ADVERSE DRUG REACTIONS - 1 IMMUNOLGICAL

DR SHAMS SULEMAN

LEARNING OBJECTIVES(KMU)

- Define adverse effects of drugs, secondary effects of drugs and intolerance to drugs
- Classify adverse drug reactions
- Describe dose-related adverse effects (side effects and toxic effects) with examples
- Describe non-dose-related adverse effects (idiosyncrasy and drug allergy) with examples.
- Describe causes of adverse drug reactions

LEARNING OBJECTIVES (KMU)

- Enlist some drugs causing hepatotoxicity
- Enlist some drugs causing renal toxicity
- Enlist some cardio toxic drugs.
- Enlist some drugs causing adverse effects on reproduction

LEARNING OBJECTIVES (SELF)

- Classify the adverse drug reaction on the basis of pathophysiology and acute or chronic manifestations
- Classify the adverse drug reaction on the basis of clinical presentations
- Describe the differences in the immunological and idiosyncratic reactions
- Describe the drug treatment of anaphylaxis
- Enlist classical drugs causing various allergic reactions

Can Any of These "Unpredictable" Reactions Be Predicted?

- Patient 1: a 10-month-old is treated with trimethoprim-sulfamethoxazole (TMP-SMX) and develops granulocytopenia with anemia
- Patient 2: a 5-year-old with acute lymphocytic leukemia (ALL) is treated with 6-mercaptopurine (6-MP) and develops severe hematopoietic toxicity
- Patient 3: a 20-year-old with epilepsy is treated with an AED and develops aplastic anemia, rash, and hepatic failure

IMPORTANCE OF ADVERSE DRUG EFFECT

- 4TH leading cause of death exceeding pulmonary disease aids, accident , and automobile death
- Account for 5% of all hospital admission
- Occurs in 10-20% of hospital inpatient
- Adversely effects patient quality of eye
- Causes patient to lose confidence in doctors
- Increases the cost of patient care

PHARMACOVIGILANCE (DAUP)

'Science and activities relating to

Detection

Assessment

Understanding

Prevention

of adverse effects or any other drug related problems'

- Useful in educating doctors and in the official regulation of drug use.
- **Rational Therapeutics**
- Provides the basis for assessing **safety** of medicines.


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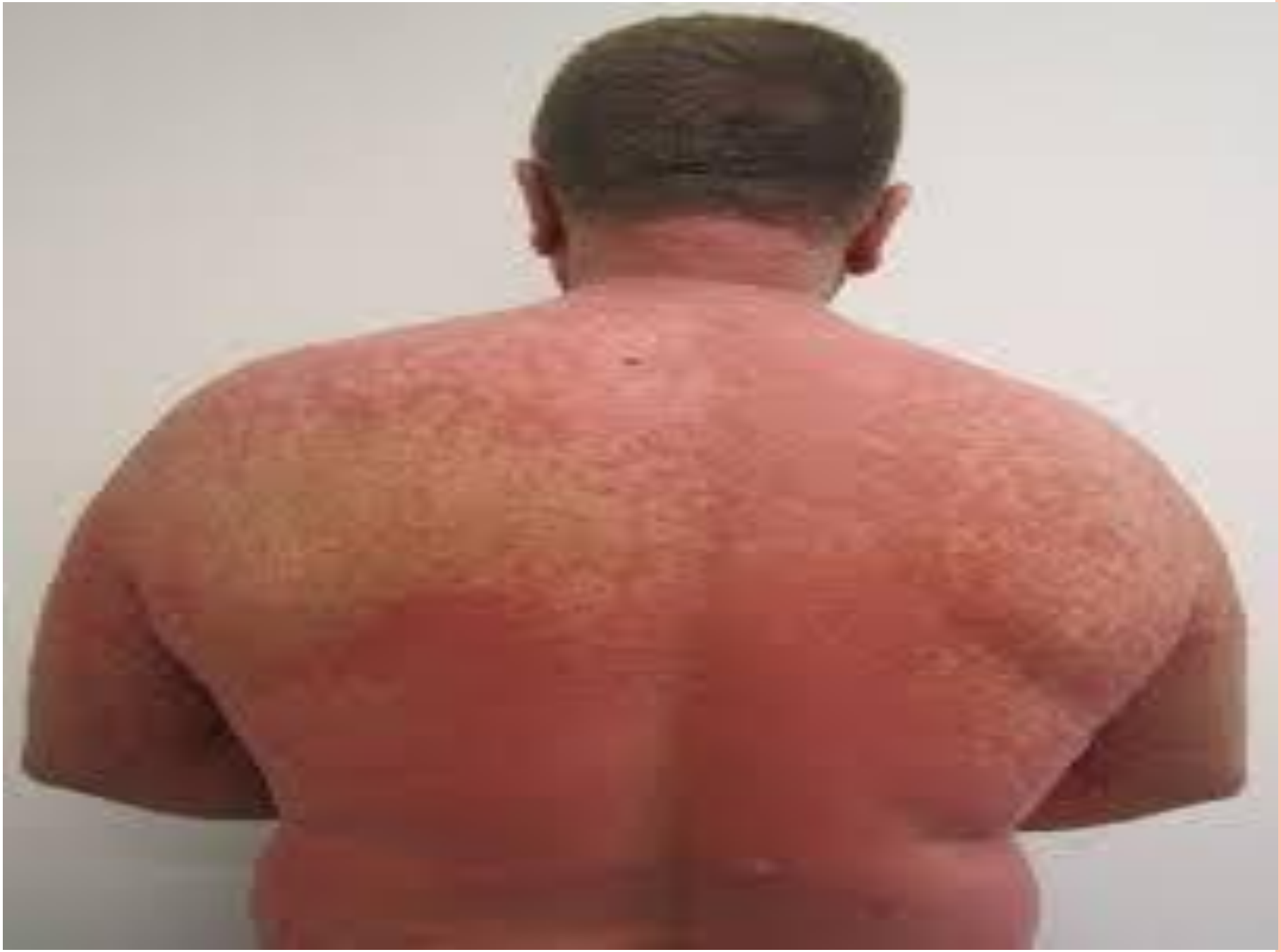

