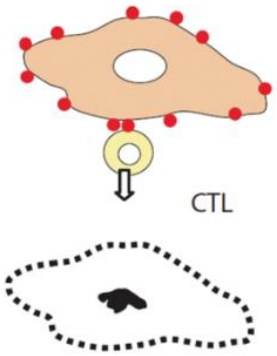
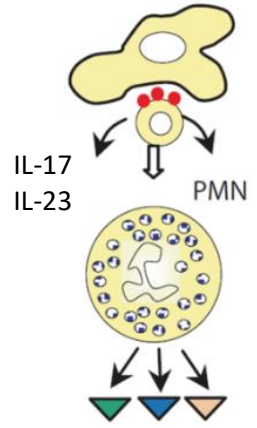
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ granzyme B (CTL)	IL-17, IL-22 (Th17)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
				**IDR tuberculine** **Rejet de greffe** **Polyarthrite** **Diabète** **Vitiligo** **Pelade** **Eczéma contact** **Exanthème** **Lyell** **Stevens-Johnson**			

HSI non allergique

HSI allergique

Hypersensibilités
Classification de Gell & Coombs

Antibody → ← Lymphocytes

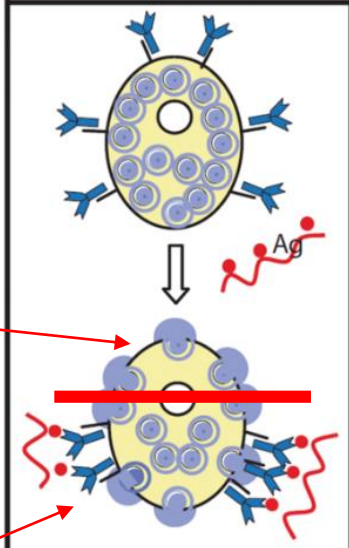
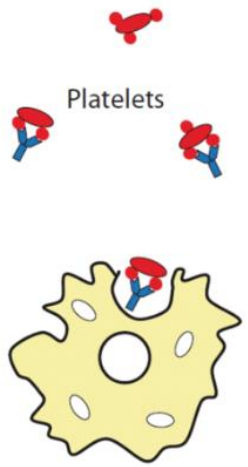
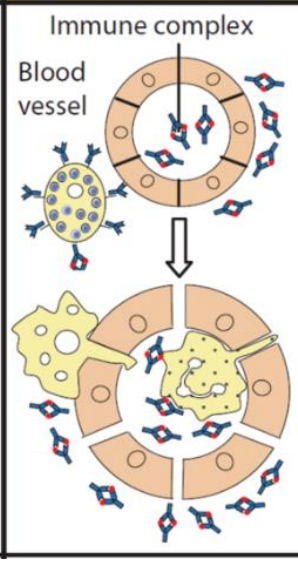
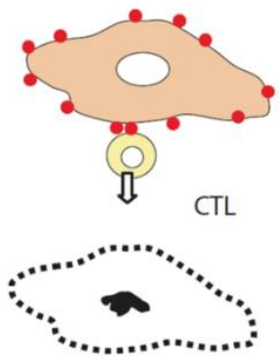
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	**Th2/Tc2/ILC2 Type 2 inflammation**	Perforin/ granzyme B (CTL)	IL-17, IL-22 (Th17)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
				**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme T2 Rhinite, Conjonctivite Œsophagite eosin.**		
				Vitiligo Pelade Eczéma contact	**Dermatite atopique Prurigo nodulaire Urticaire chronique**		
				Exanthème Lyell Stevens-Johnson	**DRESS**		Cytokines, inflammatory mediators

HSI non allergique

HSI allergique

Hypersensibilités
Classification de Gell & Coombs

Antibody → ← Lymphocytes

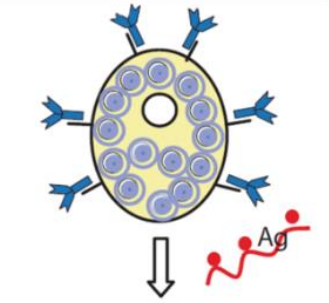
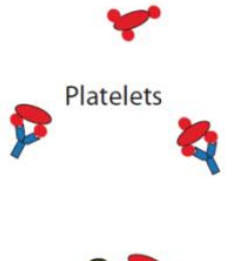
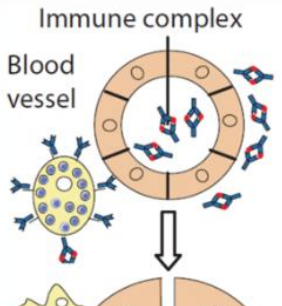
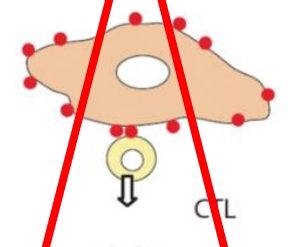
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	**Th2/Tc2/ILC2 Type 2 inflammation**	Perforin/ granzyme B (CTL)	**Th17/Tc17/ILC3 Type 3 (17) inflammation**
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
				**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme T2 Rhinite, Conjonctivite Œsophagite eosin.**		**Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.**
				Vitiligo Pelade Eczéma contact	**Dermatite atopique Prurigo nodulaire Urticaire chronique**		**Psoriasis**
				Exanthème Lyell Stevens-Johnson	**DRESS**		**Pustulose exanthématique aigue généralisée**

HSI non allergique

HSI allergique

Hypersensibilités
Classification de Gell & Coombs

Antibody → ← Lymphocytes

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	**Th2/Tc2/ILC2 Type 2 inflammation**	Perforin/ granzyme B (CTL)	**Th17/Tc17/ILC3 Type 3 (17) inflammation**
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
HSI non allergique				**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme T2 Rhinite, Conjonctivite Œsophagite eosin.**		**Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.**
				Vitiligo Pelade Eczéma contact	**Dermatite atopique Prurigo nodulaire Urticaire chronique**		**Psoriasis**
HSI allergique				**Exanthème Lyell Stevens-Johnson**	**DRESS**		**Pustulose exanthématique aigue généralisée**

Hypersensibilités
Classification de Gell & Coombs

Antibody → ← Lymphocytes

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	**Th2/Tc2/ILC2 Type 2 inflammation**	Perforin/ granzyme B (CTL)	**Th17/Tc17/ILC3 Type 3 (17) inflammation**
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
Maladies autoimmunes, allergiques et HS	**Anaphylaxie Rhinite Asthme**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme T2 Rhinite, Conjonctivite Œsophagite eosin.**		**Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.**
Dermatoses autoimmunes, allergiques et HS	**Urticaire SAMa**	**Pemphigus Pemphigoide Urticaire chroni.**	**Vascularites**	**Vitiligo Pelade Eczéma contact**	**Dermatite atopique Prurigo nodulaire Urticaire chronique**		**Psoriasis**
Allergie et HS médicaments	**Choc anaphylactique Urticaire aux médicaments**	**Cytopénies medic.**	**Vascularites immuno-allerg.**	**Exanthème Lyell Stevens-Johnson**	**DRESS**		**Pustulose exanthématique aigue généralisée**

Plan

- Présentation du département Allergologie et Immunologie Clinique Lyon-Sud
- Généralités sur les Maladies Allergiques
- Hypersensibilités allergiques et non allergiques
  - Définition immunologique: type I (IgE); type IV (lymphocytes T)
  - Définition allergologique: type I (mastocyte); type IV (lymphocytes)
- Classification des Hypersensibilités: Gell & Coombs (1975-2024)
  - Type I
  - Type II
  - Type III
  - Type IV
- **Nouvelle classification des Hypersensibilités: EAACI (2023)**

Nomenclature 2023 des maladies allergiques et des réactions d'hypersensibilité: EAACI.

du classique, du très bon, du surprenant!

Received: 12 August 2023 | Revised: 1 September 2023 | Accepted: 5 September 2023
DOI: 10.1111/all.15889

EAACI POSITION PAPER

Allergy EAACI WILEY

Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper

Marek Jutel[1,2] | Ioana Agache[3] | Magdalena Zemelka-Wiacek[1] | Mübeccel Akdis[4] | Tomás Chivato[5] | Stefano del Giacco[6,7] | Pawel Gajdanowicz[1] | Ibon Eguiluz Gracia[8] | Ludger Klimek[9,10] | Antti Lauerma[11] | Markus Ollert[12,13] | Liam O'Mahony[14] | Jürgen Schwarze[15] | Mohamed H. Shamji[16,17] | Isabel Skypala[18,19] | Oscar Palomares[20] | Oliver Pfaar[21] | Maria Jose Torres[8] | Jonathan A. Bernstein[22] | Alvaro A. Cruz[23] | Stephen R. Durham[24] | Stephen J. Galli[25] | R. Maximiliano Gómez[26] | Emma Guttman-Yassky[27] | Tari Haahtela[28] | Stephen T. Holgate[29] | Kenji Izuhara[30] | Kenji Kabashima[31] | Désirée E. Larenas-Linnemann[32] | Erica von Mutius[33,34,35] | Kari C. Nadeau[36] | Ruby Pawankar[37] | Tomas A. E. Platts-Mills[38] | Scott H. Sicherer[39] | Hae-Sim Park[40] | Stefan Vieths[41] | Gary Wong[42] | Luo Zhang[43,44] | M. Beatrice Bilò[45] | Cezmi A. Akdis[4]

Correspondence
Marek Jutel, Department of Clinical Immunology, Wroclaw Medical University, Wroclaw, Poland.
Email: marek.jutel@all-med.wroclaw.pl

Ioana Agache, Faculty of Medicine, Transylvania University, Brasov, Romania.
Email: ibrumaru@unitbv.ro

Cezmi A. Akdis, Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.
Email: cezmi.akdis@siaf.uzh.ch

Abstract

The exponential growth of precision diagnostic tools, including omic technologies, molecular diagnostics, sophisticated genetic and epigenetic editing, imaging and nano-technologies and patient access to extensive health care, has resulted in vast amounts of unbiased data enabling in-depth disease characterization. New disease endotypes have been identified for various allergic diseases and triggered the gradual transition from a disease description focused on symptoms to identifying biomarkers and intricate pathogenetic and metabolic pathways. Consequently, the current disease taxonomy has to be revised for better categorization. This European Academy of Allergy and Clinical Immunology Position Paper responds to this challenge and provides a modern nomenclature for allergic diseases, which respects the earlier classifications back to the

https://hub.eaaci.org/education_webinars/nomenclature-of-allergic-diseases-and-hypersensitivity-reactions-adapted-to-modern-needs-an-eaaci-position-paper/

Definitions/Terminology

- **Hypersensitivity:** refers to an undesirable, uncomfortable, or damaging response that arises from immune system overreaction or tissue dysfunction
- **Allergy:** is an abnormal or exaggerated reaction to exogenous stimuli which involves various types of hypersensitivity reactions engaging antibody, cell-mediated, tissue-driven, or metabolic mechanisms resulting in the development of respiratory, skin, eye, gastrointestinal, and other symptoms, including anaphylaxis
- **Anaphylaxis:** is a serious allergic reaction that is rapid in onset and might cause death
- **Atopy**: deeply enrooted, but limited use today, based mainly on the symptomatic definition of diseases and does not represent the current understanding of the pathophysiology

Jutel M et al. **Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper**. Allergy. 2023 Nov;78(11):2851-2874. doi: 10.1111/all.15889. Epub 2023 Oct 10.

ACD, allergic contact dermatitis; AD,atopic dermatitis; ADCC, antibody-dependent cellular cytotoxicity; AERD, aspirin-exacerbated respiratory diseases; AGEP, acute generalized exanthematous pustulosis; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; B, B lymphocytes; BAS, basophil; CRS, chronic rhinosinusitis; DRESS, severe drug reaction with eosinophilia and systemic symptoms; EoE, eosinophilic oesophagitis; EOS, eosinophil; FPIES, food protein-induced enterocolitis syndrome; IFN-γ, interferon-gamma; Ig (E, G, M), immunoglobulin (type E, G, M); IL, interleukin; ILC1/2/3, innate lymphoid cells type 1/2/3; MO, monocyte; MΦ, macrophage; NEU, neutrophils; NK, natural killer cell; NK-T, natural killer T cell; SJS, Stevens-Johnson syndrome; T1/T2/T3, type 1/2/3 immune response; Tc1/2/17, T cytotoxic lymphocyte type 1/2/17; TEN, toxic epidermal necrolysis; Th, T helper lymphocytes; TLSP, thymic stromal lymphopoietin; TNF-α, tumour necrosis factor-alpha.

HYPERSENSITIVITY REACTIONS ▶ AUTOIMMUNITY

ALLERGY

INFLAMMATION / IMMUNE SYSTEM-DRIVEN

ANTIBODY-MEDIATED

Type I Immediate	Type II Cytotoxic	Type III Immune complexes
B cells: IgE Th2, ILC2 (IL-4, IL-5, IL-9, IL-13) Mast cells/BAS	B cells: IgM, IgG Phagocytes: NEU, MΦ C-dependent cytotoxicity, NK (ADCC)	B cells: IgM, IgG Immune complexes Complement, BAS, Mast cells, Platelets Phagocytes: NEU, MO, MΦ
AR/ARC, asthma, AD, acute urticaria/ angioedema, food allergy, venom allergy, drug allergy	Drug-induced cytopenia	Acute phase of hypersensitivity pneumonitis, drug-induced vasculitis, serum sickness/ Arthus reaction

CELL-MEDIATED

Type IVa T1	Type IVb T2	Type IVc T3
Th1, ILC1, Tc1, NK (IFN-γ, TNF-α, granzyme B, perforines) MΦ (granulomas)	Th2, ILC2, Tc2, NK-T (IL-4, IL-5, IL-9, IL-13, IL-31) EOS, B cells, Mast cells/BAS	Th17, ILC3, Tc17 (IL-17, IL-22, IL-23) NEU
ACD, acute phase of hypersensitivity pneumonitis, celiac disease, asthma, AR/ARC, CRS, AD, drug allergy (TEN, SJS, erythema multiforme)	Asthma, AR/CRS AD (T2 endotypes), EoE, food allergy, drug allergy (DRESS)	Neutrophilic asthma, AD, drug allergy (AGEP)

TISSUE-DRIVEN MECHANISMS

Type V Epithelial	Type VI Metabolic
Epithelial barrier defect, leaky junctions Resident cells changes (smooth muscle cells, mucous glands, neuroimmune interactions) Immune modulation (alarmins: TSLP, IL-25, IL-33) Epigenetic impact	Metabolic-induced immune dysregulation, short-chain fatty acids and other microbiome metabolites
Asthma, AR/ARC, CRS, AD, FPIES, EoE, celiac disease	Obesity & asthma, histamine-driven disorders

DIRECT RESPONSE TO CHEMICALS

Type VII
Direct cellular and inflammatory response to chemical substances
AERD, idiosyncratic reactions AR, ARC, asthma, AD, acute urticaria/angioed ema and drug allergy

ACD, allergic contact dermatitis; AD,atopic dermatitis; ADCC, antibody-dependent cellular cytotoxicity; AERD, aspirin-exacerbated respiratory diseases; AGEP, acute generalized exanthematous pustulosis; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; B, B lymphocytes; BAS, basophil; CRS, chronic rhinosinusitis; DRESS, severe drug reaction with eosinophilia and systemic symptoms; EoE, eosinophilic oesophagitis; EOS, eosinophil; FPIES, food protein-induced enterocolitis syndrome; IFN-γ, interferon-gamma; Ig (E, G, M), immunoglobulin (type E, G, M); IL, interleukin; ILC1/2/3, innate lymphoid cells type 1/2/3; MO, monocyte; MΦ, macrophage; NEU, neutrophils; NK, natural killer cell; NK-T, natural killer T cell; SJS, Stevens-Johnson syndrome; T1/T2/T3, type 1/2/3 immune response; Tc1/2/17, T cytotoxic lymphocyte type 1/2/17; TEN, toxic epidermal necrolysis; Th, T helper lymphocytes; TLSP, thymic stromal lymphopoietin; TNF-α, tumour necrosis factor-alpha.

HYPERSENSITIVITY REACTIONS ▶ AUTOIMMUNITY

ALLERGY

INFLAMMATION / IMMUNE SYSTEM-DRIVEN

ANTIBODY-MEDIATED

Type I Immediate	Type II Cytotoxic	Type III Immune complexes
B cells: IgE Th2, ILC2 (IL-4, IL-5, IL-9, IL-13) Mast cells/BAS	B cells: IgM, IgG Phagocytes: NEU, MΦ C-dependent cytotoxicity, NK (ADCC)	B cells: IgM, IgG Immune complexes Complement, BAS, Mast cells, Platelets Phagocytes: NEU, MO, MΦ
AR/ARC, asthma, AD, acute urticaria/ angioedema, food allergy, venom allergy, drug allergy	Drug-induced cytopenia	Acute phase of hypersensitivity pneumonitis, drug-induced vasculitis, serum sickness/ Arthus reaction

CELL-MEDIATED

Type IVa T1	Type IVb T2	Type IVc T3
Th1, ILC1, Tc1, NK (IFN-γ, TNF-α, granzyme B, perforines) MΦ (granulomas)	Th2, ILC2, Tc2, NK-T (IL-4, IL-5, IL-9, IL-13, IL-31) EOS, B cells, Mast cells/BAS	Th17, ILC3, Tc17 (IL-17, IL-22, IL-23) NEU
ACD, acute phase of hypersensitivity pneumonitis, celiac disease, asthma, AR/ARC, CRS, AD, drug allergy (TEN, SJS, erythema multiforme)	Asthma, AR/CRS AD (T2 endotypes), EoE, food allergy, drug allergy (DRESS)	Neutrophilic asthma, AD, drug allergy (AGEP)

TISSUE-DRIVEN MECHANISMS

Type V Epithelial	Type VI Metabolic
Epithelial barrier defect, leaky junctions Resident cells changes (smooth muscle cells, mucous glands, neuroimmune interactions) Immune modulation (alarmins: TSLP, IL-25, IL-33) Epigenetic impact	Metabolic-induced immune dysregulation, short-chain fatty acids and other microbiome metabolites
Asthma, AR/ARC, CRS, AD, FPIES, EoE, celiac disease	Obesity & asthma, histamine-driven disorders

DIRECT RESPONSE TO CHEMICALS

Type VII
Direct cellular and inflammatory response to chemical substances
AERD, idiosyncratic reactions AR, ARC, asthma, AD, acute urticaria/angioedema and drug allergy

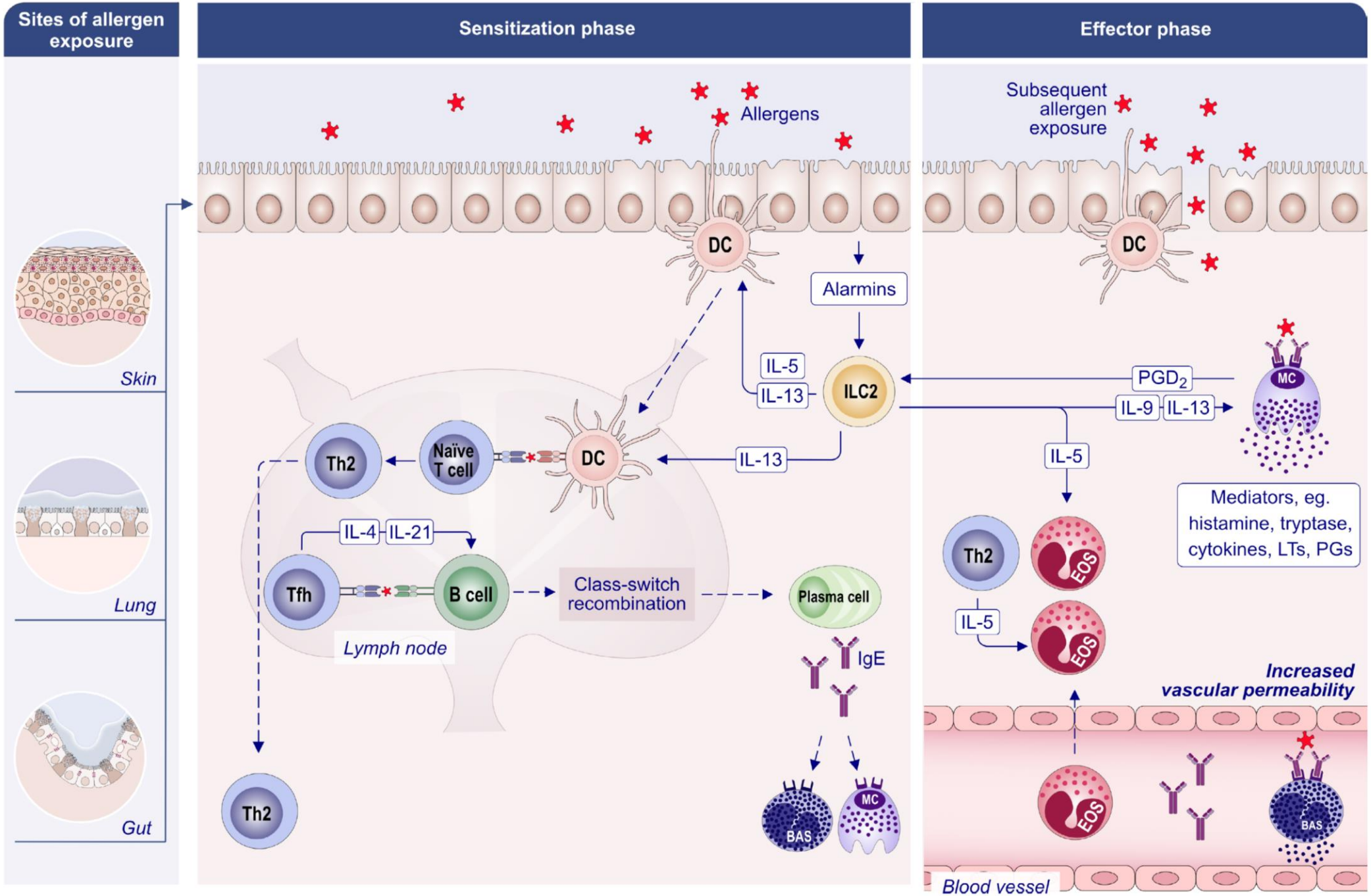
HS type I

HS immédiate

Mechanisms of type I hypersensitivity in AR, ARC, asthma, AD, acute urticaria/ angioedema, food, venom and drug allergy.

The allergen is deposited on the epithelial cells, in the respiratory tract, gut or skin. The sensitization phase occurs after the first contact with the allergen, APCs, for example, DCs, present the antigen to the naïve Th. ILC2 are activated by cytokines released by epithelial cells (called alarmins), such as IL-25, IL-33 and TSLP. Upon activation, they produce large amounts of type 2 cytokines, including IL-5, IL-9 and IL-13, further supporting the T2-cell response. Tfh help B cells to maturate and produce high-affinity sIgE. MC and BAS possess the highaffinity receptor for the Fc fragment of sIgE (FcεRI) and are coated with sIgE, thus concluding the sensitization phase. The effector phase occurs upon subsequent exposure to the same allergen. The allergen crosslinks sIgE bound to MC and BAS, triggering degranulation. MCs are located in various tissues throughout the body, while BAS circulate in the blood. Preformed mediators inside MC and BAS, like histamine, induce symptoms upon release into the microenvironment, like vasodilation, bronchial muscle contraction and increased mucus secretion. Eosinophils play a significant role in the delayed allergic response and the persistence of inflammation, engaging mechanisms related to type IVb hypersensitivity. Therefore, the mutual interaction between type I and IVb-related processes is vital to both the sensitization and the chronic phase. Asthma, AR, ARC and AD endotypes can show T2-type cytokine overexpression (IL-4, IL-5 and IL-13) and high serum sIgE levels. Food/venom/drug allergy can be induced directly by a trigger with a potentially life-threatening anaphylactic reaction. Acute urticaria/angioedema can be induced by allergens (e.g. foods, medications, insect bites or stings).

B, B lymphocyte; BAS, basophil; DC, dendritic cell; EOS, eosinophil; IL, interleukin; ILC2, type 2 innate lymphoid cell; LT, leukotrienes; MC, mast cell; PG(D2), prostaglandin (D2); sIgE, allergen-specific immunoglobulin E; Tfh, T follicular helper cell; Th naïve/2, T helper lymphocyte naïve/type 2; TSLP, thymic stromal lymphopoietin.

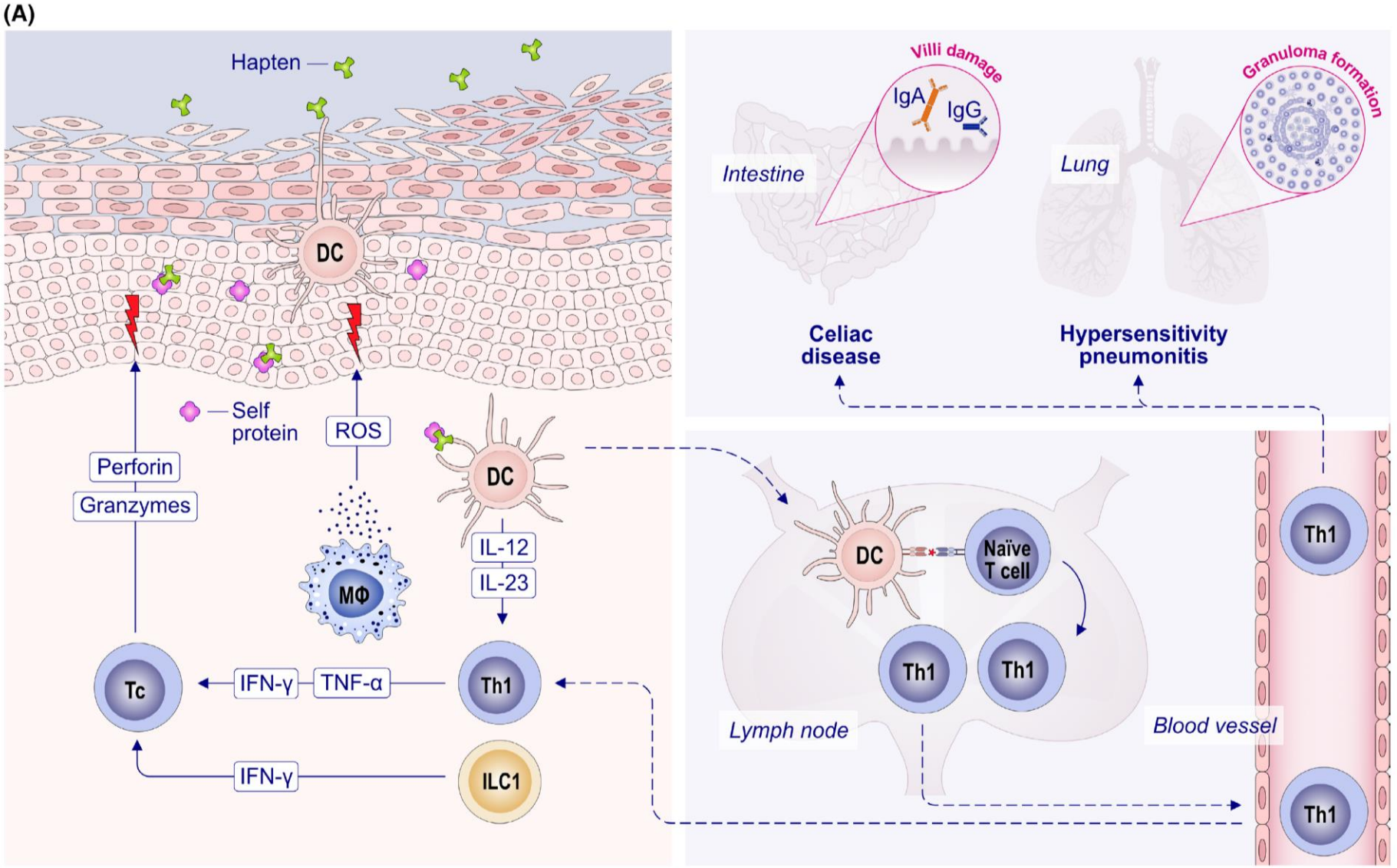


HS type IVa
Inflammation type 1

Mechanisms of type IVa hypersensitivity, including (A) ACD, chronic phase of hypersensitivity pneumonitis and celiac disease, (B) but also including non-T2 endotypes of asthma or AD.

APC presents antigen/hapten to Th1 memory cells, which acquire their phenotypeupon cytokine exposure, leading to the activation, proliferation and production of IFN-γ and TNF-α. These cytokines recruit and activate immune cells, leading to inflammation and tissue damage. Mϕ are producing ROS, Tc and NK cells release granzymes and perforins. Innate immune cells, especially ILC1s, amplify the response by producing a large amount of IFN-γ. Clinical manifestation of type IVa reaction is typical in ACD, where the triggering hapten is a small molecule which needs to associate with a host protein (e.g., an epidermal protein) to become immunogenic in a process called harmonization. In the intestine, celiac disease is mediated by gliadin-specific Th1 cells inducing intestinal inflammation upon the intake of wheat and other cereals. Chronic intestinal inflammation with damage of villi is associated with the generation of IgA and IgG antibodies against tissue proteins: anti-tissue transglutaminase Ab (tTG-IgA), anti-endomysial Ab (EMA-IgA), anti-deamidated gliadin peptides Ab (DGP-IgA and DGP-IgG), which turns the disease into a mixed allergic-autoimmune condition. The chronic phase of hypersensitivity pneumonitis is directed against airborne allergens that mediate inflammation in the lung parenchyma, ultimately leading to lung granuloma formation and scarring (fibrosis) of the lung tissue. (B) Th2 cells that migrate to the asthmatic bronchi, nasal mucosa or atopic skin often skew to additionally producing T1 effector cytokines: IFN-γ, TNF-α and Fas-ligand (death signals) that can induce bronchial epithelial or keratinocyte apoptosis followed by remodelling. The CD8+ T cells (Tc1), which respond to viral infections, can contribute to tissue inflammation and remodelling. Viruses activate Tc1 cells, which produce IFN-γ, granzyme, etc. and induce airway hyperreactivity.

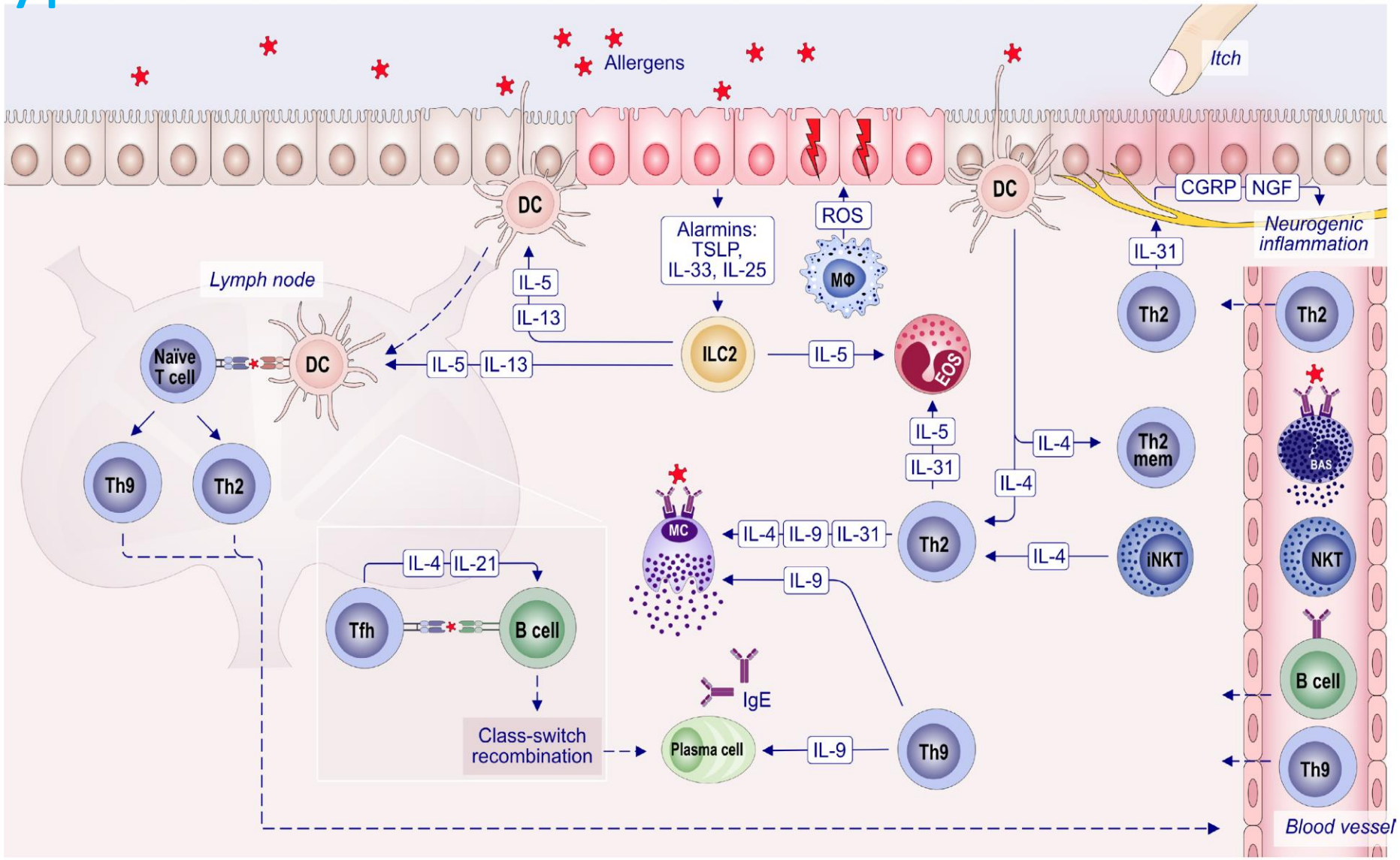
ACD, allergic contact dermatitis; AD, atopic dermatitis; DC, dendritic cell; IFN-γ, interferon-gamma; IgA/G, immunoglobulin A/G; IL, interleukin; ILC1, type 1 innate lymphoid cell; Mϕ, macrophage; ROS, reactive oxygen species; Th naïve/1/2, T helper lymphocyte naïve/1/2 type; Tc, cytotoxic lymphocyte; TNF-α, tumour necrosis factor-alpha.



HS type IVb
Inflammation type 2

Mechanisms of type IVb hypersensitivity, including AR, AD, chronic rhinosinusitis with nasal polyposis and asthma (T2 endotype), but also EoE and food allergy.

In Type IVb hypersensitivity reactions, Th2 cells play a central role, driven by cytokines such as IL-4, IL-13, IL-5, IL-9 and IL-31. These cytokines stimulate B cells to class switch to IgE (IL-4 and IL-13) and mediate eosinophilia (IL-5), causing inflammation and tissue damage. IL-31 mainly produced by Th2 cells, activates IL-31 receptors on sensory neurons, which release CGRP and NGF causing neurogenic inflammation and itch. Th9 cells, which differentiate with IL-4 and TGF-β, contribute significantly to this response, enhancing sIgE synthesis and promoting MC growth. The response is further complicated by the ILC2 cells, MC and alternatively activated Mϕ. ILC2, DC and Th2 cells, activated by IL-25, IL-33 or TSLP, cooperate, producing cytokines and affecting epithelial barriers. They facilitate eosinophil and basophil recruitment and modulate APC function, contributing to the chronicity of Type IVb reactions. iNK-T cells contribute to this response by producing IL-4 and IL-13, which induce alternative activation in Mϕ and promote inflammation. Eosinophils migrate to inflammatory sites, activate various cytokines and chemokines and release cytotoxic granules contributing to tissue damage, cell death and chronic inflammation. At the final stage when IgE synthesis is triggered, type IVb and I overlap. T2-high asthma is characterized by eosinophilic airway infiltrates and Th2-dependent cytokine overexpression (IL-4, IL-5 and IL-13). In AD, the most common endotype is characterized by high serum IgE levels and a strong association with other allergic diseases such as asthma and AR. Both IgE-dependent and IgE-independent pathways characterize mixed food allergy. Atopic manifestations arising from IgE-independent factors include delayed food-allergy-associated atopic dermatitis (6–48 h post-exposure) caused by the T2 cells (hypersensitivity type IVb), and eosinophilic gastrointestinal disorders, such as EoE. The oesophageal epithelium is the source of the IL-1 cytokine family members (IL-33, IL-36) and TSLP, involved in the balancing of pro- and anti-inflammatory responses.



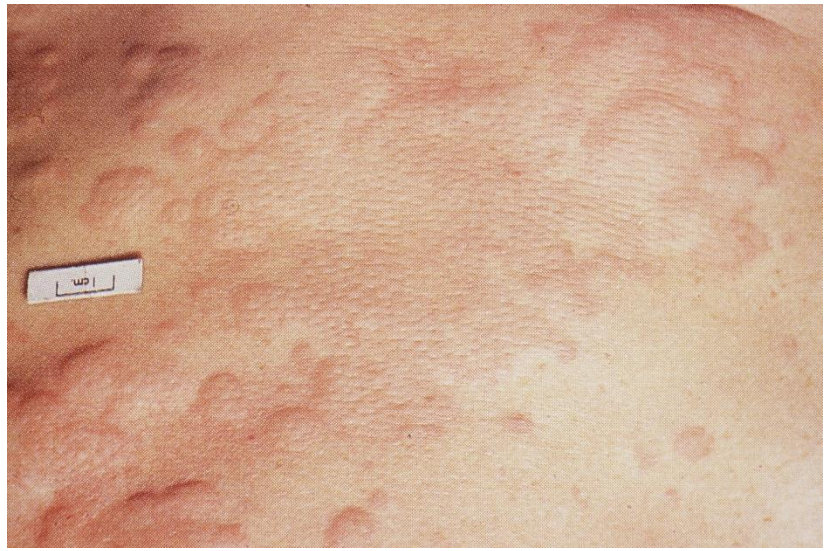
AD, atopic dermatitis; AR, allergic rhinitis; APC, antigen-presenting cell; B, B lymphocyte; BAS, basophil; CGRP, calcitonin gene-related peptide; DC, dendritic cell; EOS, eosinophil; EoE, eosinophilic oesophagitis; (s) IgE, (allergen-specific) immunoglobulins class E; ILC2, type 2 innate lymphoid cell; IL, interleukin; (i)NKT, (invariant) natural killer T cells; Mϕ, macrophage; MC, mast cell; Mf, macrophage; NGF, nerve growth factor; ROS, reactive oxygen species; Th0/2/9, T helper lymphocyte naïve/ type 2 or 9; T2, type 2 immune response; Tfh, T follicular helper cell; TGF-β, tumour necrosis factor beta; Th mem, Th memory cells; TSLP, thymic stromal lymphopoietin.