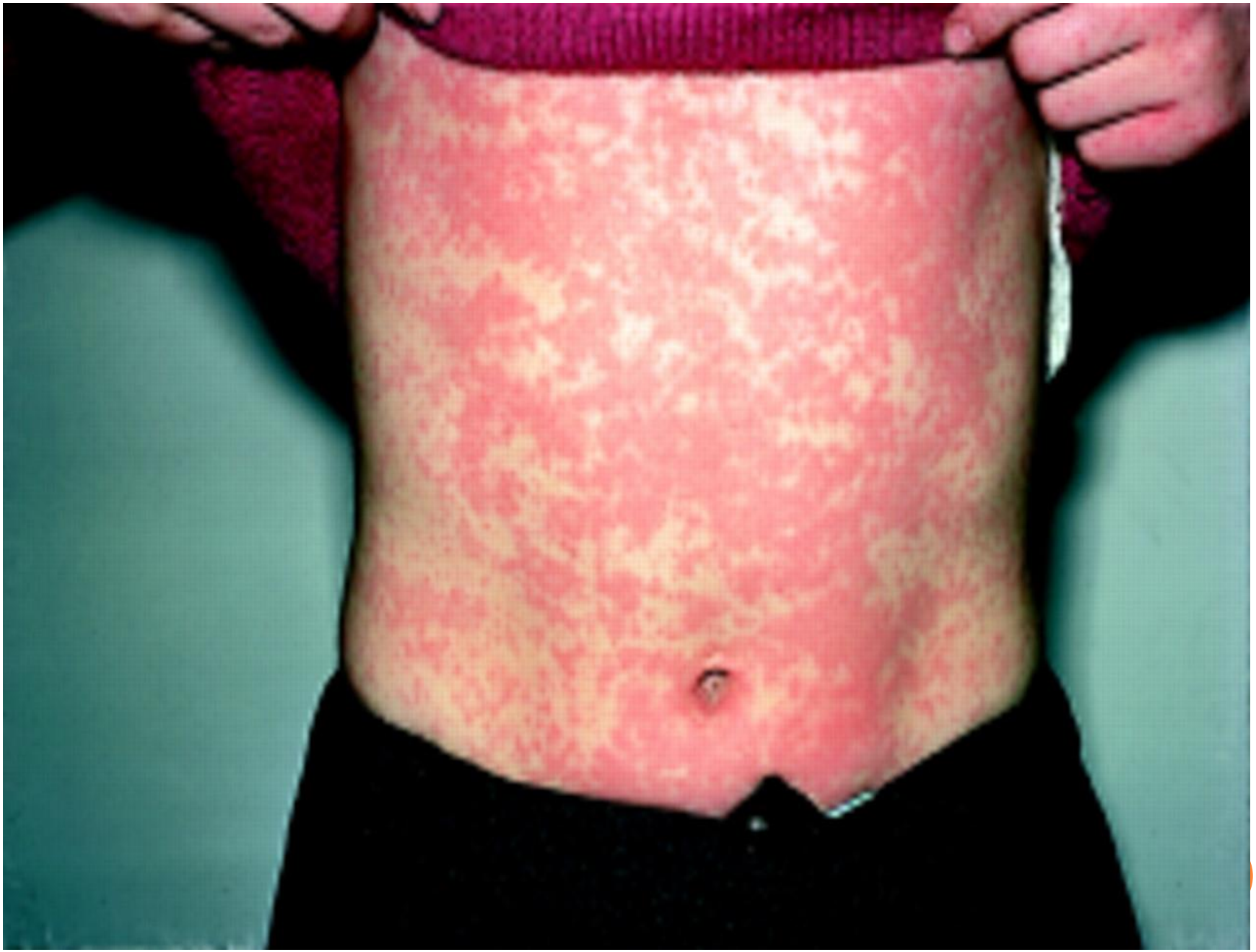

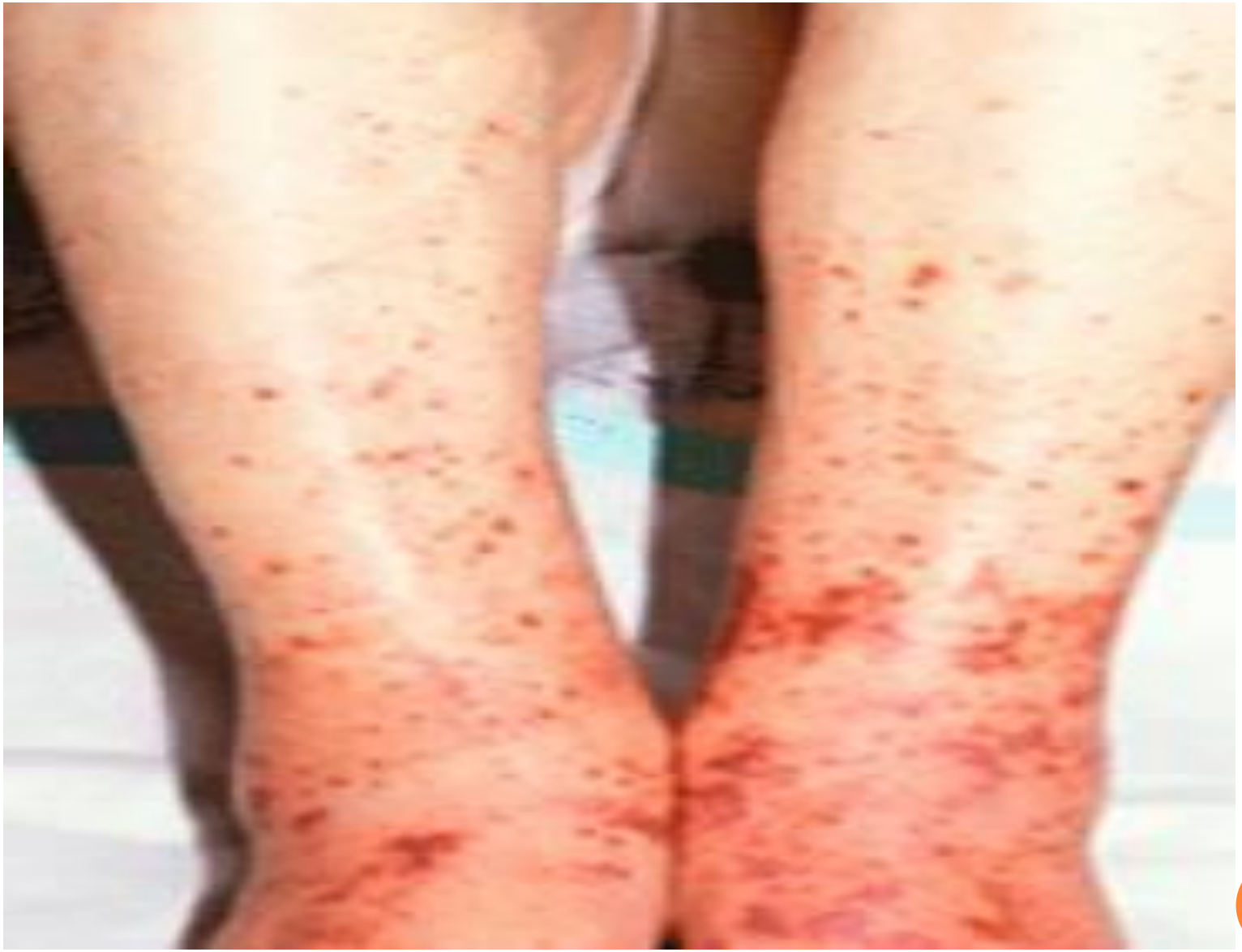