Hypersensibilités
Classification de Gell & Coombs

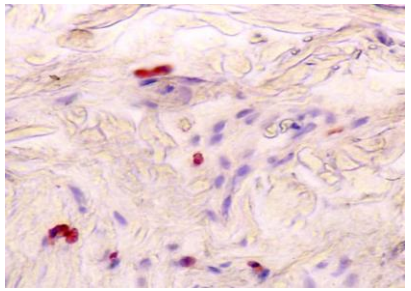
Antibody → ← Lymphocytes

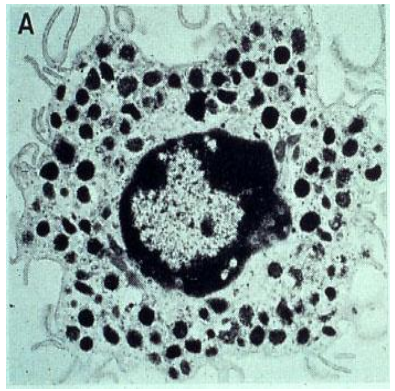
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	**Th2/Tc2/ILC2 Type 2 inflammation**	Perforin/ granzyme B (CTL)	**Th17/Tc17/ILC3 Type 3 (17) inflammation**
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
Maladies autoimmunes, allergiques et HS	**Anaphylaxie Rhinite Asthme**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme T2 Rhinite, Conjonctivite Œsophagite eosin.**		**Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.**
Dermatoses autoimmunes, allergiques et HS	**Urticaire SAMa**	**Pemphigus Pemphigoide Urticaire chroni.**	**Vascularites**	**Vitiligo Pelade Eczéma contact**	**Dermatite atopique Prurigo nodulaire Urticaire chronique**		**Psoriasis**
Allergie et HS médicaments	**Choc anaphylactique Urticaire aux médicaments**	**Cytopénies medic.**	**Vascularites immuno-allerg.**	**Exanthème Lyell Stevens-Johnson**	**DRESS**		**Pustulose exanthématique aigue généralisée**

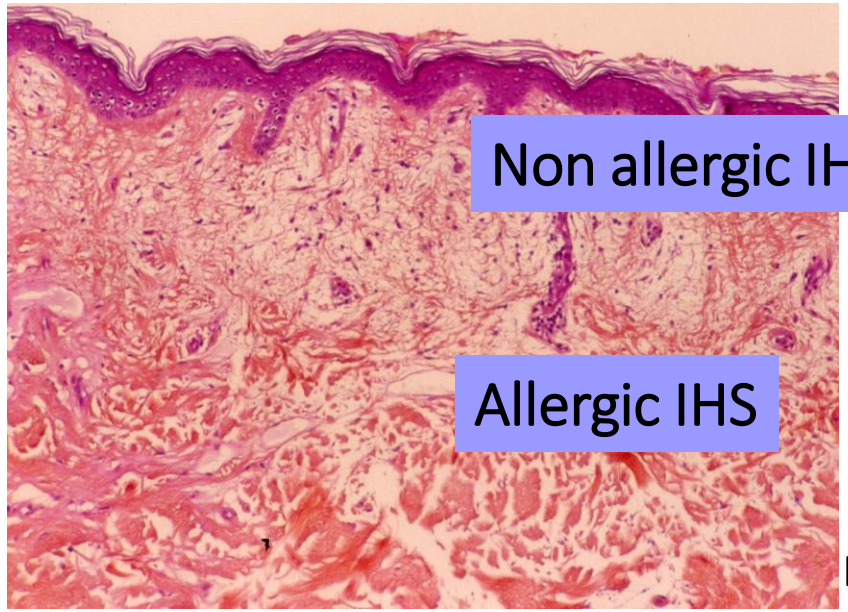
TYPE I HYPERSENSITIVITY

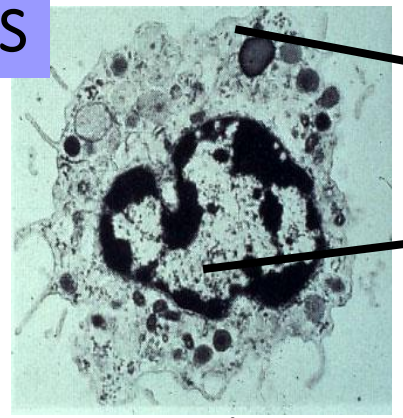


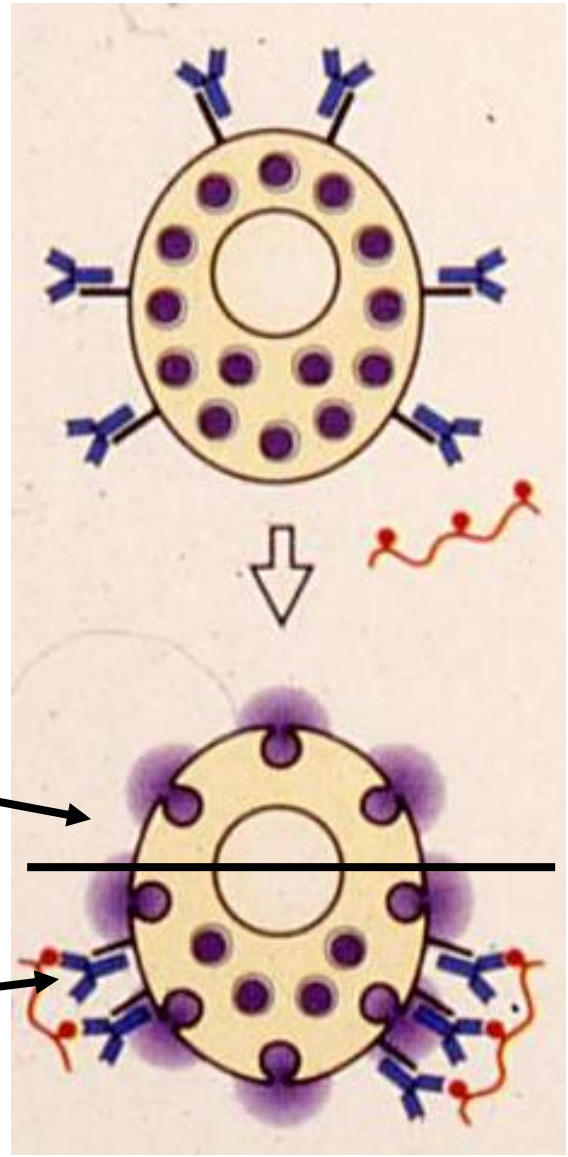
Œdème du derme / Vaisseaux





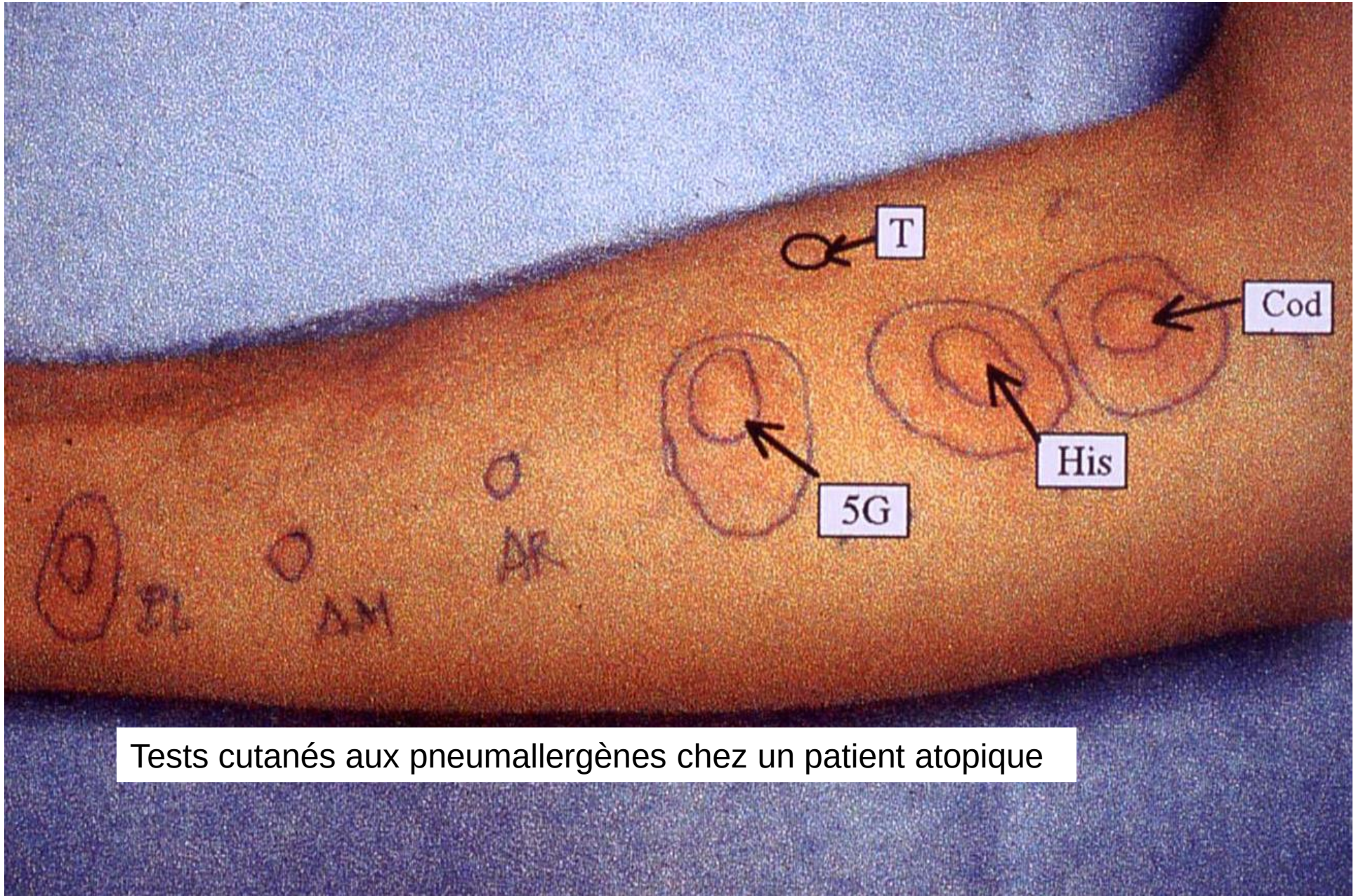






Mastocytes / Histamine

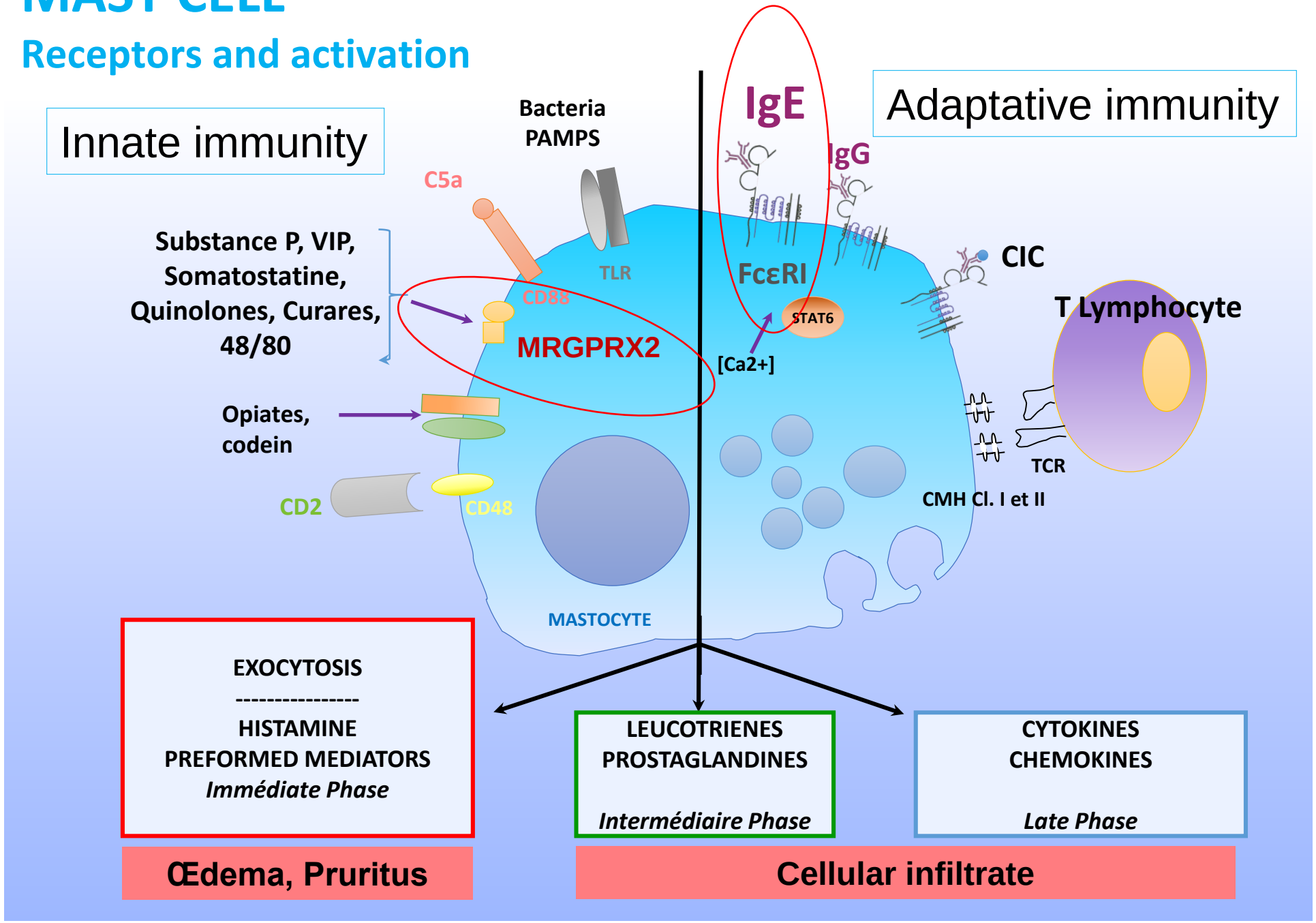
HSI allergique et non allergique



Tests cutanés aux pneumallergènes chez un patient atopique

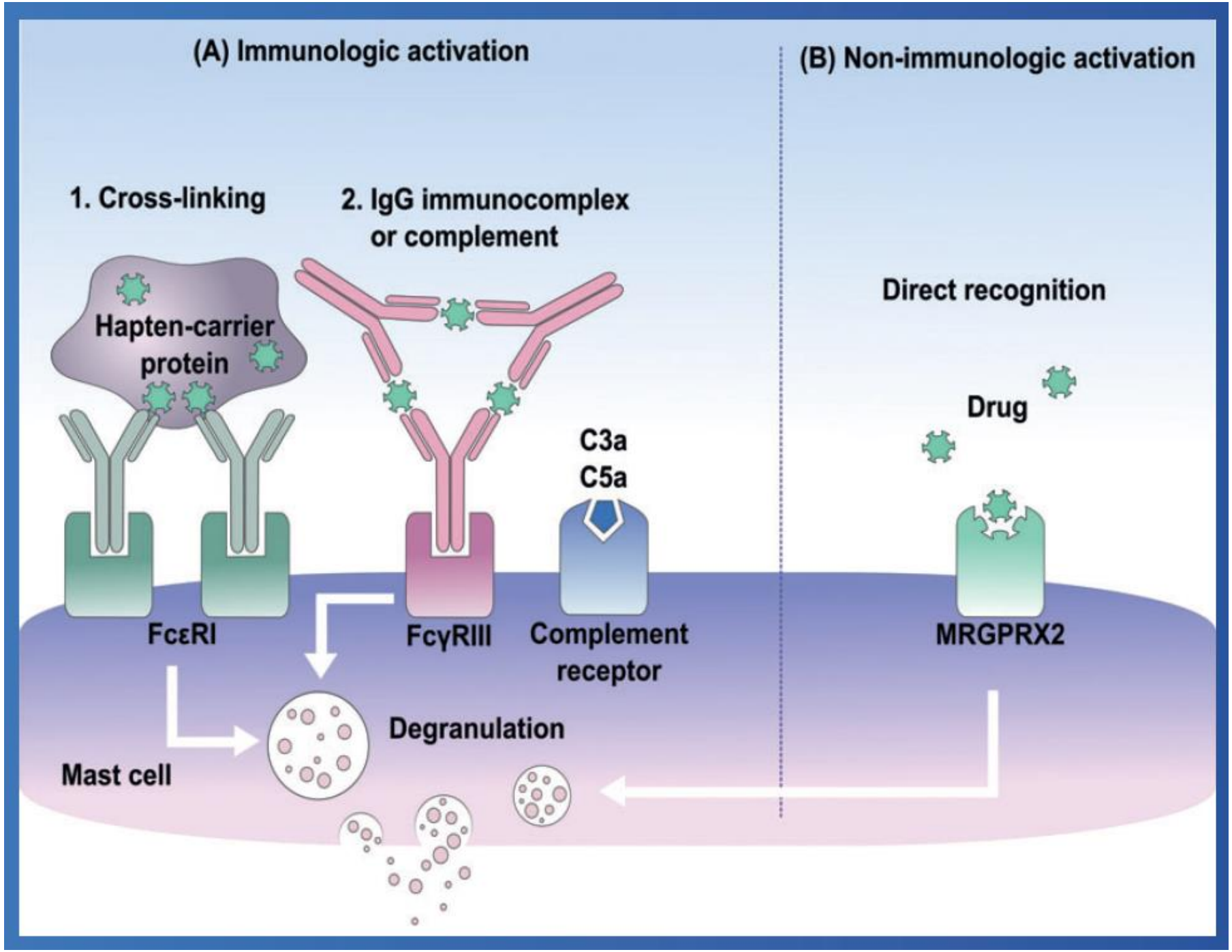
MAST CELL

Receptors and activation



MASTOCYTES

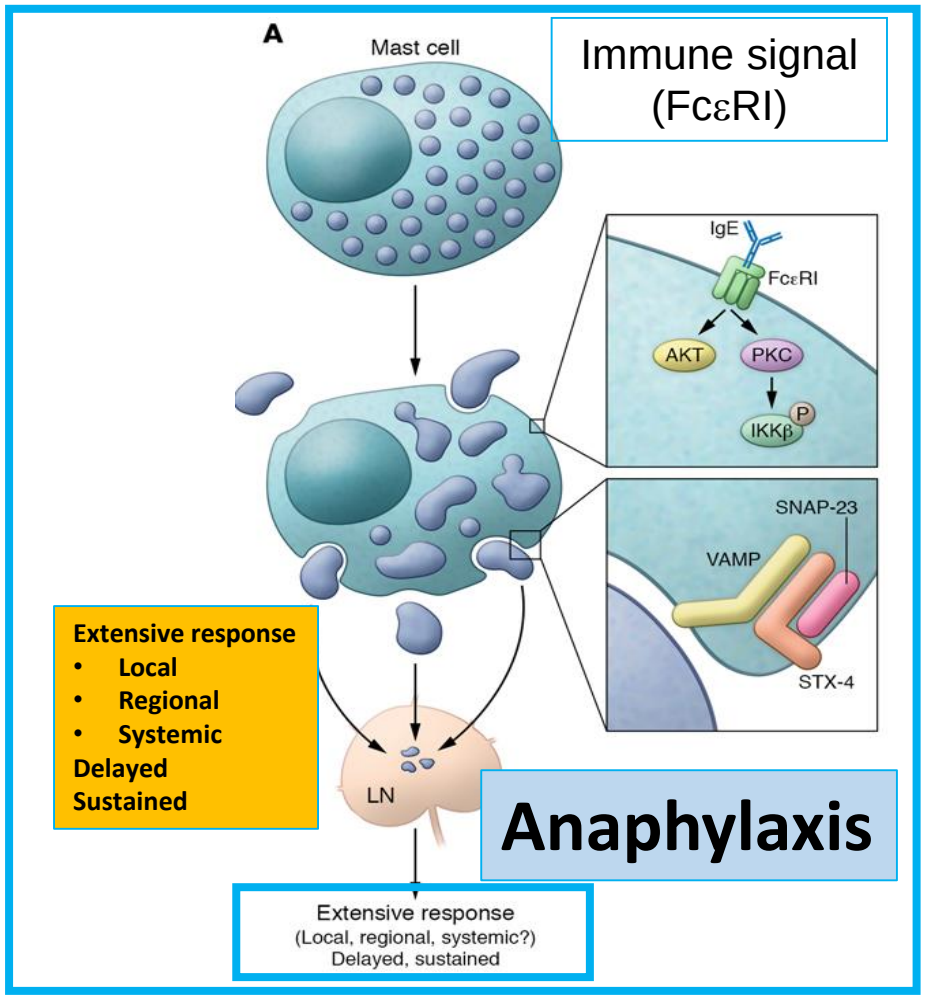
Récepteurs et activation

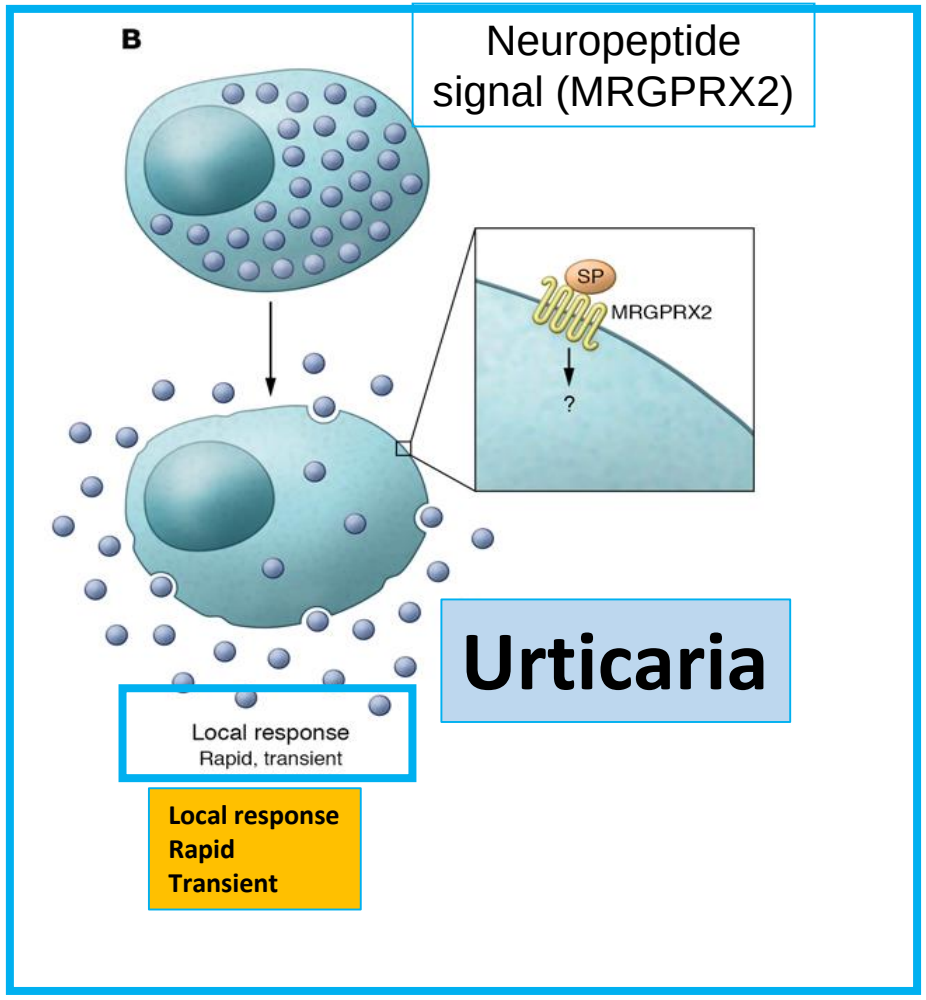


Two fundamental degranulation pathways in mast cells

IgE/FceRI

Other receptor





Gaudenzio et al. ***J Clin Invest*** *2016*

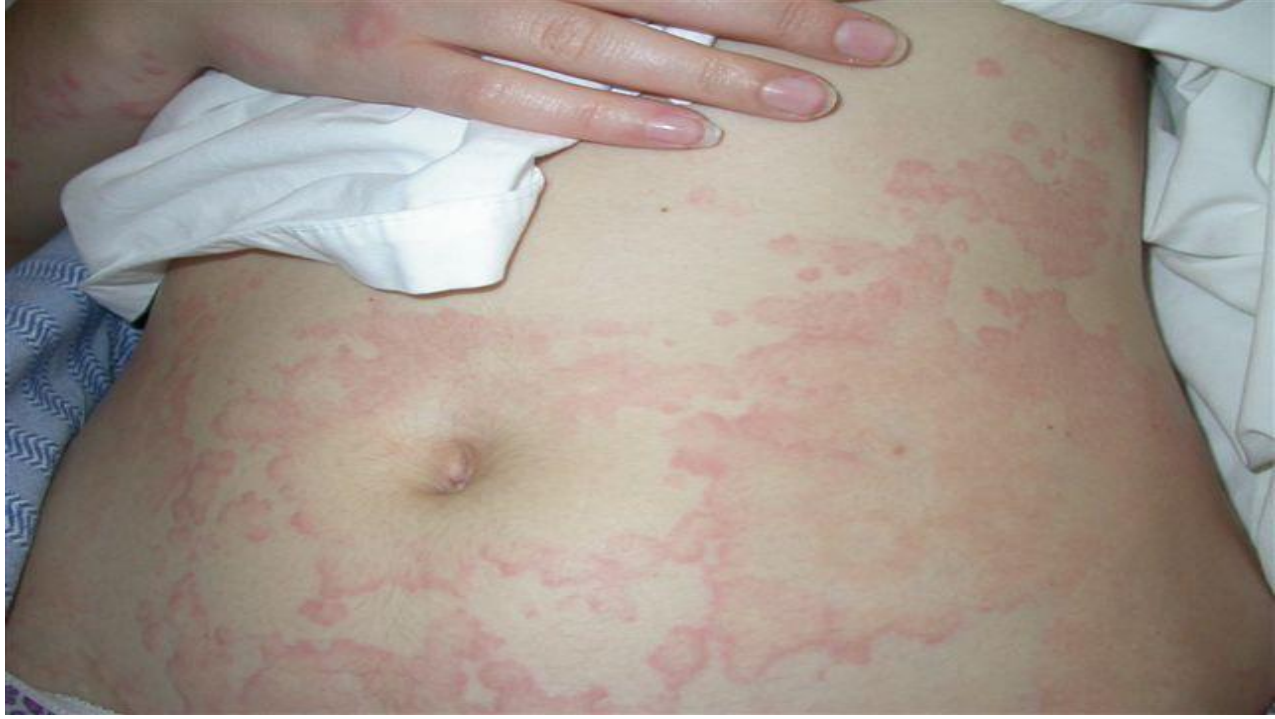
Drug-induced urticaria and angioedema

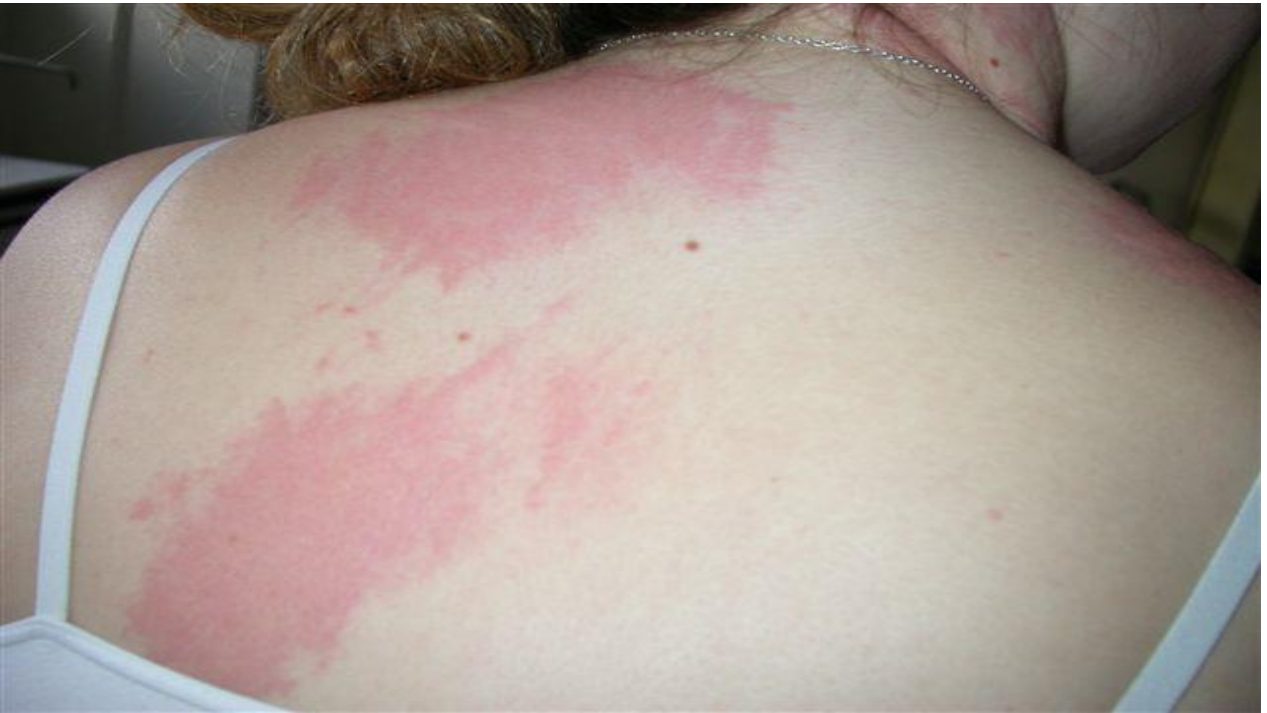
- **Allergic (IgE)**: rares (5%) and exceptionally isolated

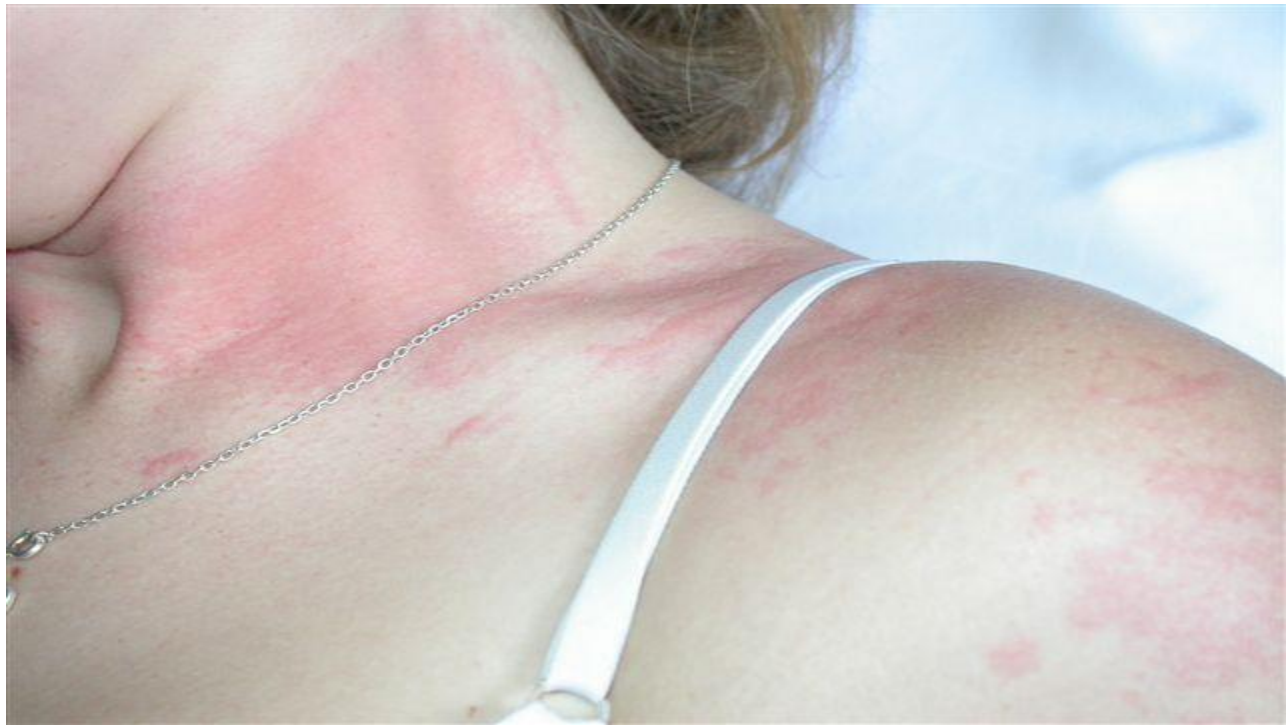
- **Non allergic**: frequent (95%) and almost always benign

- Cousin F, Philips K, Favier B, Bienvenu J**,** Nicolas JF**.** Drug-induced urticaria. **Eur J Dermatol** 2001;11(3):181-7.

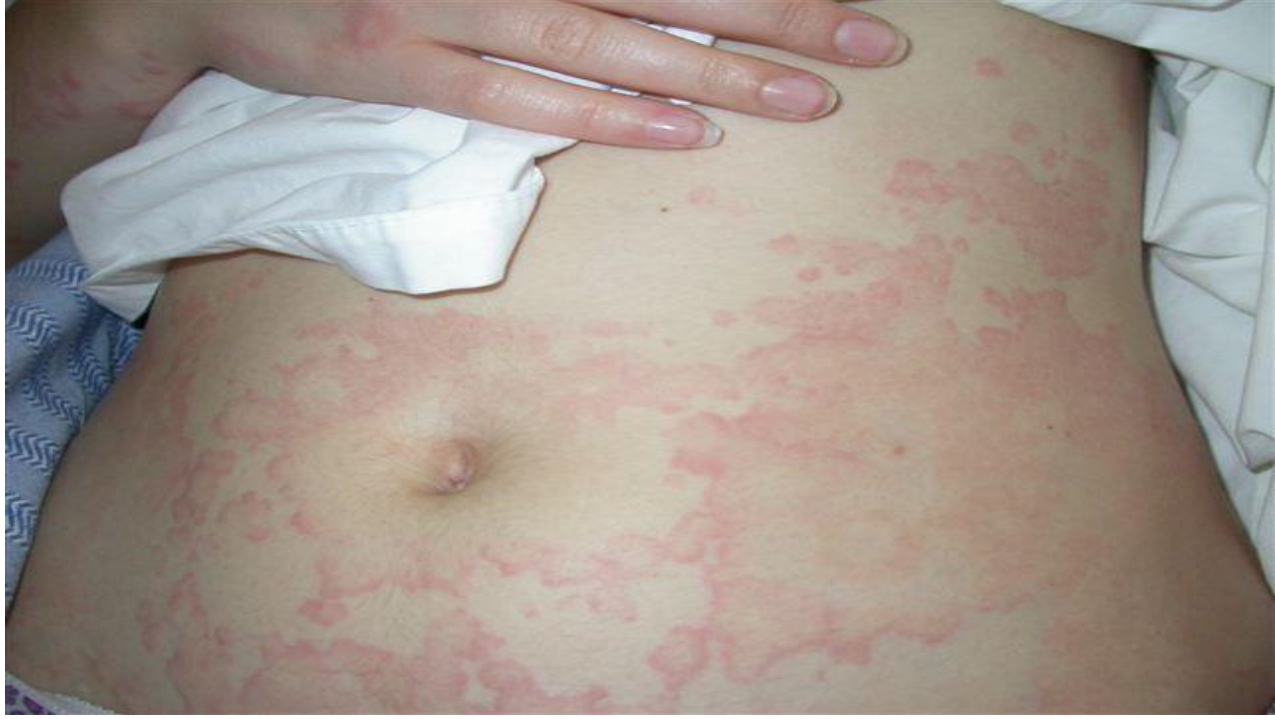
First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 11 AM