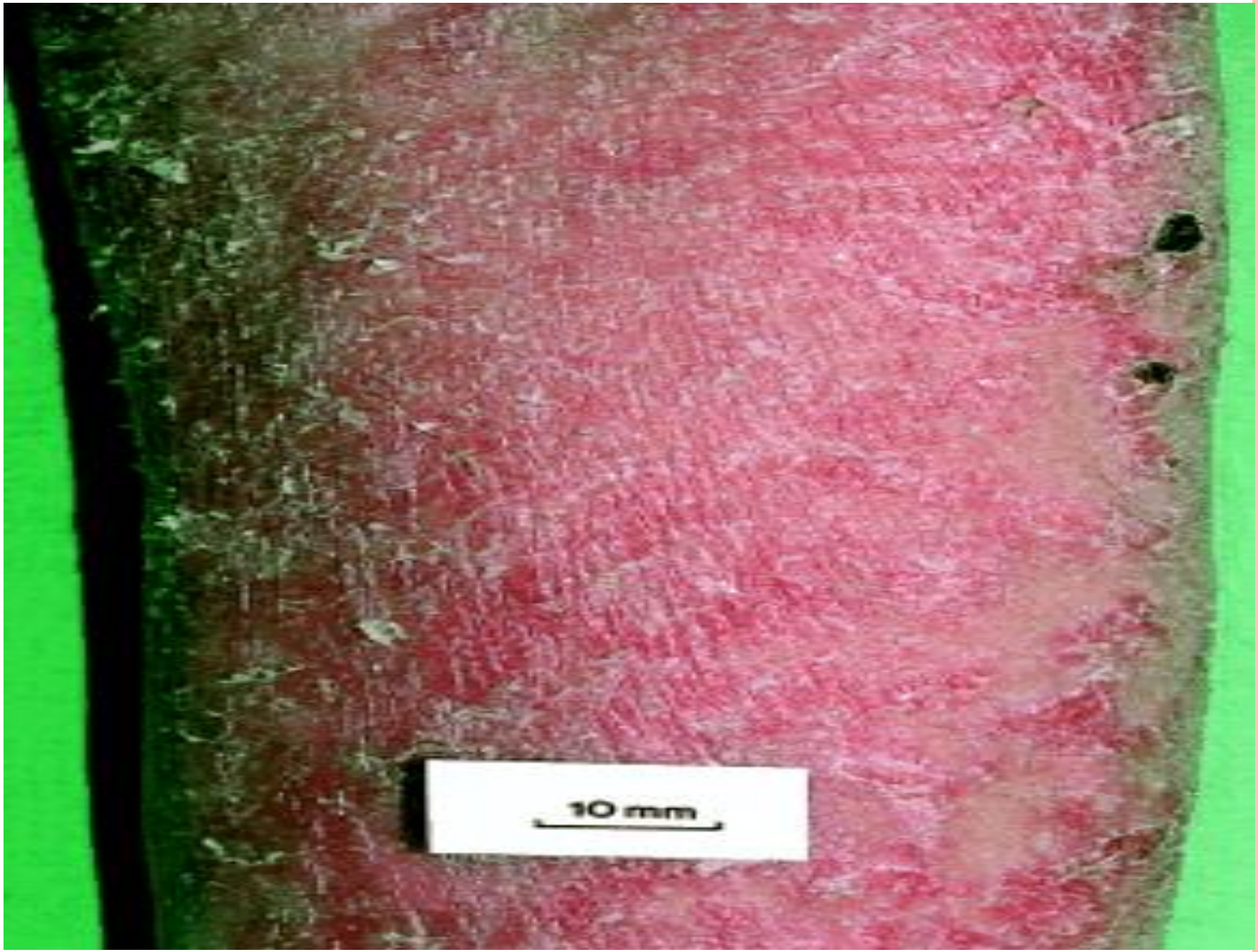