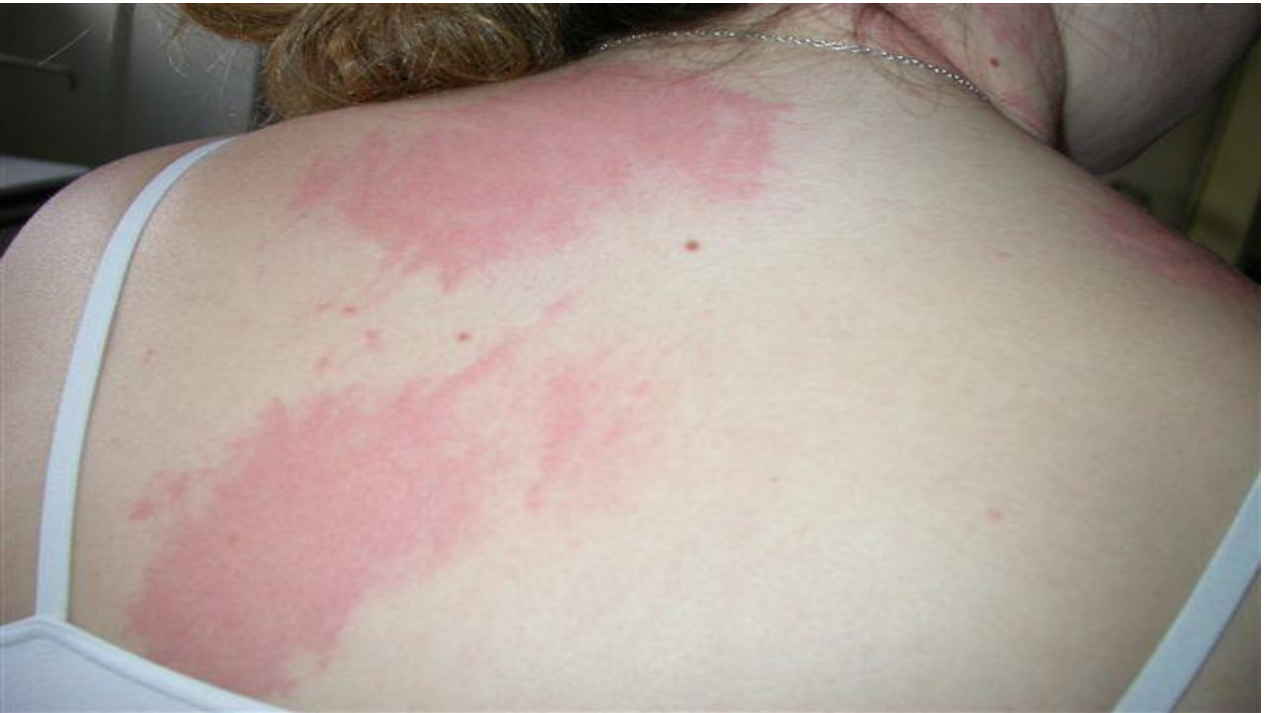


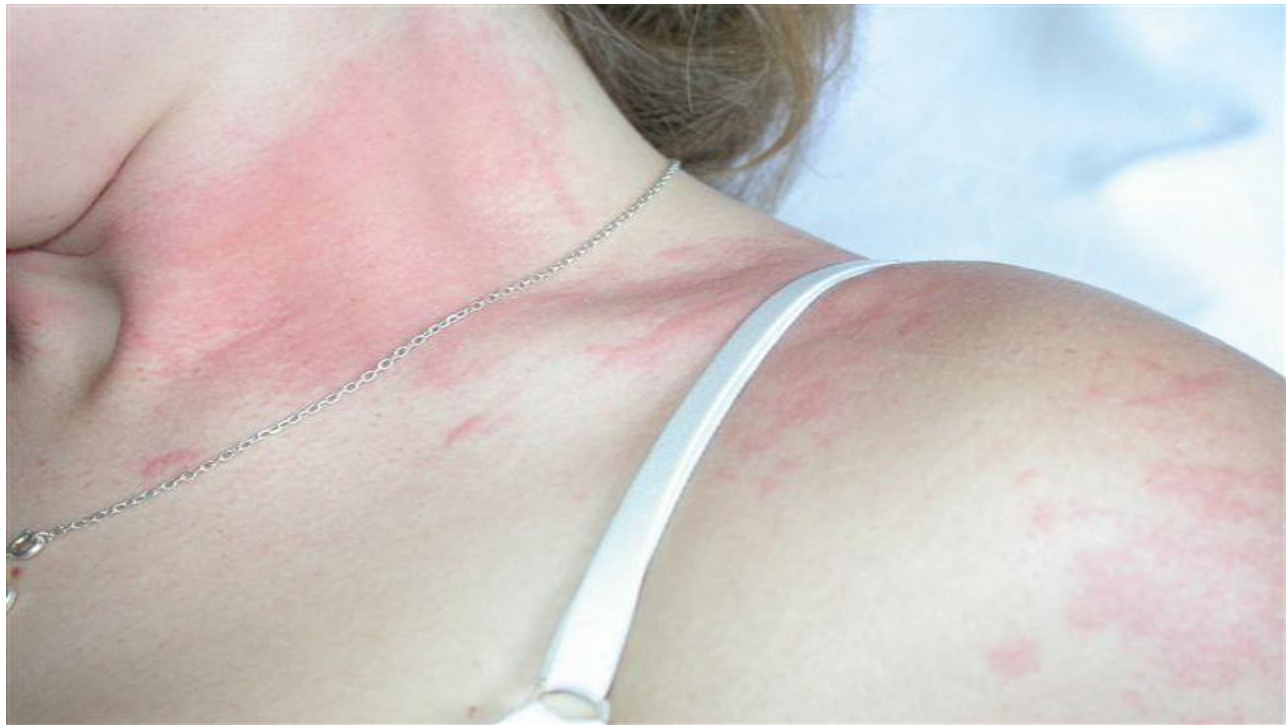


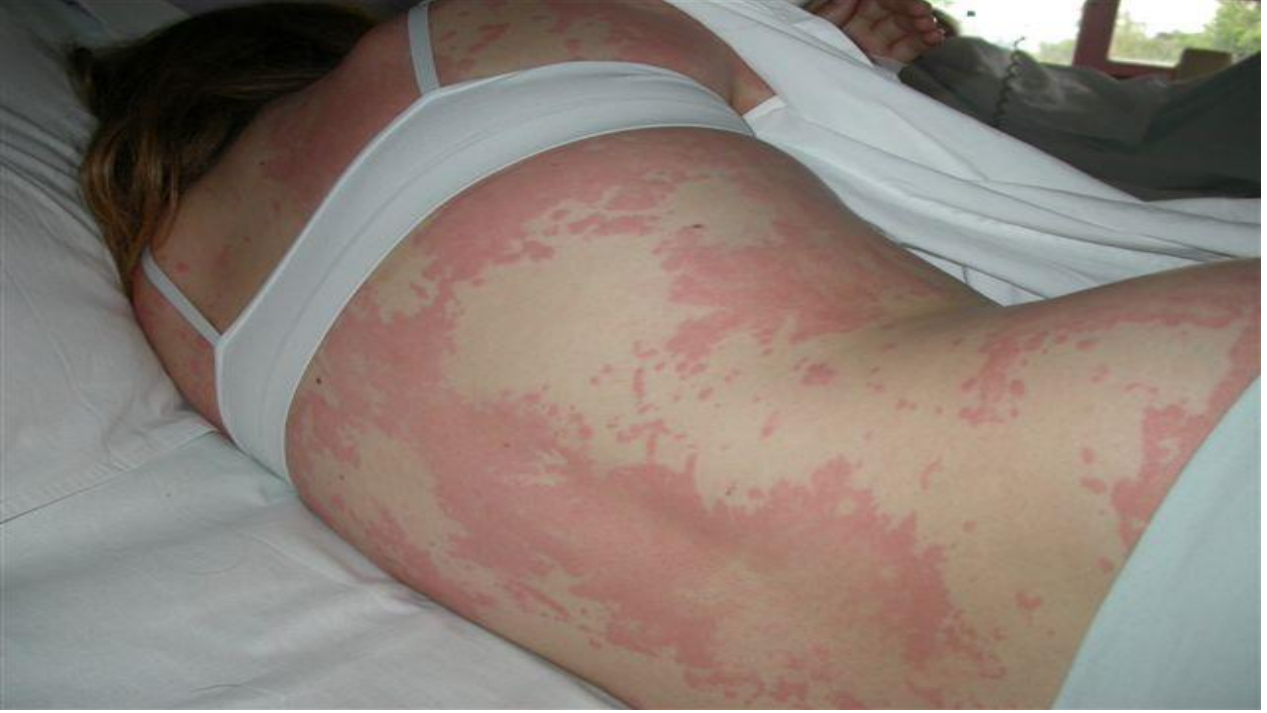


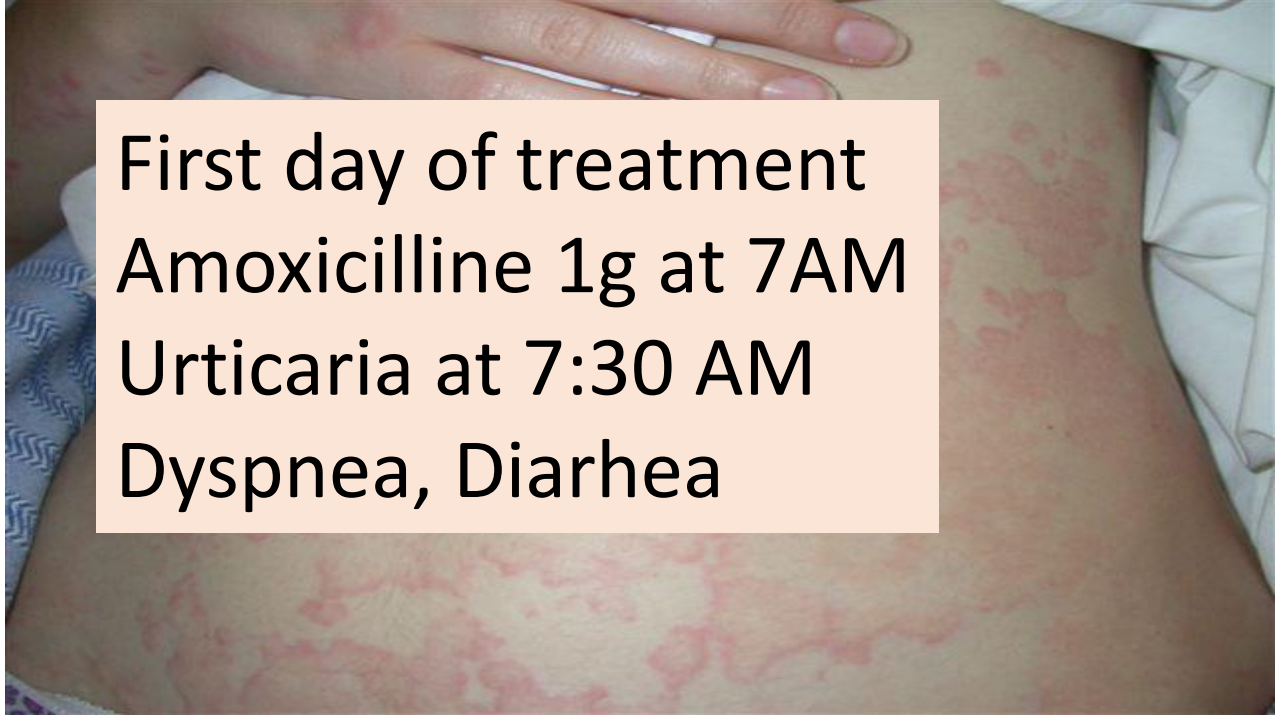

Third day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM



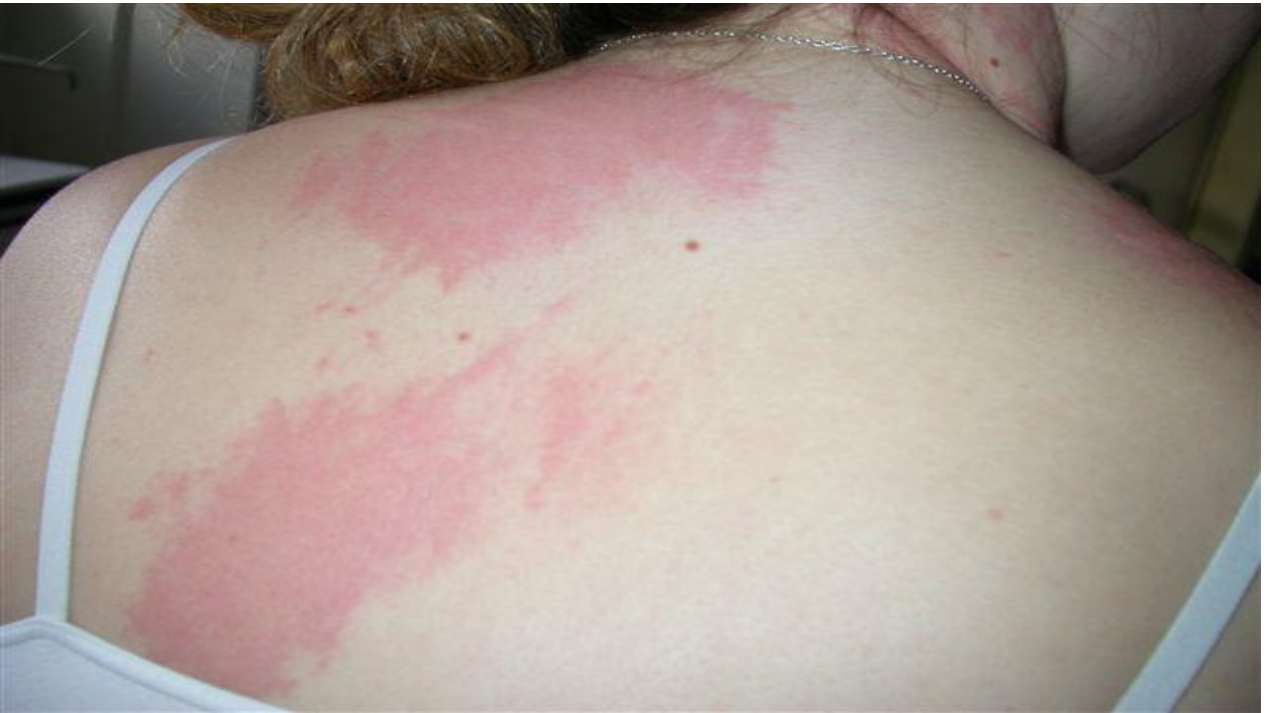


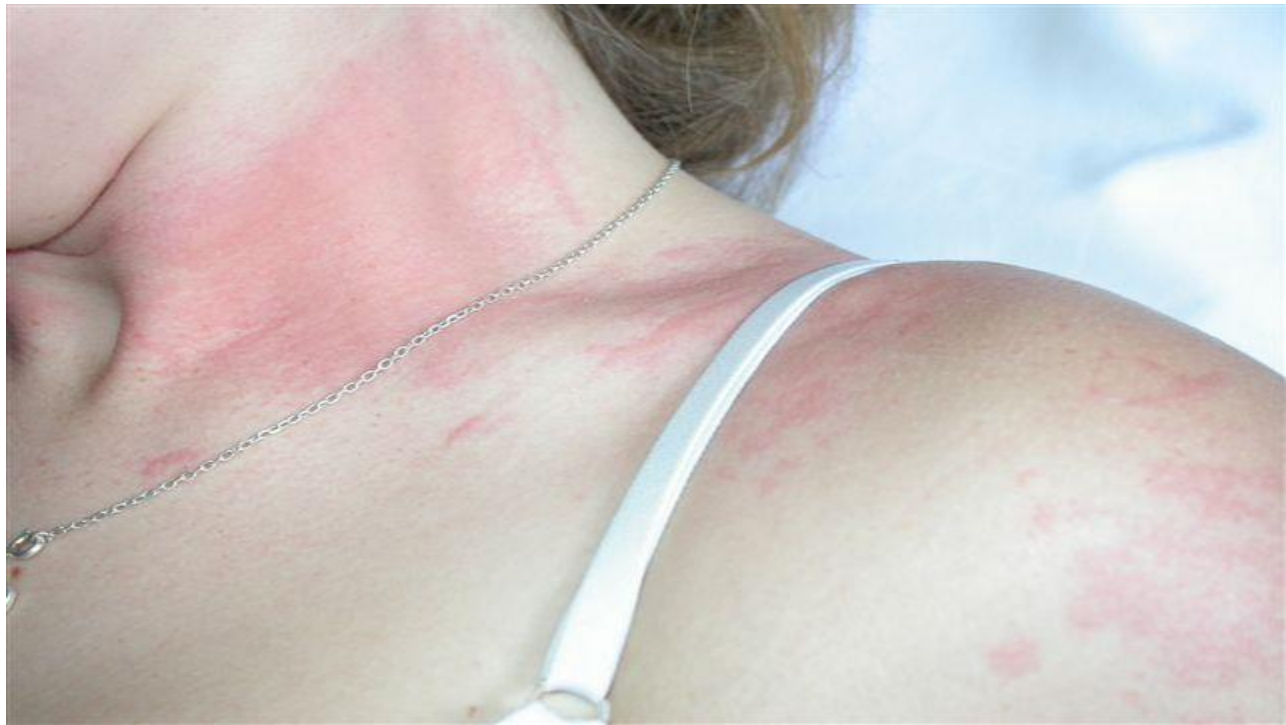


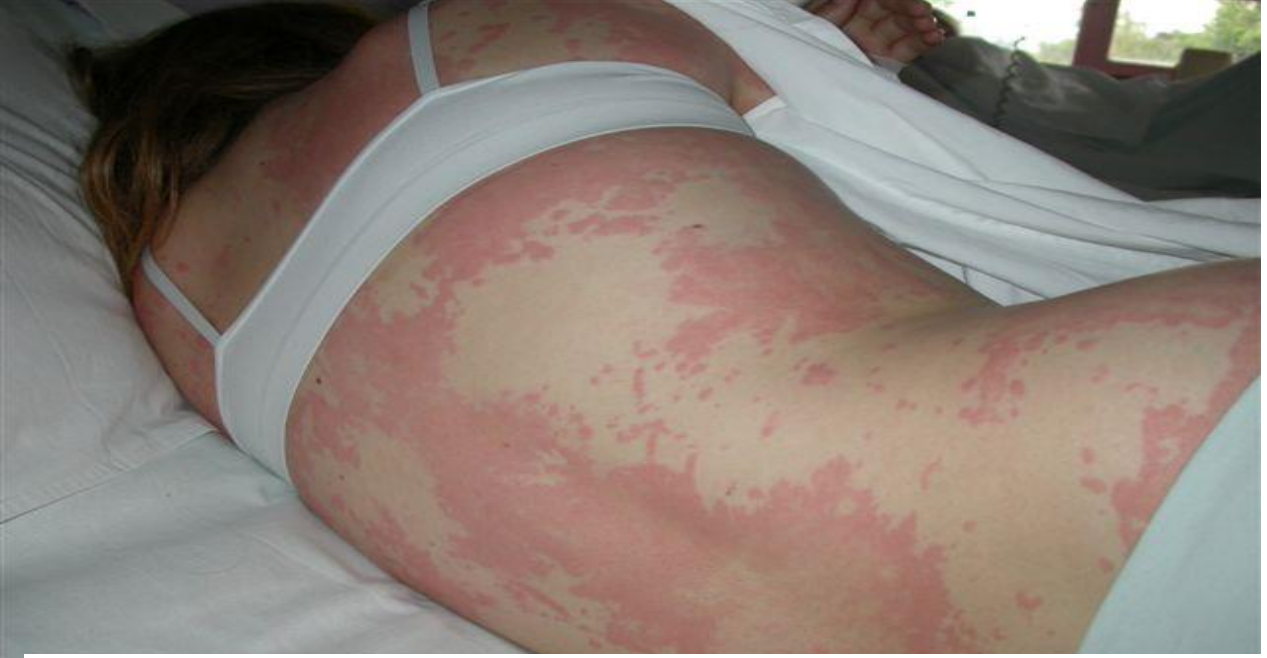


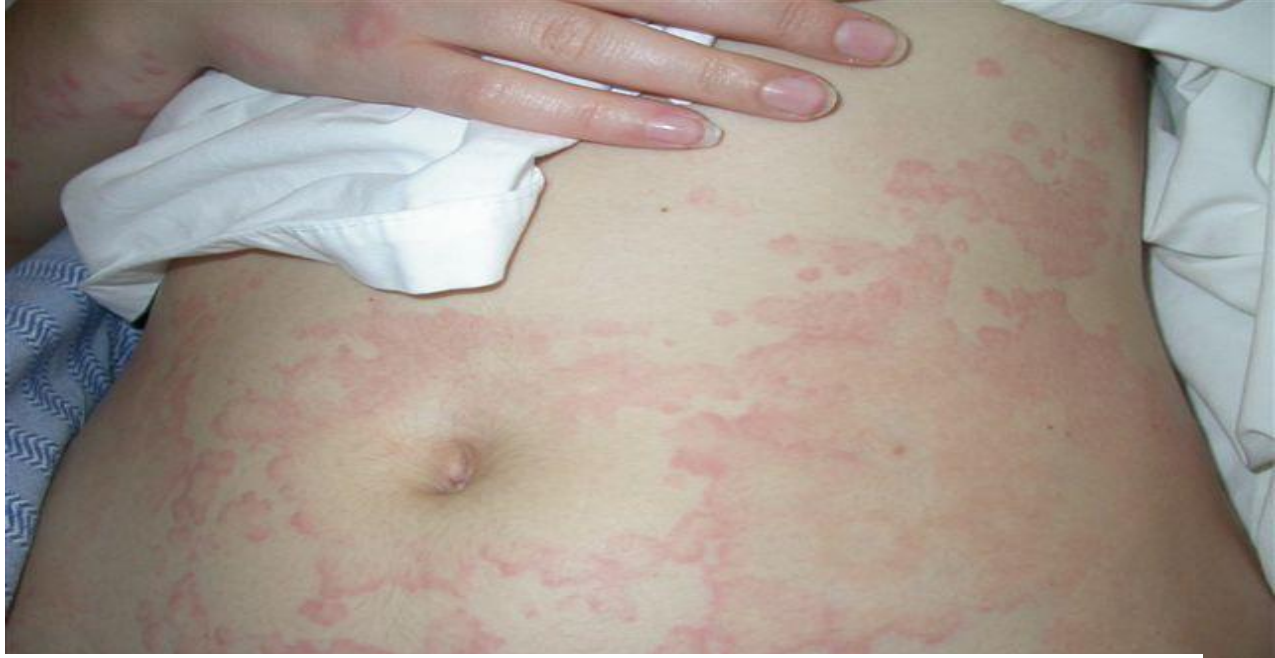


First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM
Dyspnea, Diarhea









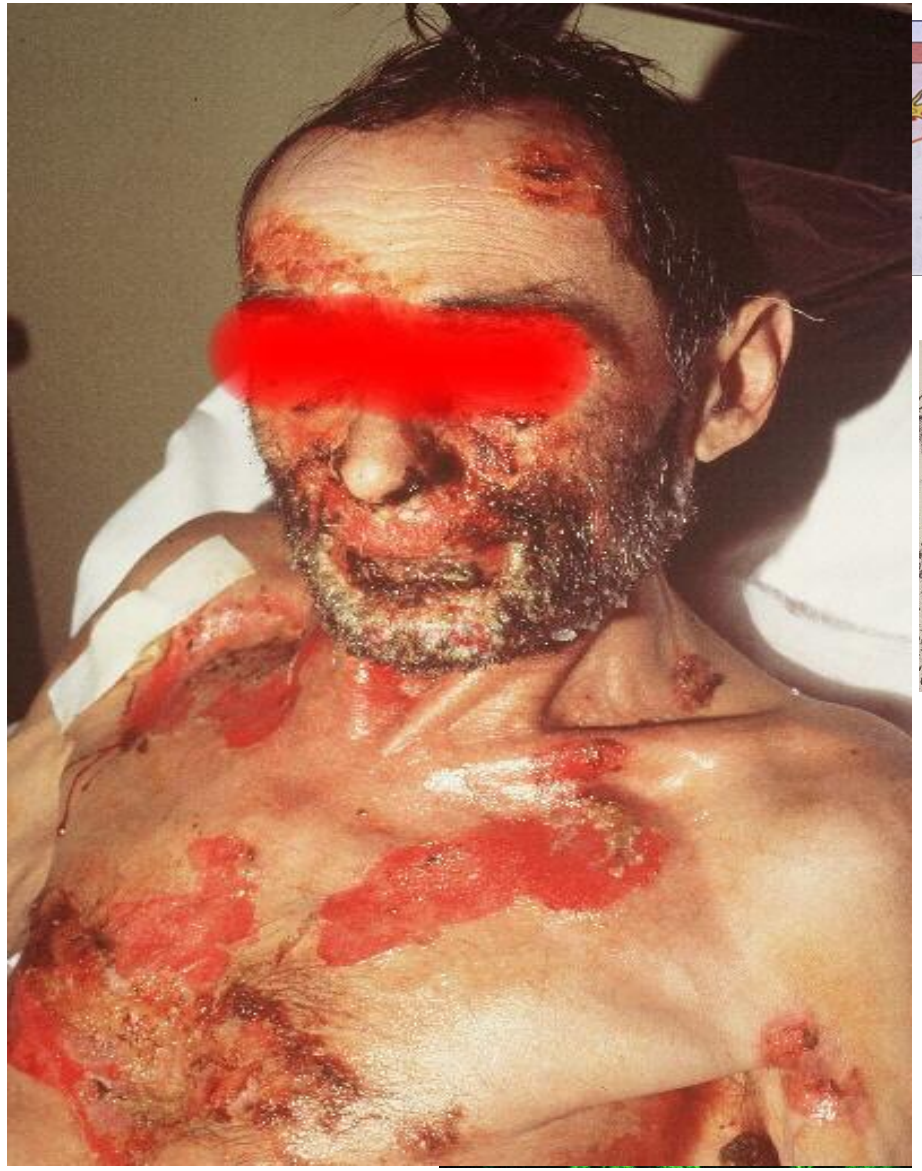
More a drug-induced reaction is severe, more it has a chance to be allergic

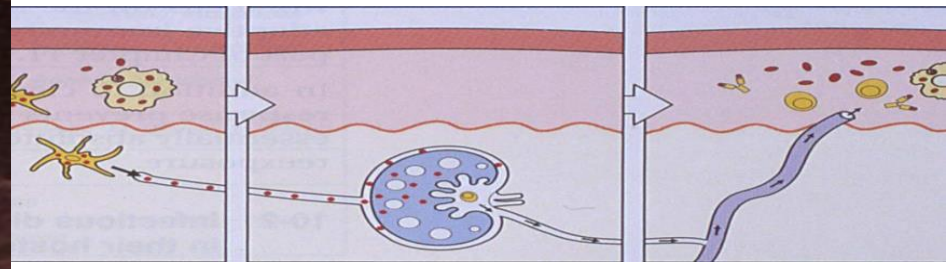
Hypersensibilités
Classification de Gell & Coombs

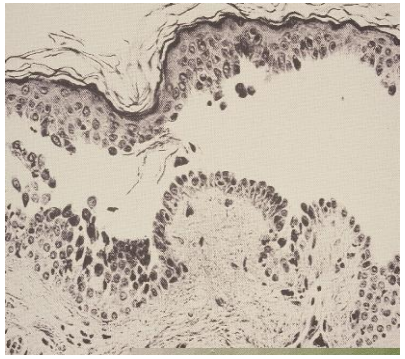
Antibody → ← Lymphocytes

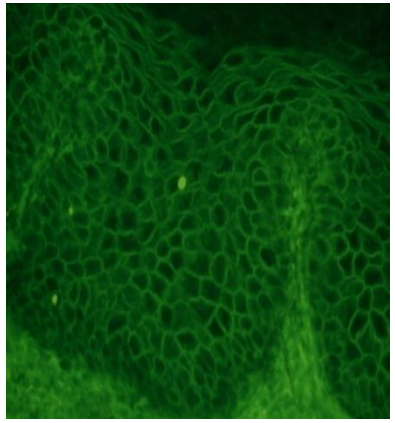
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	**Th2/Tc2/ILC2 Type 2 inflammation**	Perforin/ granzyme B (CTL)	**Th17/Tc17/ILC3 Type 3 (17) inflammation**
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
Maladies autoimmunes, allergiques et HS	**Anaphylaxie Rhinite Asthme**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme T2 Rhinite, Conjonctivite Œsophagite eosin.**		**Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.**
Dermatoses autoimmunes, allergiques et HS	**Urticaire SAMa**	**Pemphigus Pemphigoide Urticaire chroni.**	**Vascularites**	**Vitiligo Pelade Eczéma contact**	**Dermatite atopique Prurigo nodulaire Urticaire chronique**		**Psoriasis**
Allergie et HS médicaments	**Choc anaphylactique Urticaire aux médicaments**	**Cytopénies medic.**	**Vascularites immuno-allerg.**	**Exanthème Lyell Stevens-Johnson**	**DRESS**		**Pustulose exanthématique aigue généralisée**