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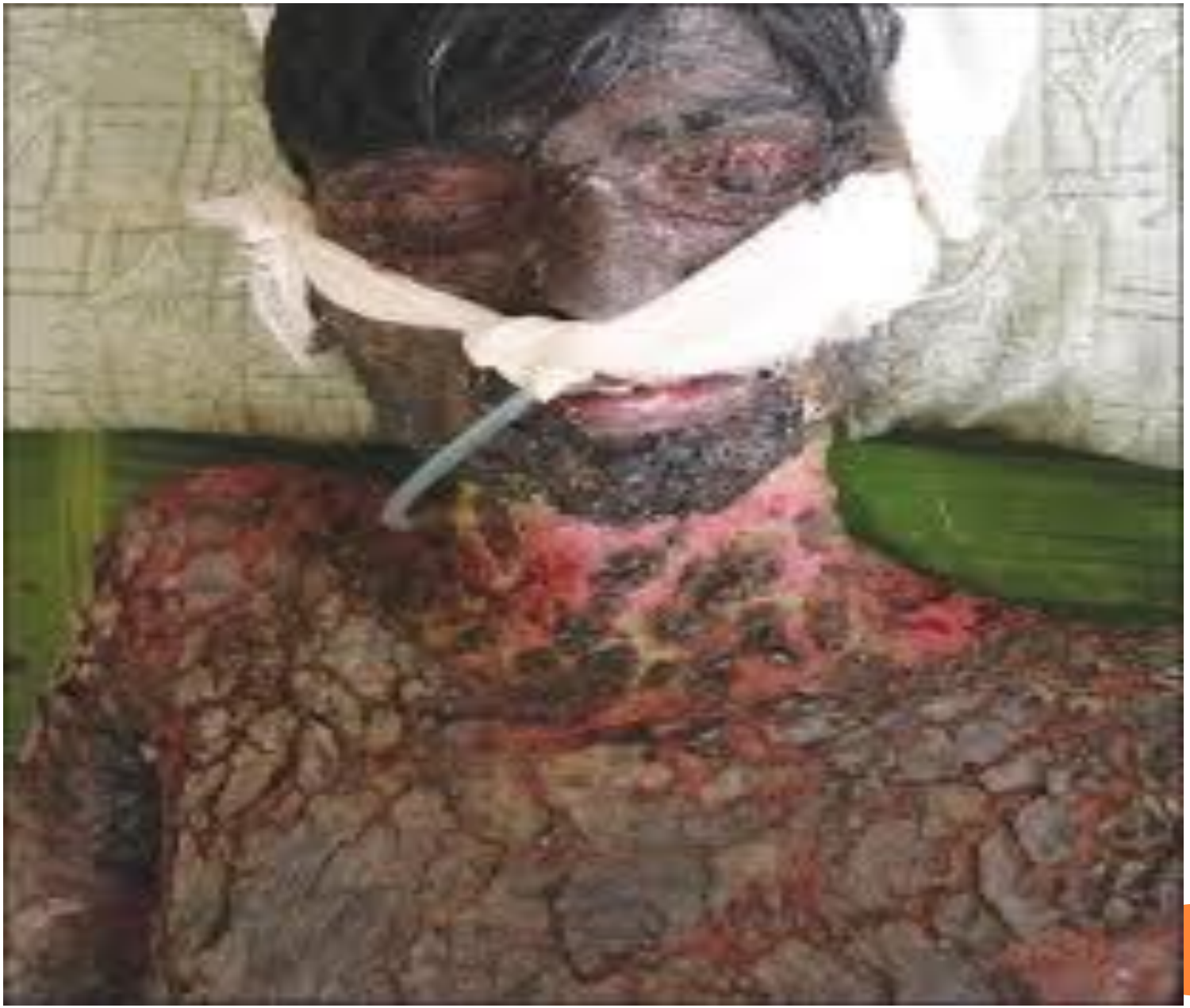