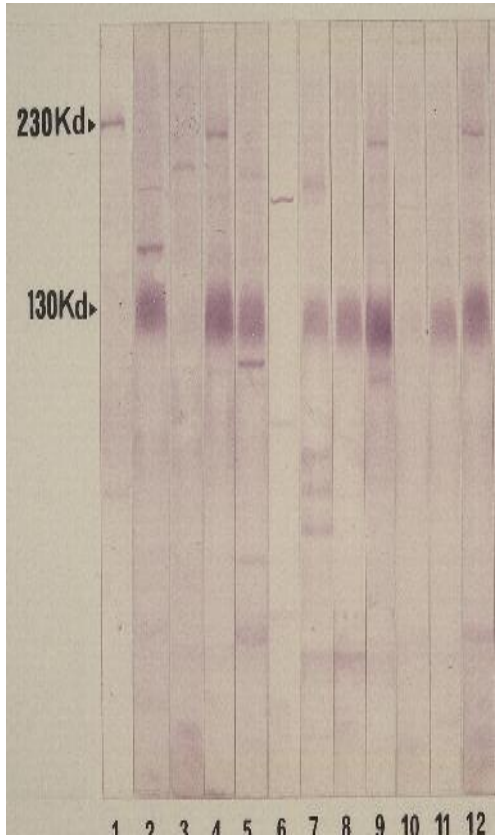
Hypersensibilité de type II due à des IgG spécifiques
PEMPHIGUS











Hypersensibilités
Classification de Gell & Coombs

Antibody → ← Lymphocytes

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	**Th2/Tc2/ILC2 Type 2 inflammation**	Perforin/ granzyme B (CTL)	**Th17/Tc17/ILC3 Type 3 (17) inflammation**
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
Maladies autoimmunes, allergiques et HS	**Anaphylaxie Rhinite Asthme**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme T2 Rhinite, Conjonctivite Œsophagite eosin.**		**Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.**
Dermatoses autoimmunes, allergiques et HS	**Urticaire SAMa**	**Pemphigus Pemphigoide Urticaire chroni.**	**Vascularites**	**Vitiligo Pelade Eczéma contact**	**Dermatite atopique Prurigo nodulaire Urticaire chronique**		**Psoriasis**
Allergie et HS médicaments	**Choc anaphylactique Urticaire aux médicaments**	**Cytopénies medic.**	**Vascularites immuno-allerg.**	**Exanthème Lyell Stevens-Johnson**	**DRESS**		**Pustulose exanthématique aigue généralisée**

Fig

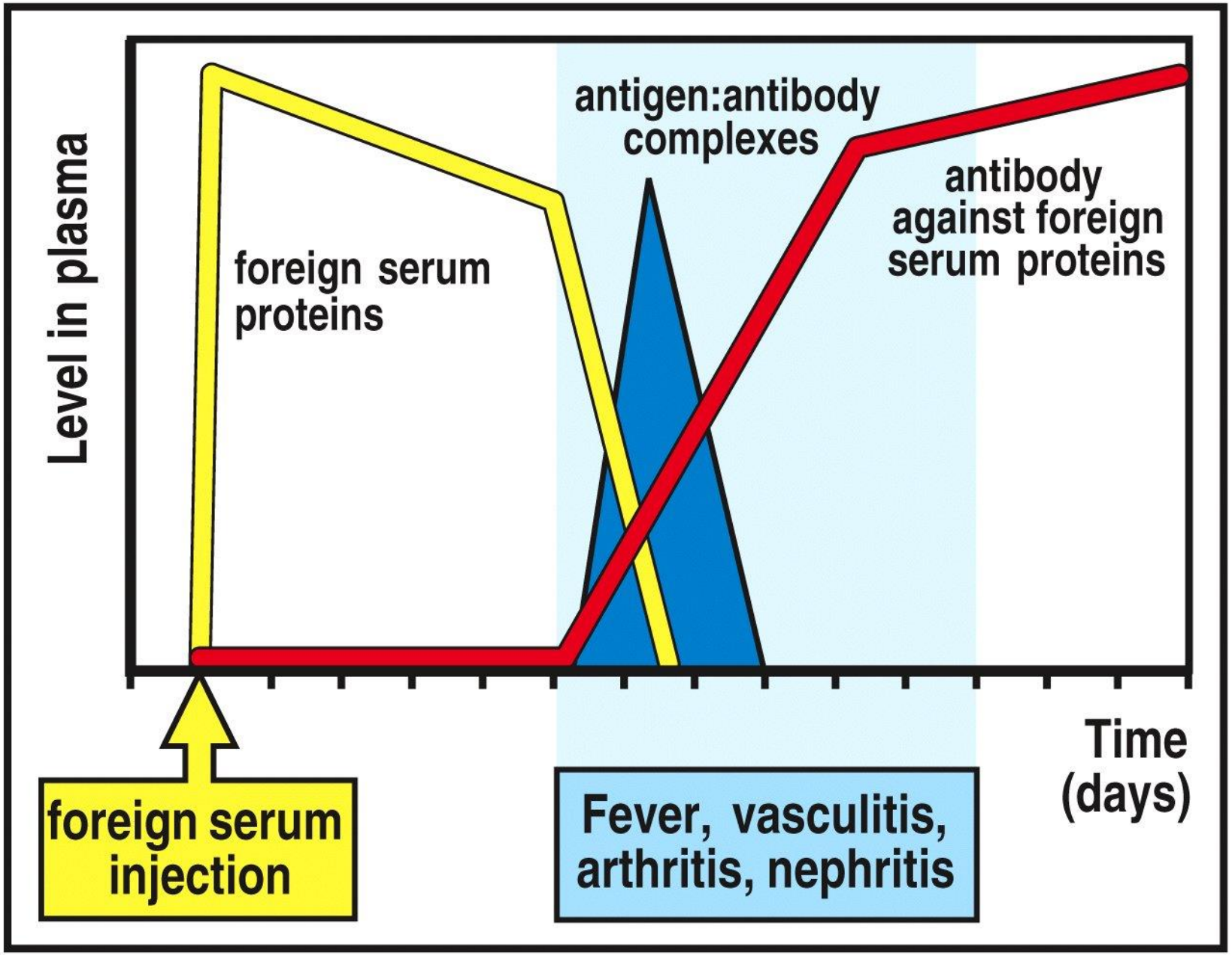
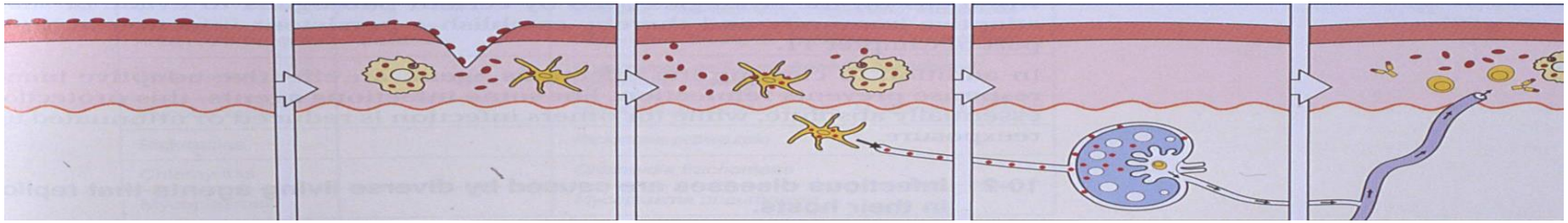
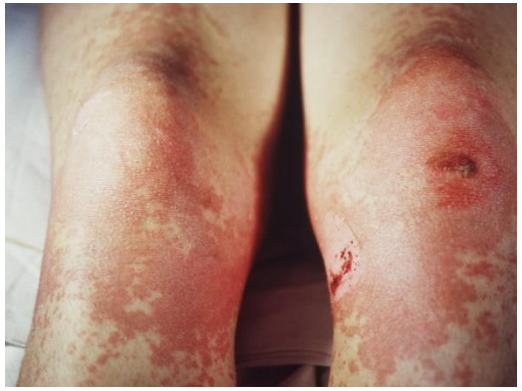
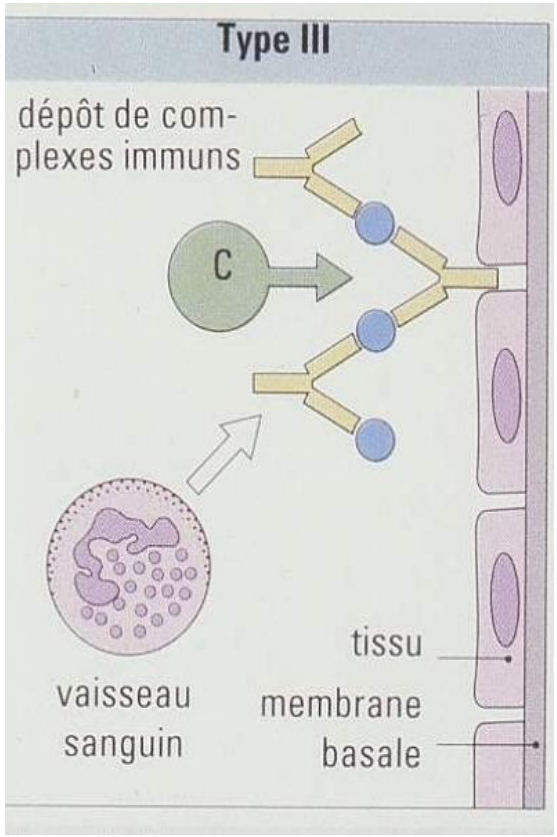


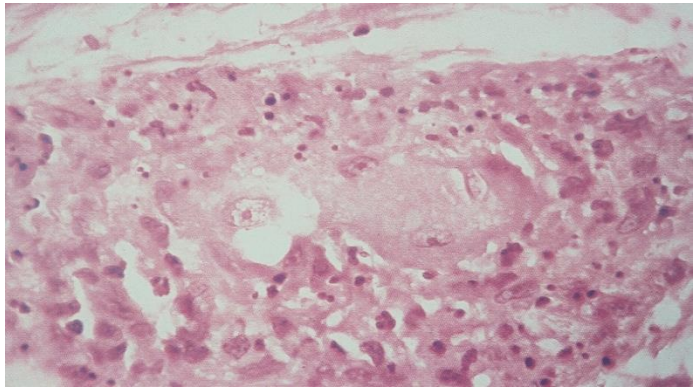
Figure 12-23 Immunobiology, 6/e. (© Garland Science 2005)

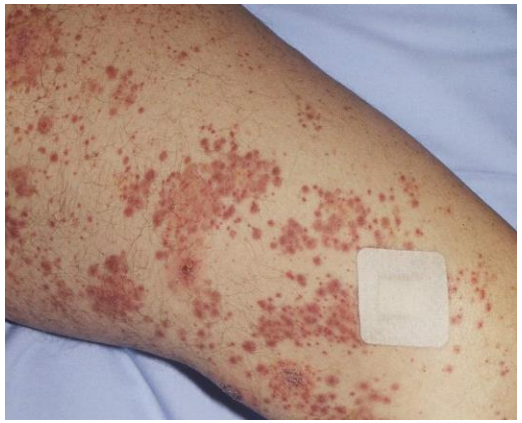
Hypersensibilité de type III due à des complexes immuns
VASCULARITES – PURPURA RHUMATOIDE

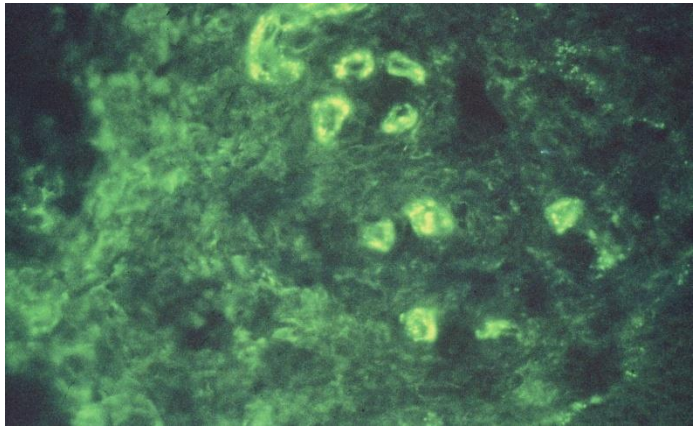












HS de type III aux antigènes inhalés

Alvéolites allergiques

- Poumon de fermier: poussière de foin moisi: actinomyces
- Maladie des éleveurs de pigeons: poussière de fiente séchée
- Maladie des manipulateurs de rats: protéines éliminées dans l'urine
- Maladie des laveurs de fromages: spores de penicillum casei
- Maladie des fourreurs: protéines de la fourrure de renard
- Maladie des écorceurs d'érable: spores de cryptostroma

Hypersensibilités
Classification de Gell & Coombs

Antibody → ← Lymphocytes

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	~~IgE~~	IgG	IgG	**Th1/Tc1/ILC1 Type 1 inflammation**	**Th2/Tc2/ILC2 Type 2 inflammation**	Perforin/ granzyme B (CTL)	**Th17/Tc17/ILC3 Type 3 (17) inflammation**
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
Maladies autoimmunes, allergiques et HS	**Anaphylaxie Rhinite Asthme**	**Réaction transf. Anémie hémol. Thyroidite Myasthénie**	**Maladie sérique Lupus érythémateux**	**IDR tuberculine Rejet de greffe Polyarthrite Diabète**	**Asthme T2 Rhinite, Conjonctivite Œsophagite eosin.**		**Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.**
Dermatoses autoimmunes, allergiques et HS	**Urticaire SAMa**	**Pemphigus Pemphigoide Urticaire chroni.**	**Vascularites**	**Vitiligo Pelade Eczéma contact**	**Dermatite atopique Prurigo nodulaire Urticaire chronique**		**Psoriasis**
Allergie et HS médicaments	**Choc anaphylactique Urticaire aux médicaments**	**Cytopénies medic.**	**Vascularites immuno-allerg.**	**Exanthème Lyell Stevens-Johnson**	**DRESS**		**Pustulose exanthématique aigue généralisée**

The 3 major types of innate and adaptive cell-mediated effector immunity

Francesco Annunziato, PhD,[a] Chiara Romagnani, MD, PhD,[b] and Sergio Romagnani, MD[a] *Florence, Italy, and Berlin, Germany*

The immune system has tailored its effector functions to optimally respond to distinct species of microbes. Based on emerging knowledge on the different effector T-cell and innate lymphoid cell (ILC) lineages, it is clear that the innate and adaptive immune systems converge into 3 major kinds of cell-mediated effector immunity, which we propose to categorize as type 1, type 2, and type 3. Type 1 immunity consists of T-bet$^+$ IFN-γ–producing group 1 ILCs (ILC1 and natural killer cells), CD8$^+$ cytotoxic T cells (T_C1), and CD4$^+$ T_H1 cells, which protect against intracellular microbes through activation of mononuclear phagocytes. Type 2 immunity consists of GATA-3$^+$ ILC2s, T_C2 cells, and T_H2 cells producing IL-4, IL-5, and IL-13, which induce mast cell, basophil, and eosinophil activation, as well as IgE antibody production, thus protecting against helminthes and venoms. Type 3 immunity is mediated by retinoic acid–related orphan receptor γt$^+$ ILC3s, T_C17 cells, and T_H17 cells producing IL-17, IL-22, or both, which activate mononuclear phagocytes but also recruit neutrophils and induce epithelial antimicrobial responses, thus protecting against extracellular bacteria and fungi. On the other hand, type 1 and 3 immunity mediate autoimmune diseases, whereas type 2 responses can cause allergic diseases. (J Allergy Clin Immunol 2015;135:626-35.)

Key words: *Type 1 immunity, type 2 immunity, type 3 immunity, innate lymphoid cells, T_H1, T_C1, T_H2, T_C2, T_H17/T_H22, T_C17/T_C22*

Abbreviations used

APC:	Antigen-presenting cell
CRTH2:	Chemoattractant receptor-homologous molecule expressed on T_H2 cells
DC:	Dendritic cell
Eomes:	Eomesodermin
IBD:	Inflammatory bowel disease
IL-7R:	IL-7 receptor
ILC:	Innate lymphoid cell
LT:	Lymphotoxin
MP:	Mononuclear phagocyte
MS:	Multiple sclerosis
NK:	Natural killer
NKp:	Natural killer progenitor
PB:	Peripheral blood
RA:	Rheumatoid arthritis
ROR:	Retinoic acid–related orphan receptor
STAT:	Signal transducer and activator of transcription
T_C:	Cytotoxic T
TSLP:	Thymic stromal lymphopoietin

whereas T_H2 cells produce IL-4, IL-5, and IL-13.[3] Subsequently, a similar dichotomy within the CD8$^+$ cytotoxic T (T_C) cell population was discovered in both mice and human subjects, and the 2 subsets were named T_C1 and T_C2,

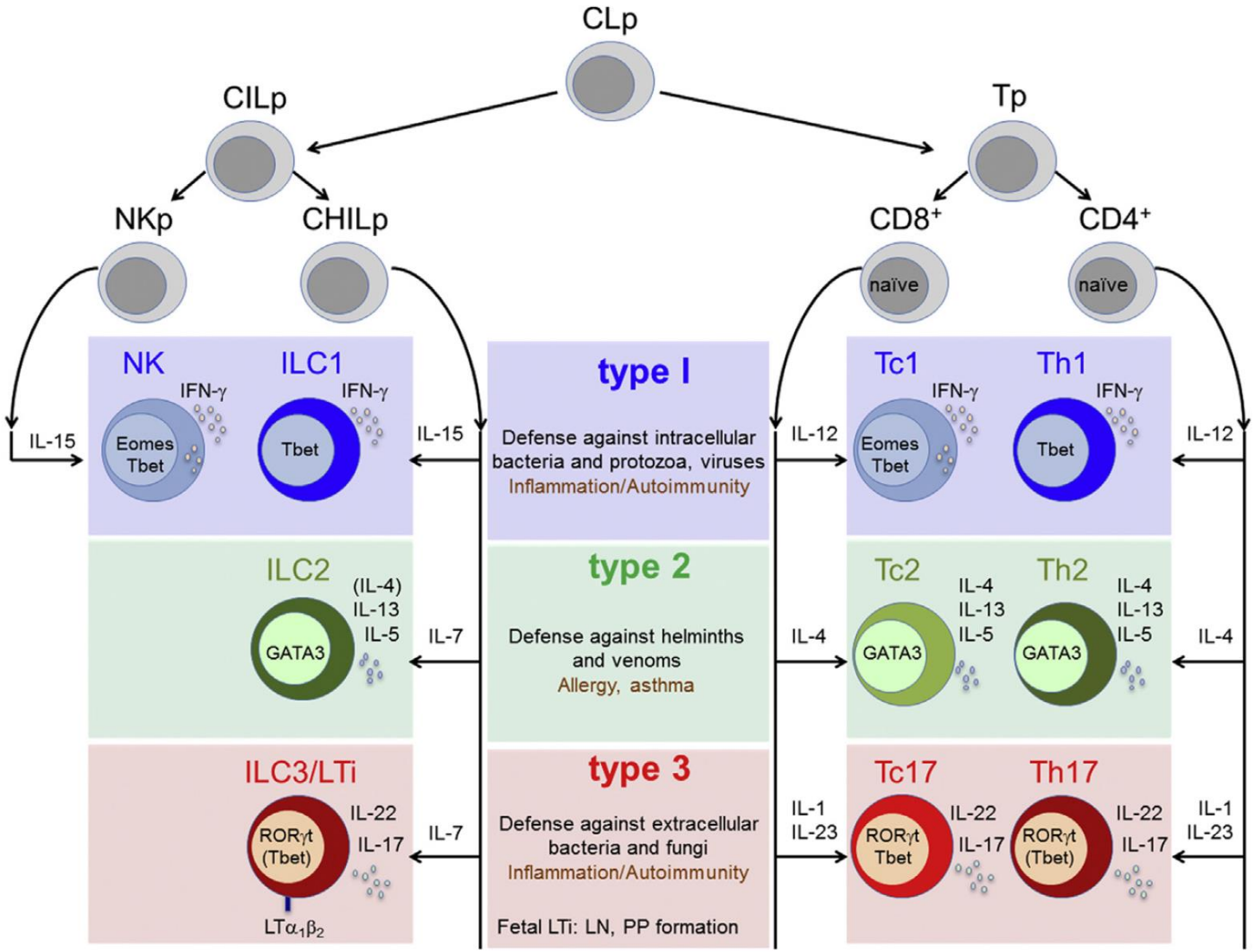
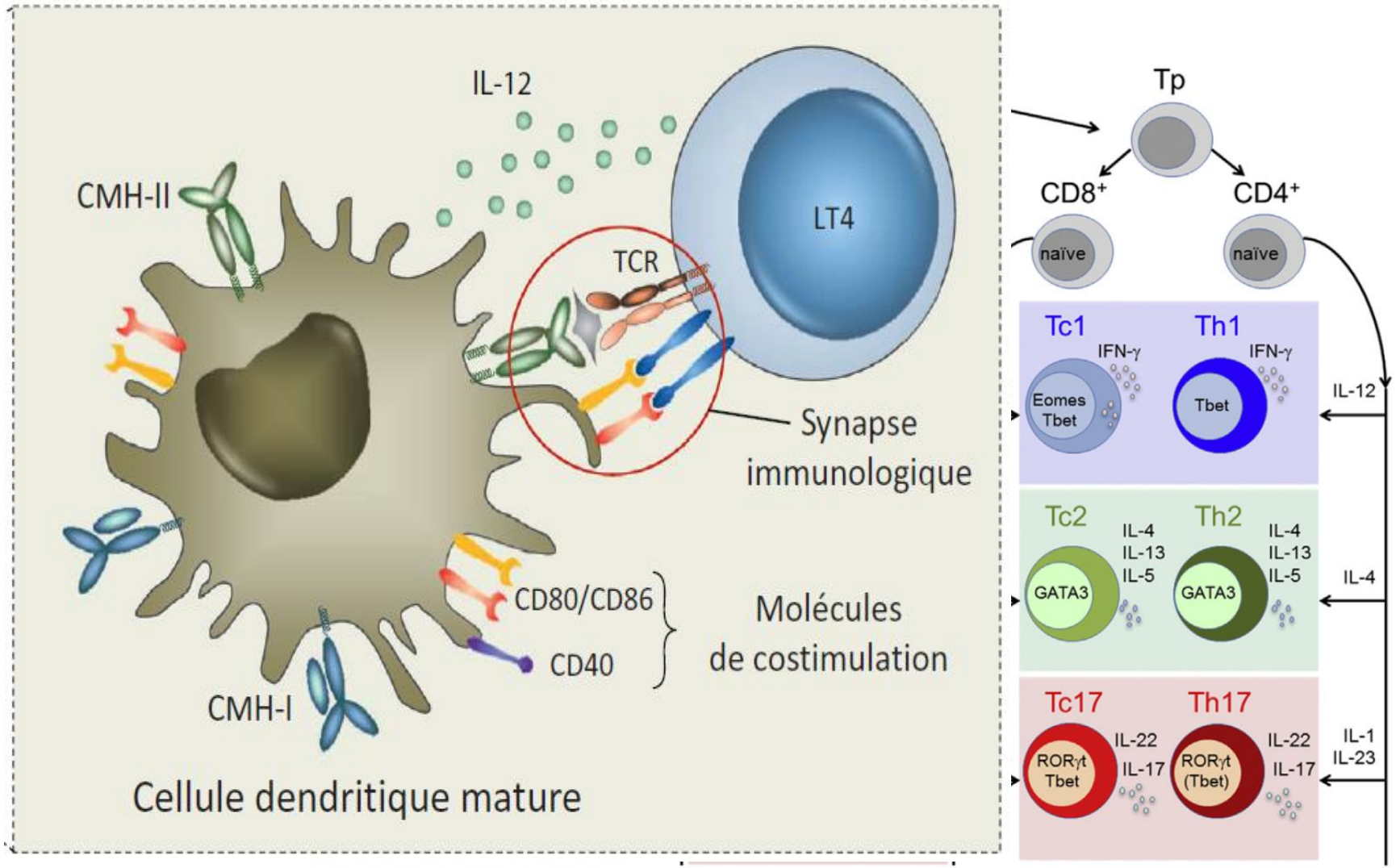