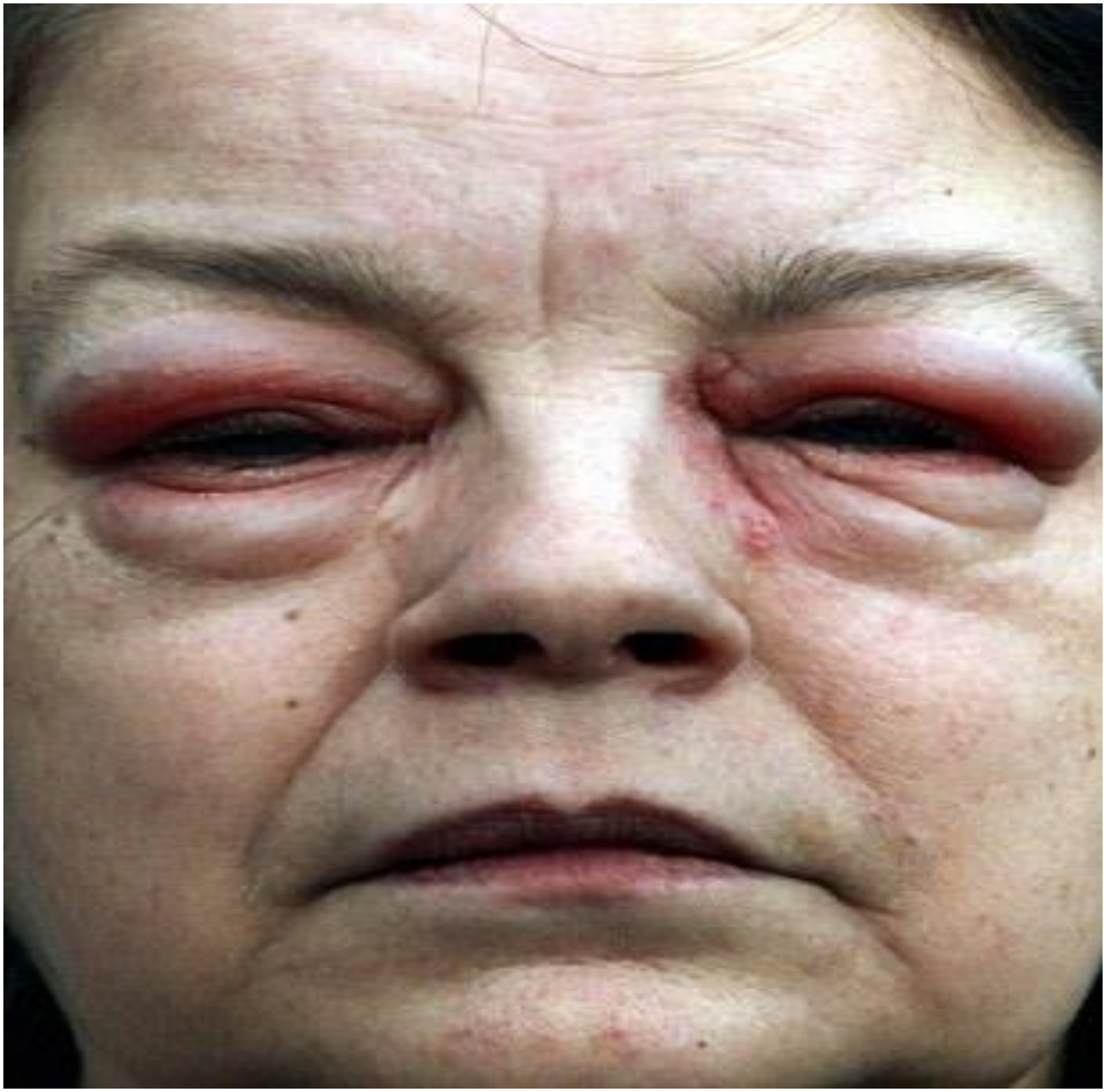