FIG 1. The 3 major types of innate and adaptive cell-mediated effector immunity. Type 1 immunity is composed of T-bet$^+$ IFN-γ–producing CD4$^+$ T_H1 cells and ILC1s and T-bet$^+$Eomes$^+$CD8$^+$ T_C1 and NK cells. Type 2 immunity is composed of GATA-3$^+$CD4$^+$ T_H2 cells, CD8$^+$ T_C2 cells, and ILC2s, which produce IL-4, IL-5, and IL-13. Type 3 immunity is composed of RORγt *(RORC)*$^+$CD4$^+$$T_H17$ cells, CD8$^+$ T_C17 cells, and ILC3s, producing IL-17, IL-22, or both. *CILp*, Common innate lymphoid precursor; *CLp*, common lymphoid precursor; *LN*, lymph node; *LTi*, lymphoid tissue inducer; *PP*, Peyer patch; *Tp*, T-cell progenitor.

The 3 major types of innate and adaptative cell-mediated immunity



Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol. **2015** Mar;135(3):626-35.

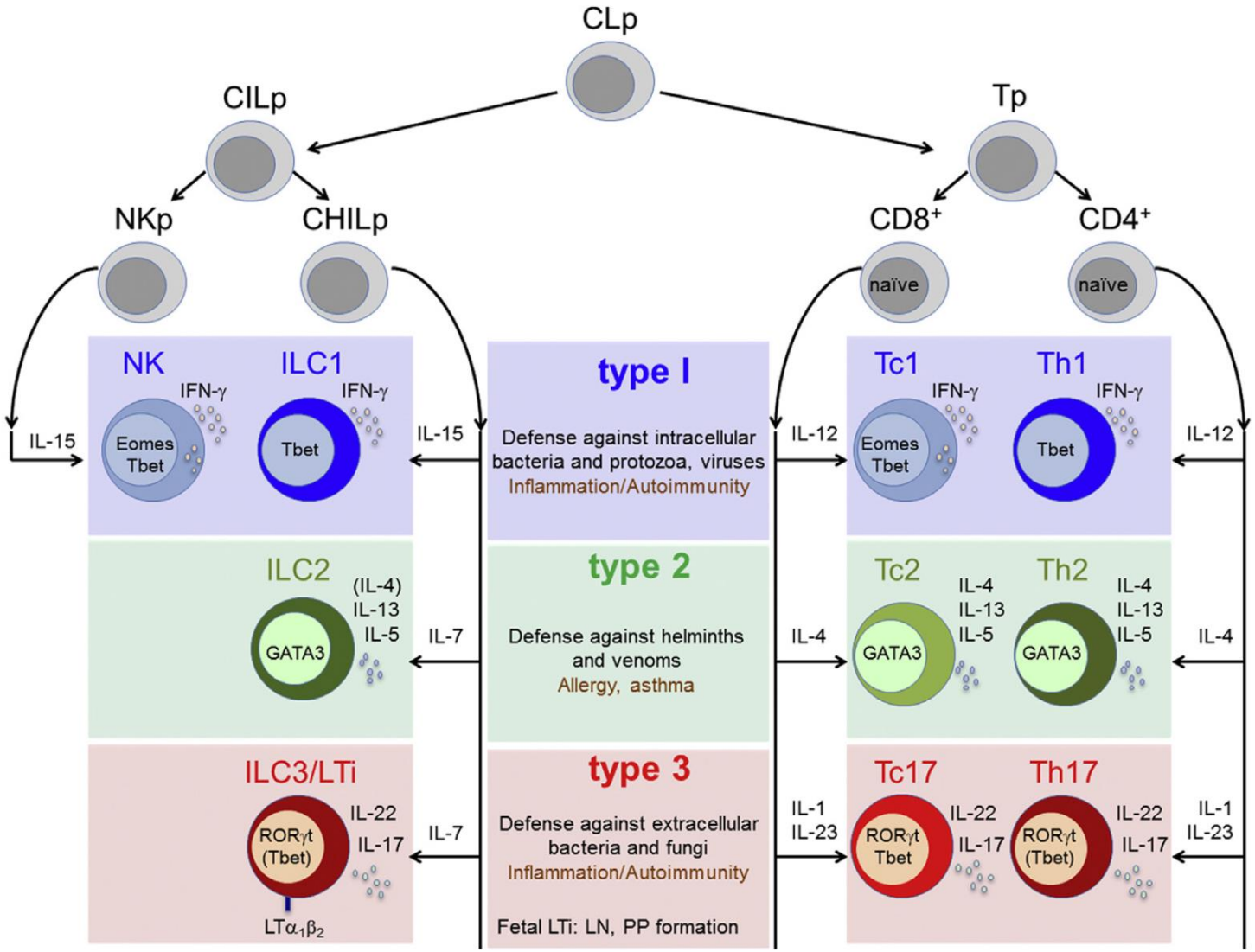
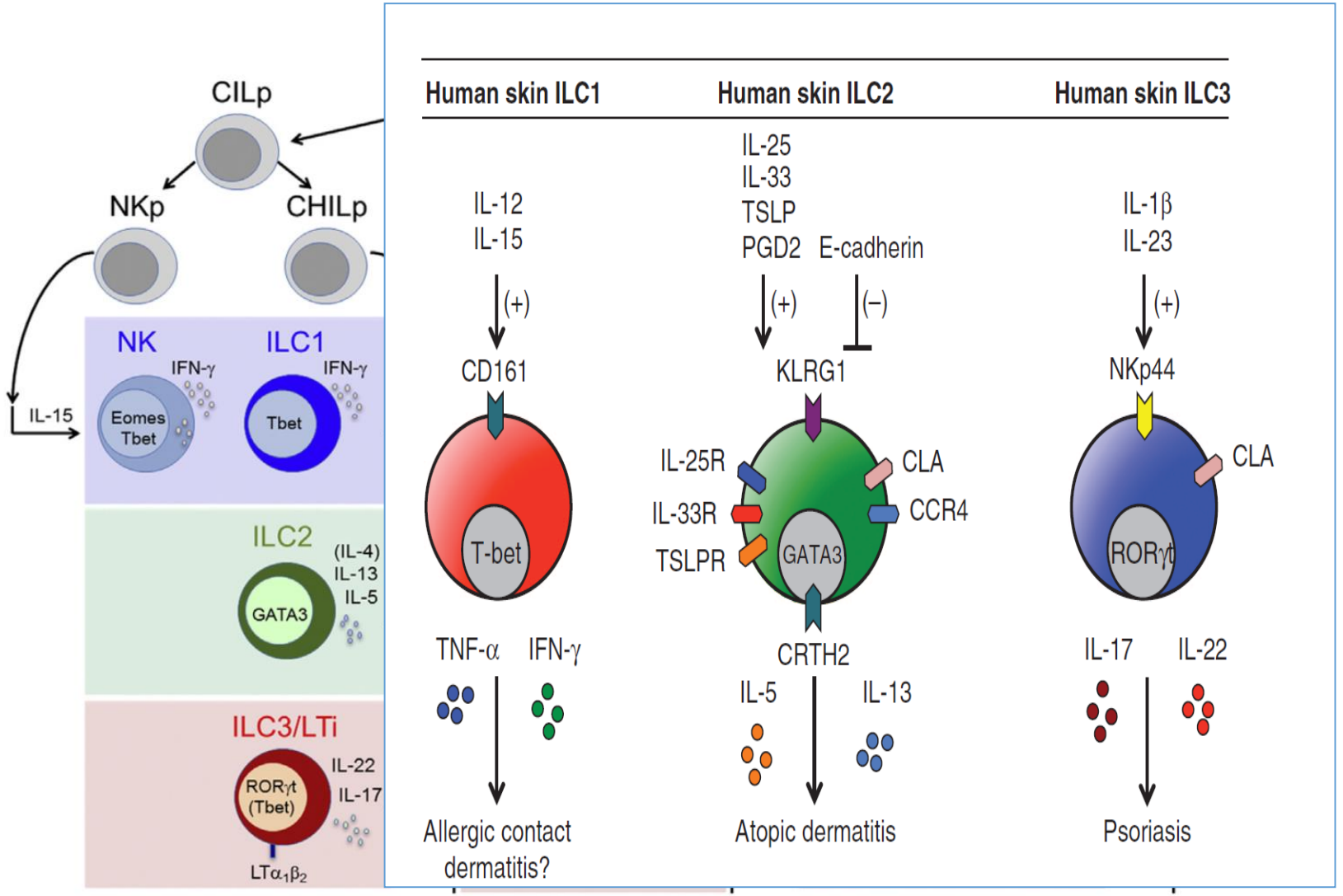


FIG 1. The 3 major types of innate and adaptive cell-mediated effector immunity. Type 1 immunity is composed of T-bet$^+$ IFN-γ–producing CD4$^+$ T_H1 cells and ILC1s and T-bet$^+$Eomes$^+$CD8$^+$ T_C1 and NK cells. Type 2 immunity is composed of GATA-3$^+$CD4$^+$ T_H2 cells, CD8$^+$ T_C2 cells, and ILC2s, which produce IL-4, IL-5, and IL-13. Type 3 immunity is composed of RORγt *(RORC)*$^+$CD4$^+$$T_H17$ cells, CD8$^+$ T_C17 cells, and ILC3s, producing IL-17, IL-22, or both. *CILp*, Common innate lymphoid precursor; *CLp*, common lymphoid precursor; *LN*, lymph node; *LTi*, lymphoid tissue inducer; *PP*, Peyer patch; *Tp*, T-cell progenitor.

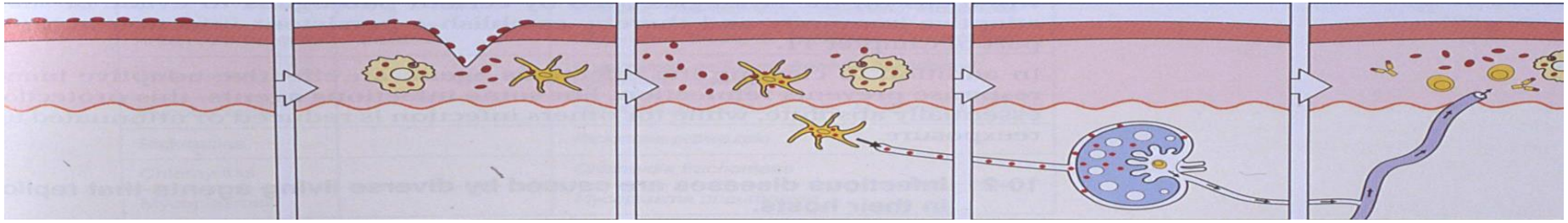
The 3 major types of innate and adaptative cell-mediated immunity

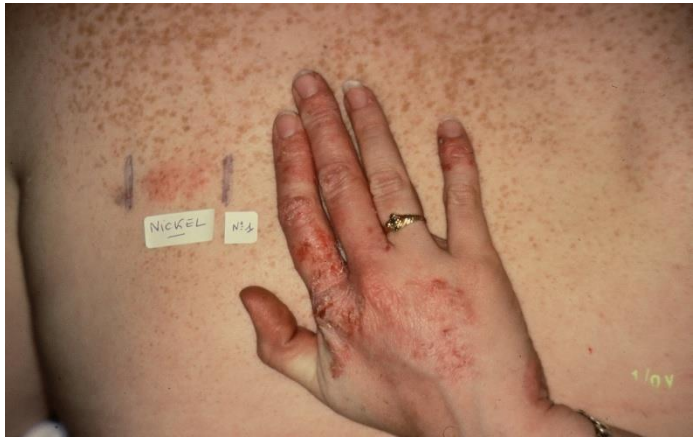


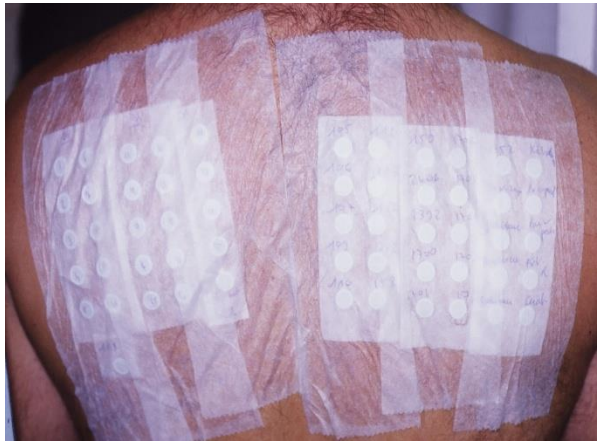
Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol. **2015** Mar;135(3):626-35.

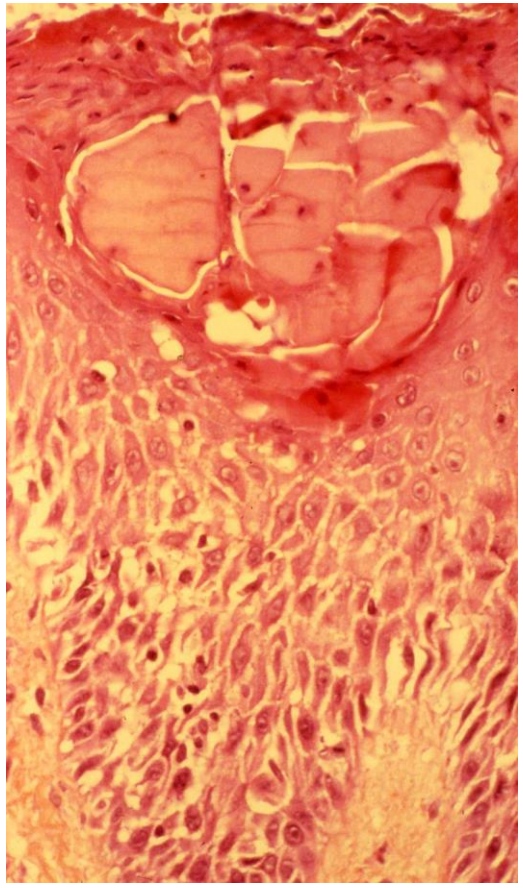
Hypersensibilité de type IV (HS retardée) due à des LT1
ECZEMA DE CONTACT

Type 1

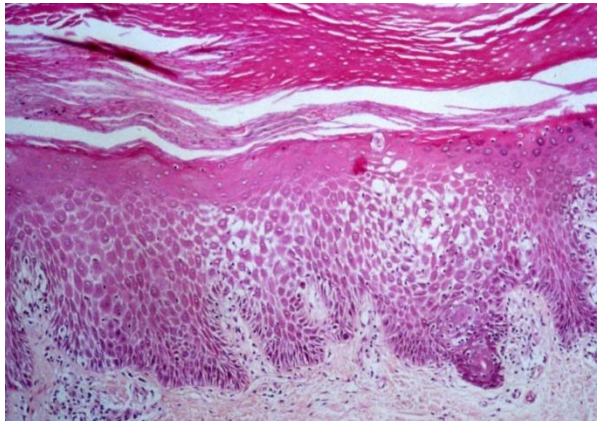






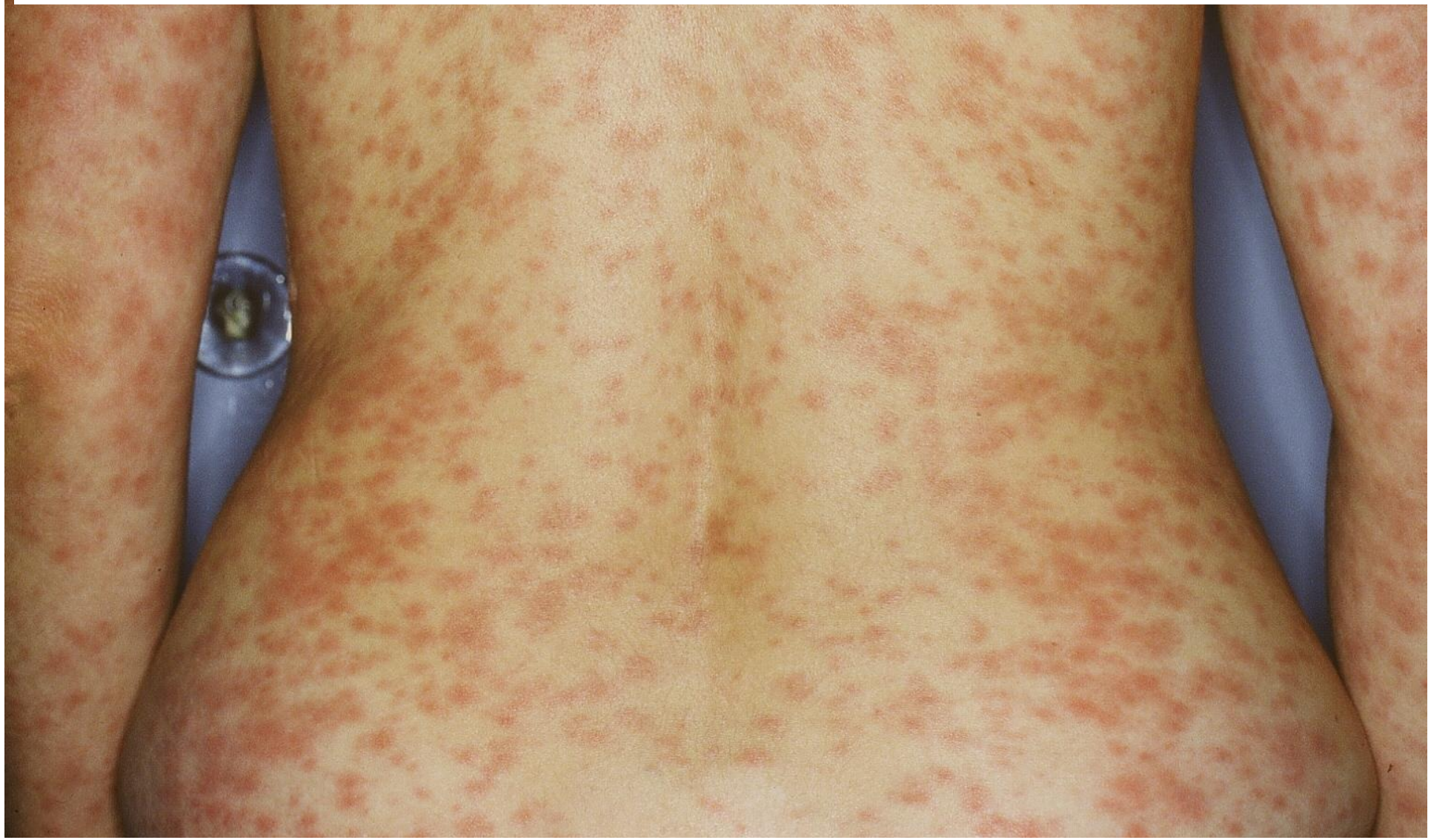


Skin tests represent experimental models of allergic type IV DTH reactions



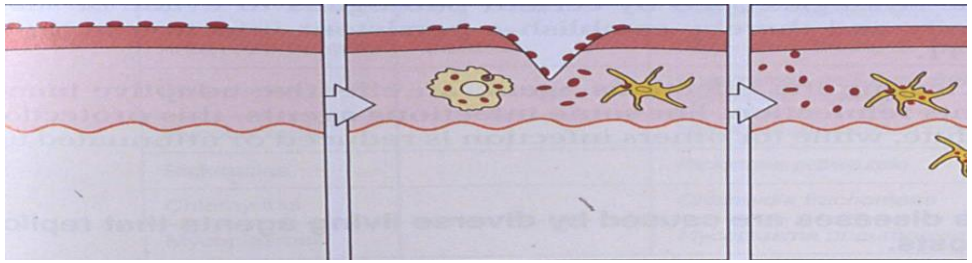
Hypersensibilité de type IV (HS retardée) due à des LT1
EXANTHEMES MEDICAMENTEUX