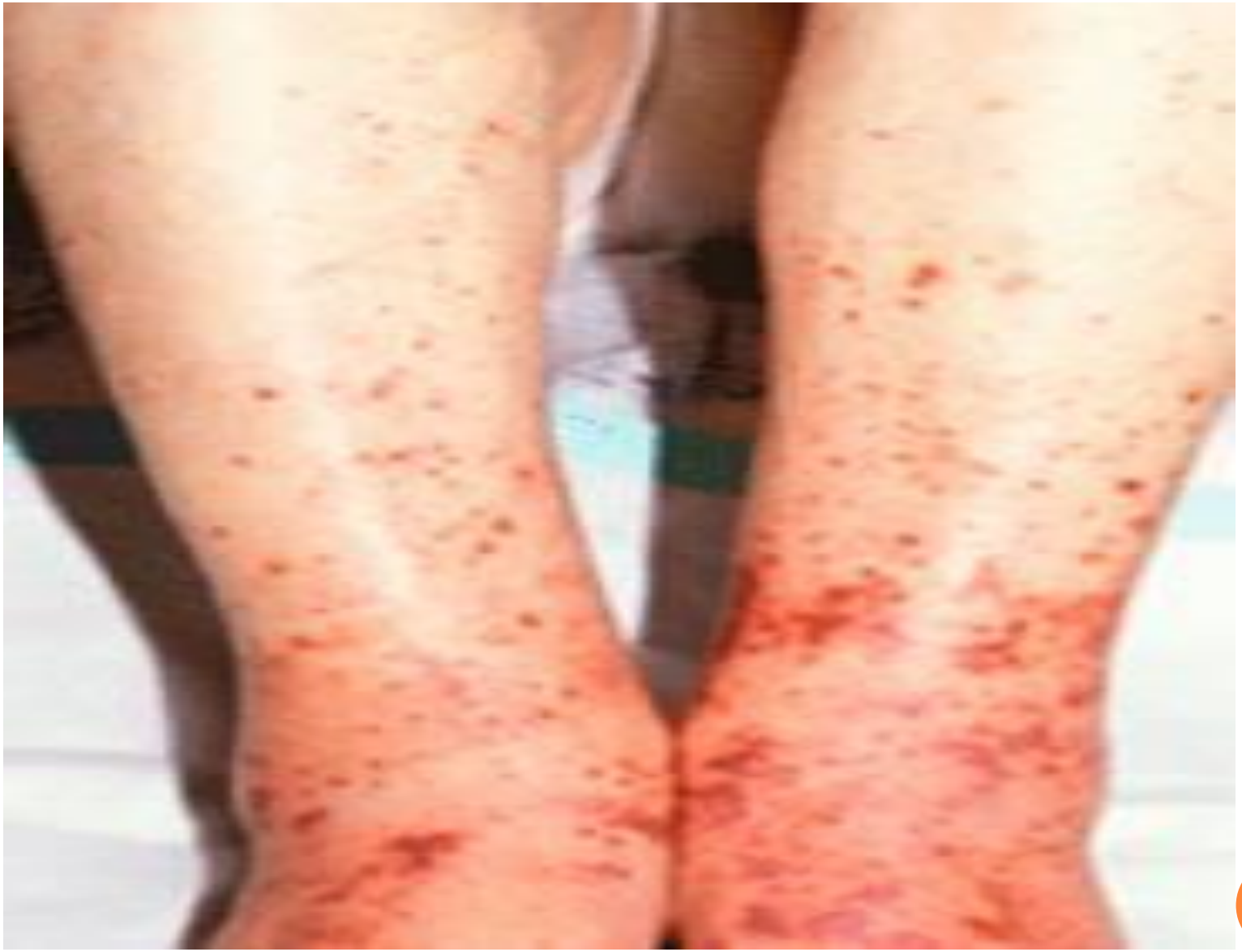
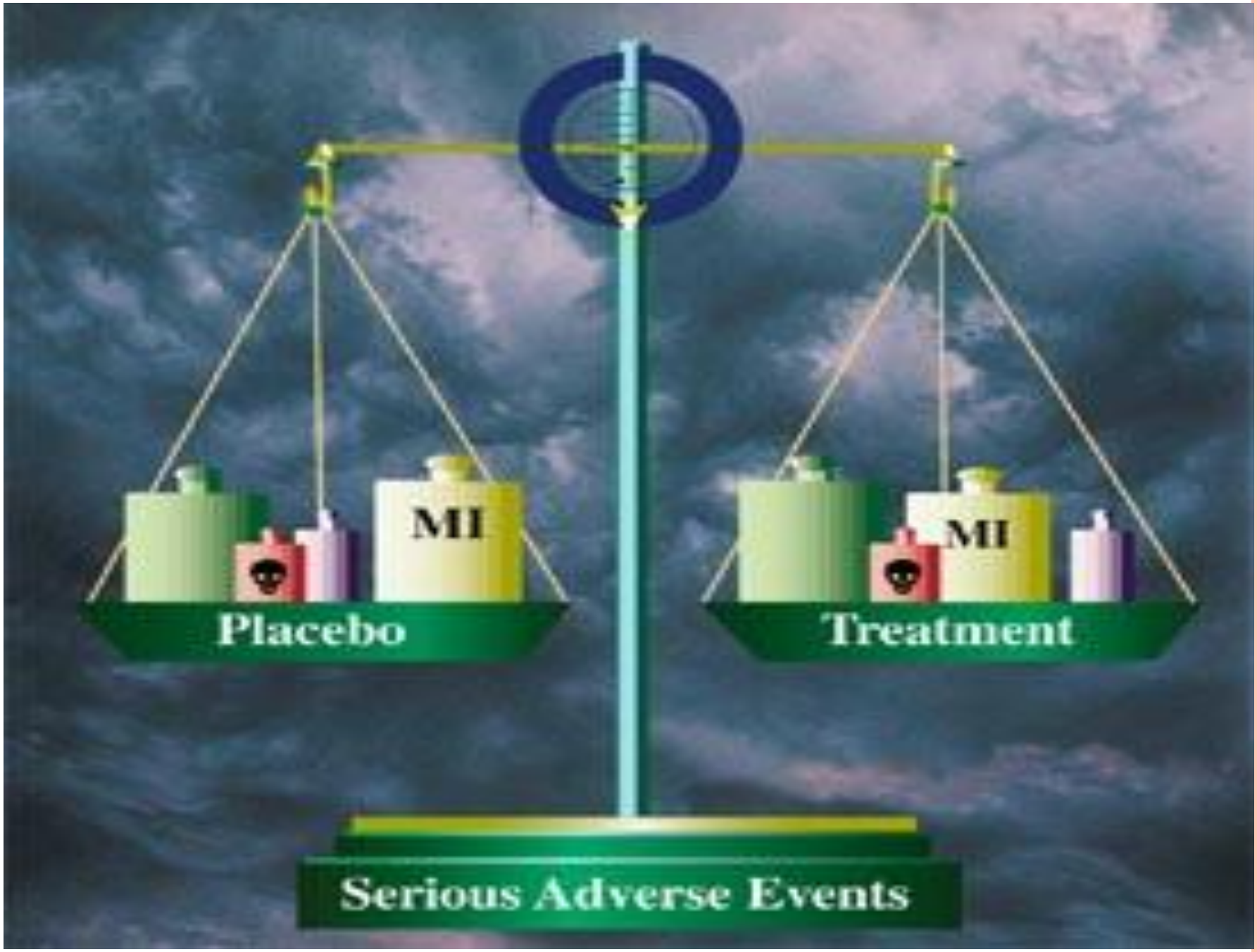