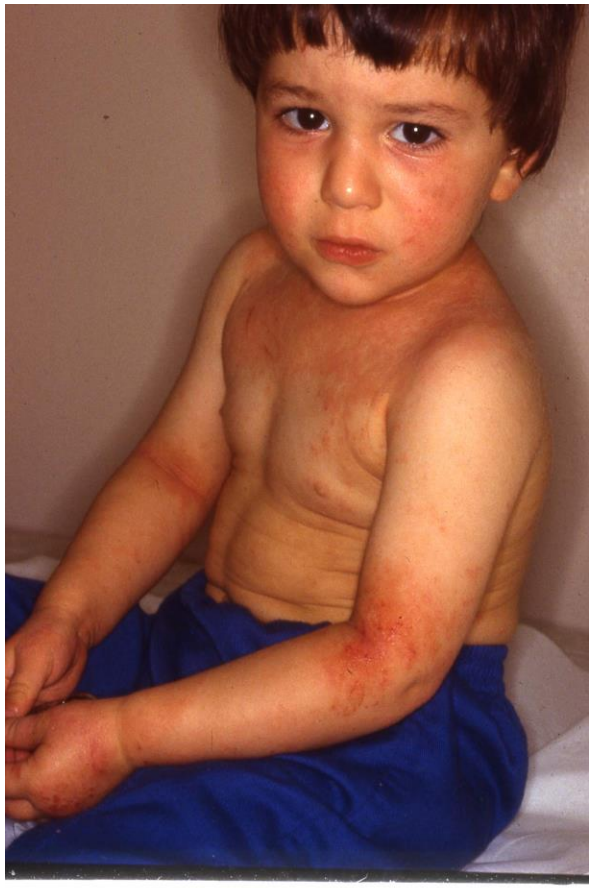
Type 1

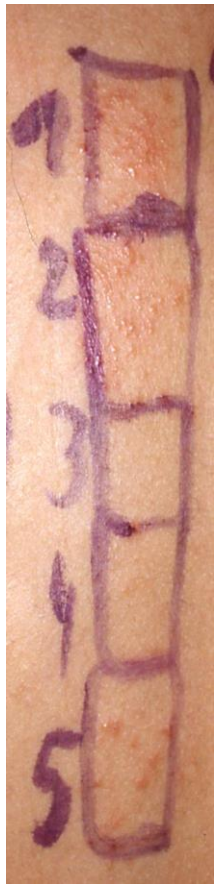


Hypersensibilité de type IV (HS retardée) due à des LT2
DERMATITE ATOPIQUE

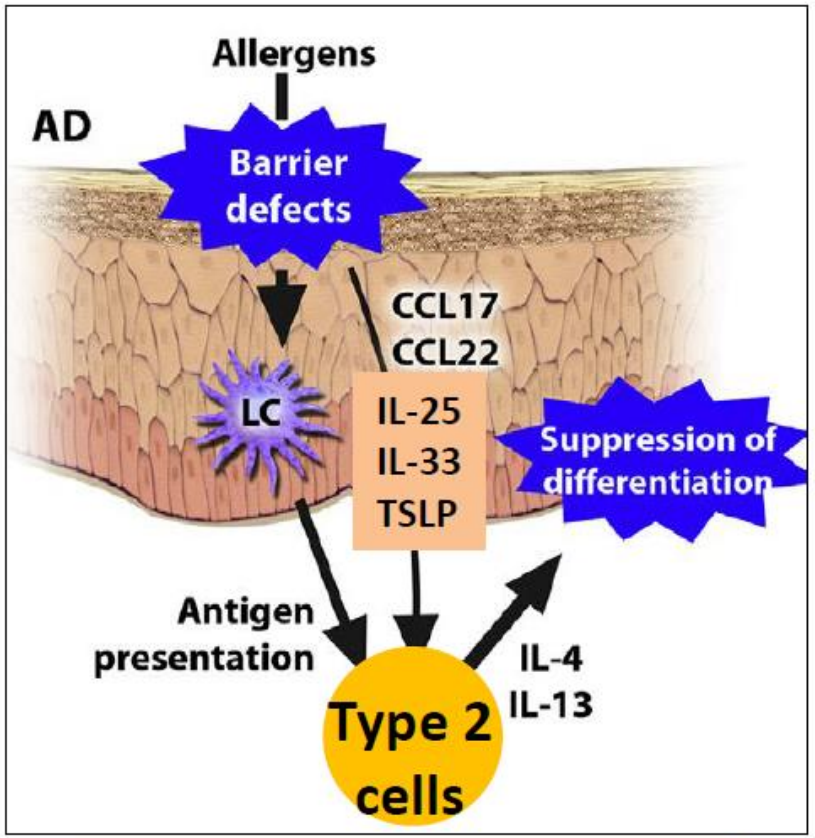
Type 2







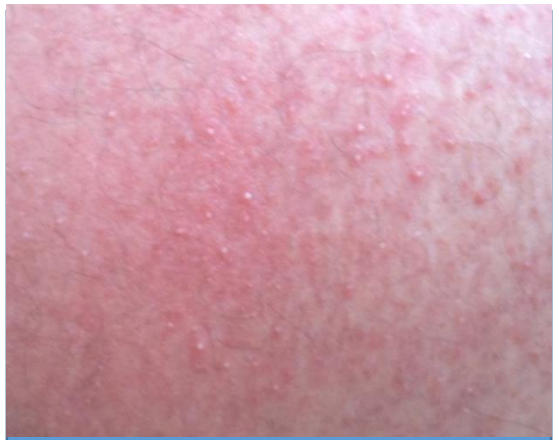
Type 2 phenotype

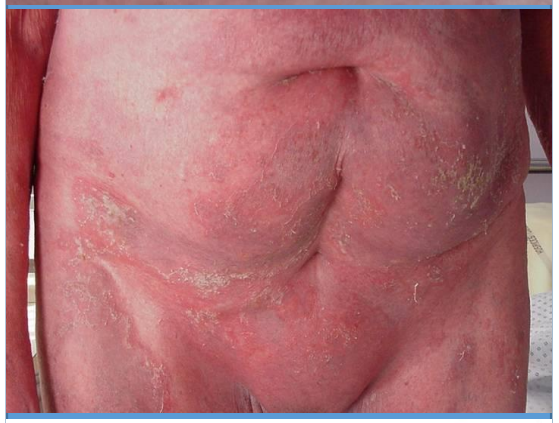


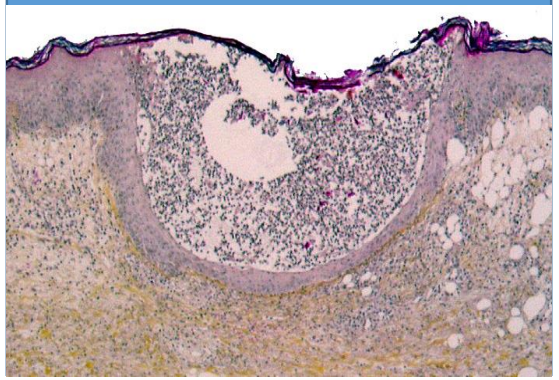
Type 2 inflammation
Type 2 immunity

Hypersensibilité de type IV (HS retardée) due à des LT 17
PEAG pustulose exanthématique aigue généralisée

Type 3 / 17



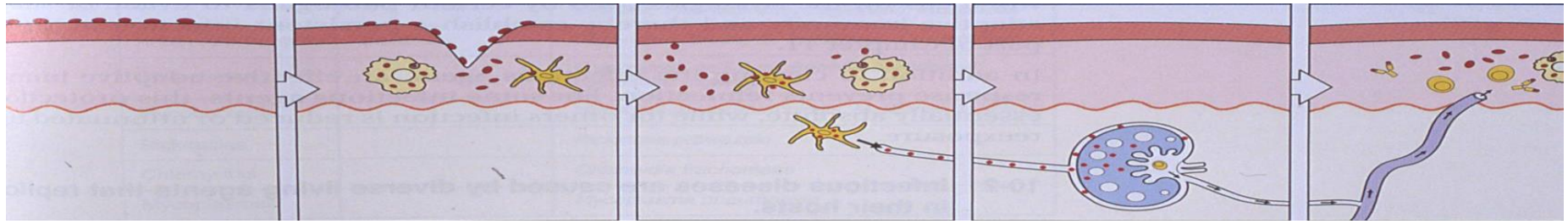


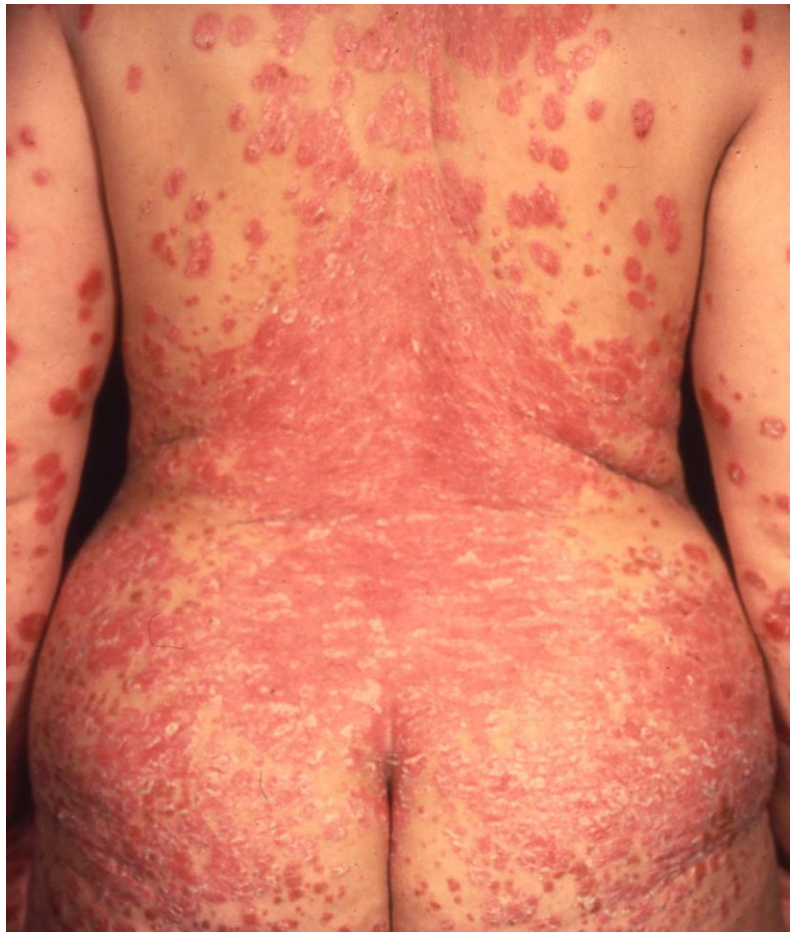


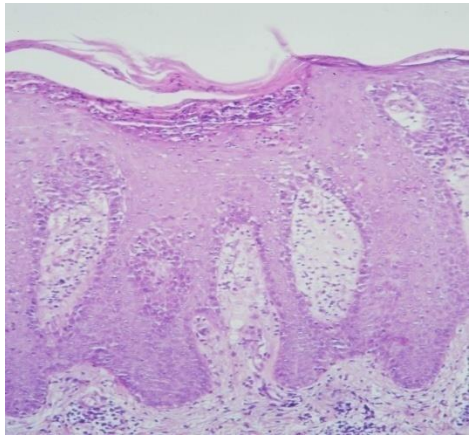
- **Physiopathologie:** hypersensibilité retardée médiée par des LT spécifiques du médicament
- **Incidence** inconnue
- **Délai :** quelques heures à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre,
  - Eruption pustuleuse des plis sur un fond érythémateux puis extension.
- **Biologie:**
  - Hyperleucocytose à PNN ou PNE,
  - Hypocalcémie
- **Atteinte viscérale:** foie, rein
- **Histologie:** pustules intraépidermiques ou sous cornées
- **Médicaments :** pénicillines, macrolides, carbamazépine, inhibiteurs calciques, terbinafine
- **Guérison** rapide (7 jours)
- **Mortalité:** 5%

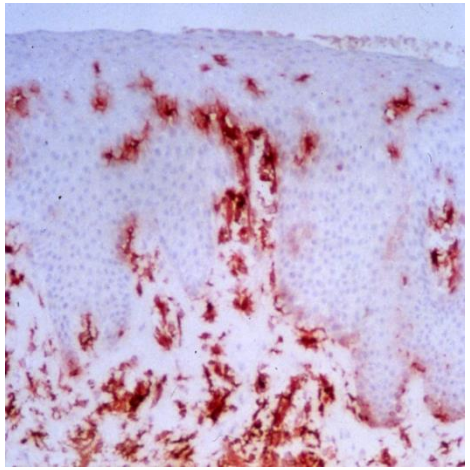
Hypersensibilité de type IV (HS retardée) due à des LT 17
PSORIASIS

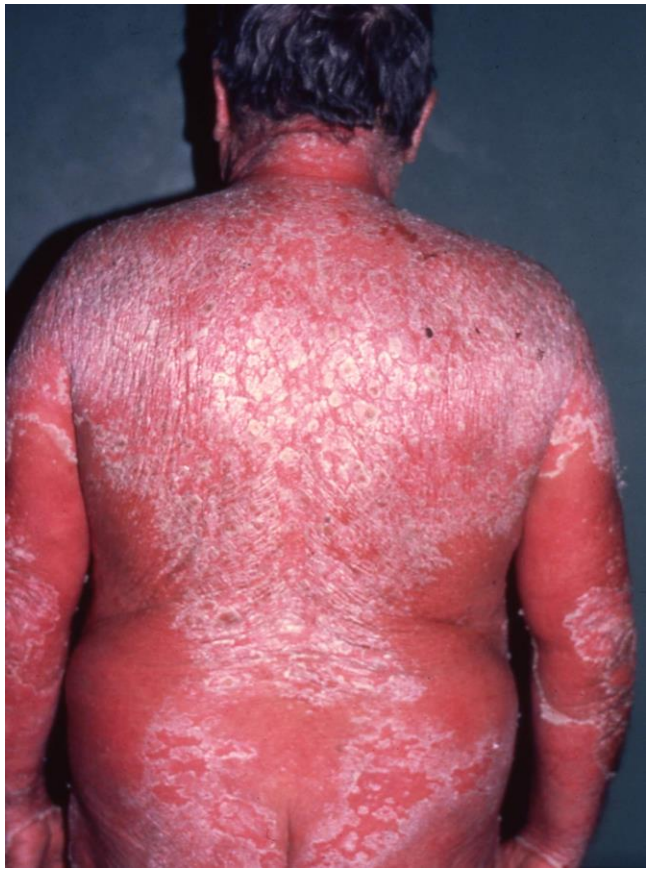
Type 3 / 17







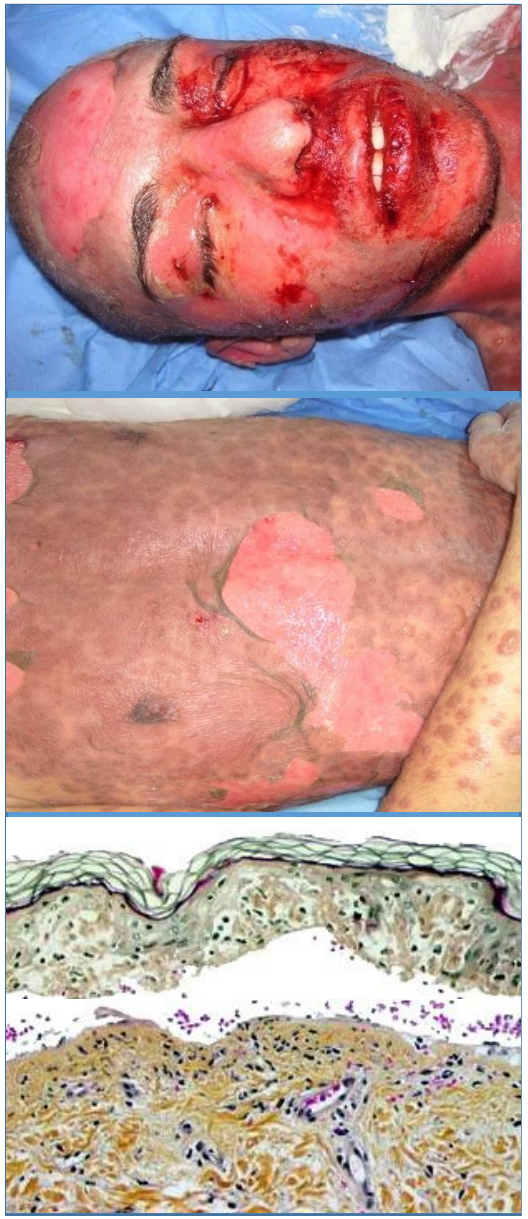


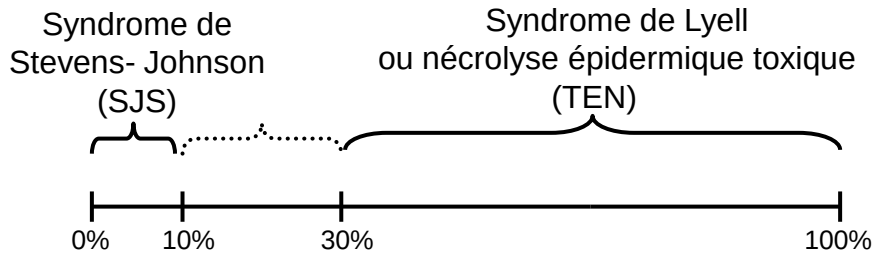


Hypersensibilité de type IV (HS retardée) due à des LT cytotoxiques

Nécrolyse épidermique toxique – Sd de Stevens-Johnson – Sd de Lyell

Type 1
Tc1





- **Physiopathologie:** apoptose kératinocytaire médiée par les LT
- **Incidence:** 1 à 3 cas/million/an.
- **Délai** : 1 à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre
  - Erosions muqueuses (>2 sites)
  - Décollements cutanés superficiels (S. de Nikolski +)
- **Biologie:** lymphopénie fréquente
- **Atteinte viscérale:** rénale, pulmonaire, digestive, foie
- **Histologie:** nécrolyse épidermique totale
- **Médicaments: allopurinol+++,** lamotrigine, carbamazépine, sulfamethoxazole, AINS (oxicams), nevirapine,…
- **Mortalité:** 30-35% (estimée par le SCORTEN)

Département Allergologie et Immunologie Clinique

Clinical Research Unit

INSERM translational research team

Allergology & Clinical Immunology Department