MI
MI
Placebo
Treatment
Serious Adverse Events

Chapter 6 Drug Toxicity

- Adverse drug reactions
- Paracelsus, a Swiss physician (1493-1541), proposed dose-toxicity relationship"*all substances are poisons; there is none which is not a poison. The right dose differentiates a poison and remedy*"
- Dose-related and Non-dose related
- genetic makeup, age, underlying pathology, status of immune system.

ADVERSE DRUG REACTION DEFINITION:- WHO:

Any response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnoses, or therapy of disease or for the modification of physiological function.

- Including any undesirable or unexpected event that requires discontinuing a drug, modifying a dose, prolonging hospitalization or administering supportive treatment

Types of adverse drug reactions

- **IMMUNOLOGICAL (ALLERGIC)**
- **HEREDITARY (IDIOSYNCRATIC)**

ADVERSE DRUG REACTIONS

GENETIC

- ✓ Idiosyncrasy
- ✓ Dose unrelated

NON GENETIC

- ✓ Dose related
- ✓ Dose unrelated
- ✓ Immunological
- ✓ Non immunological

DRUG ALLERGY

IMMUNOLOGICAL

IMMUNOLOGICAL: CHARACTERISTICS

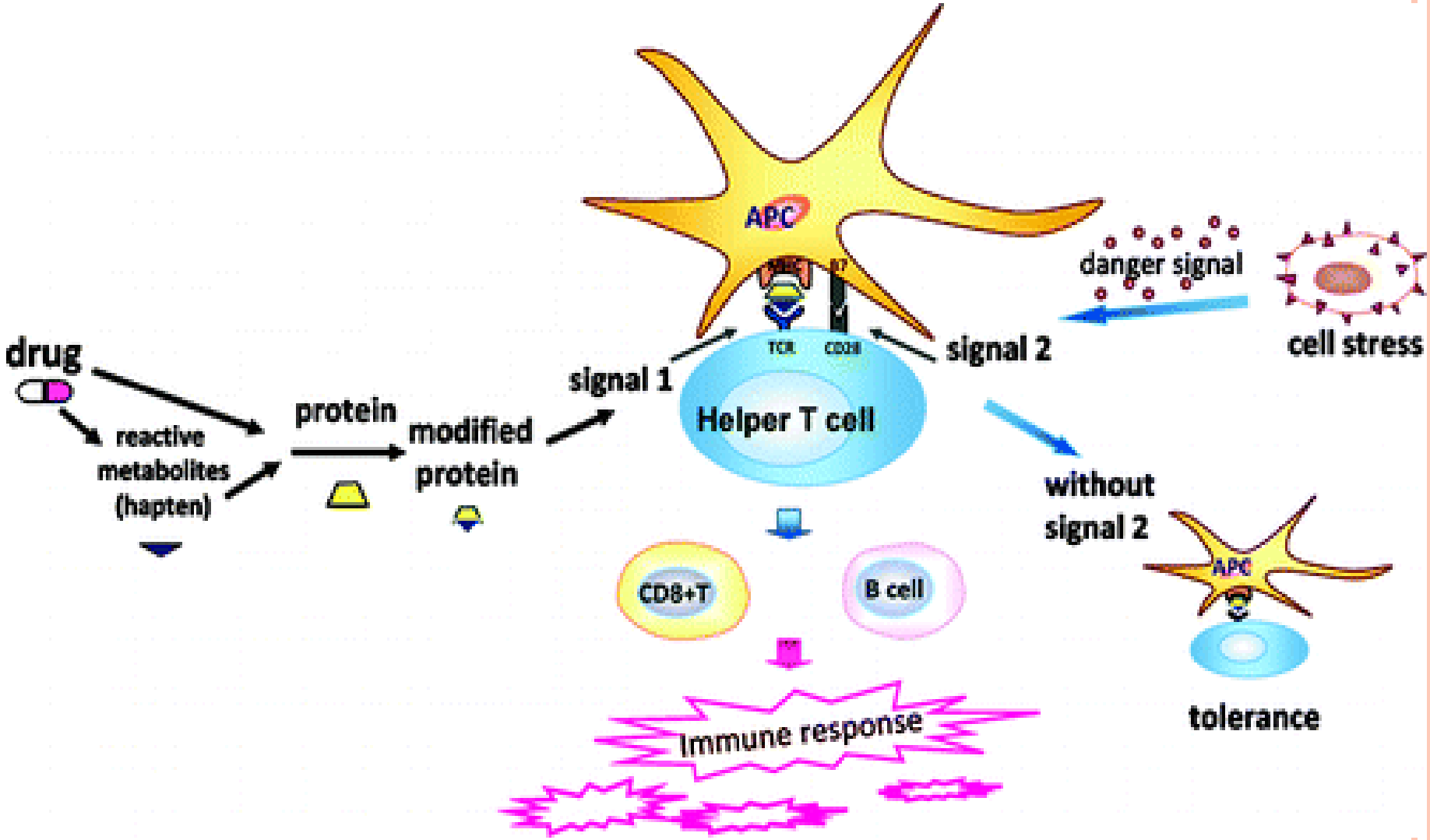
- Cross allergy
- Unpredictable; occurring in minority
- Nonlinear; possible response to desensitization
- Cutaneous, systemic
- Induction period on primary exposure, not on re exposure
- Abates on stopping, reappears on re exposure
- May be temporary

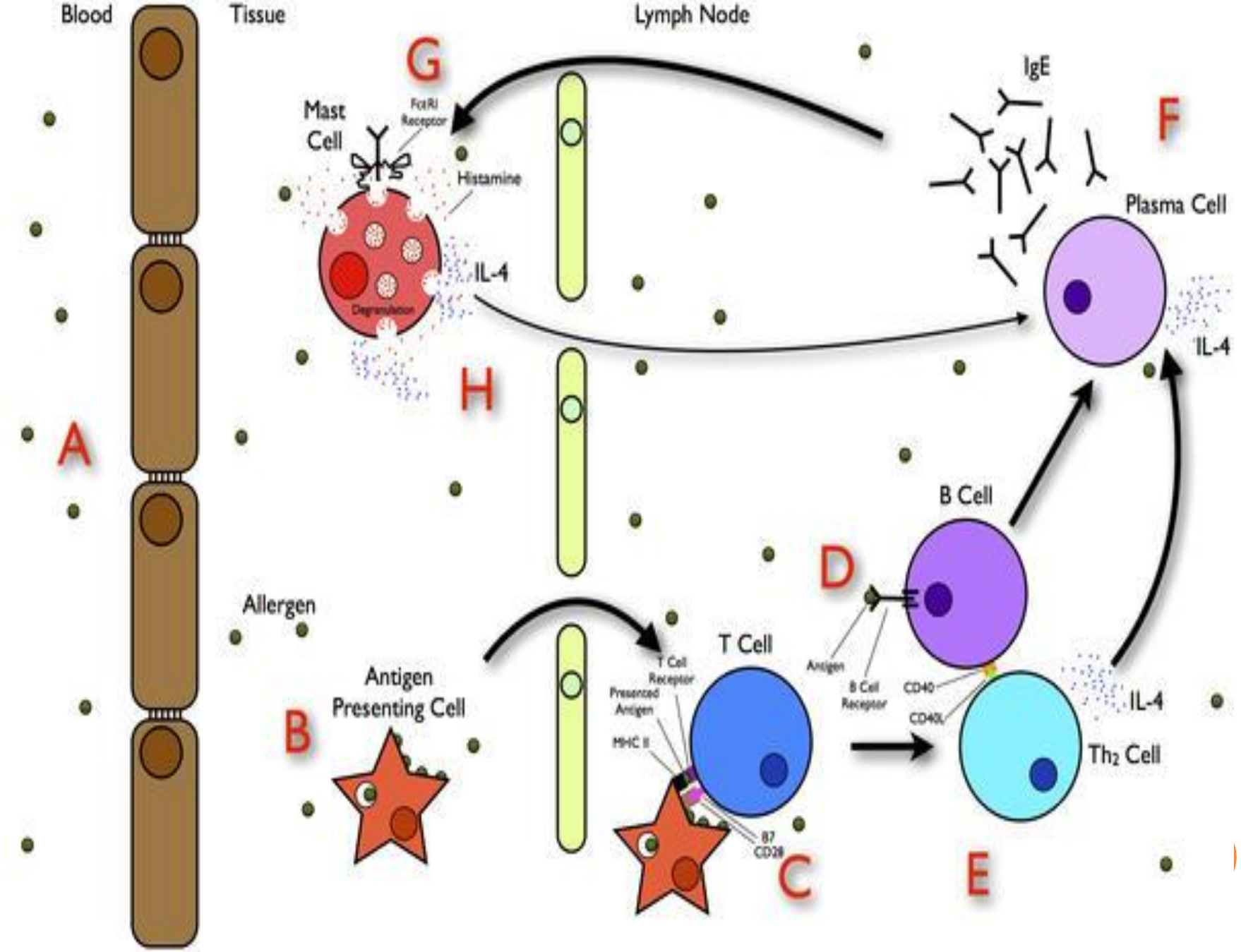
IMMUNOLOGICAL.....

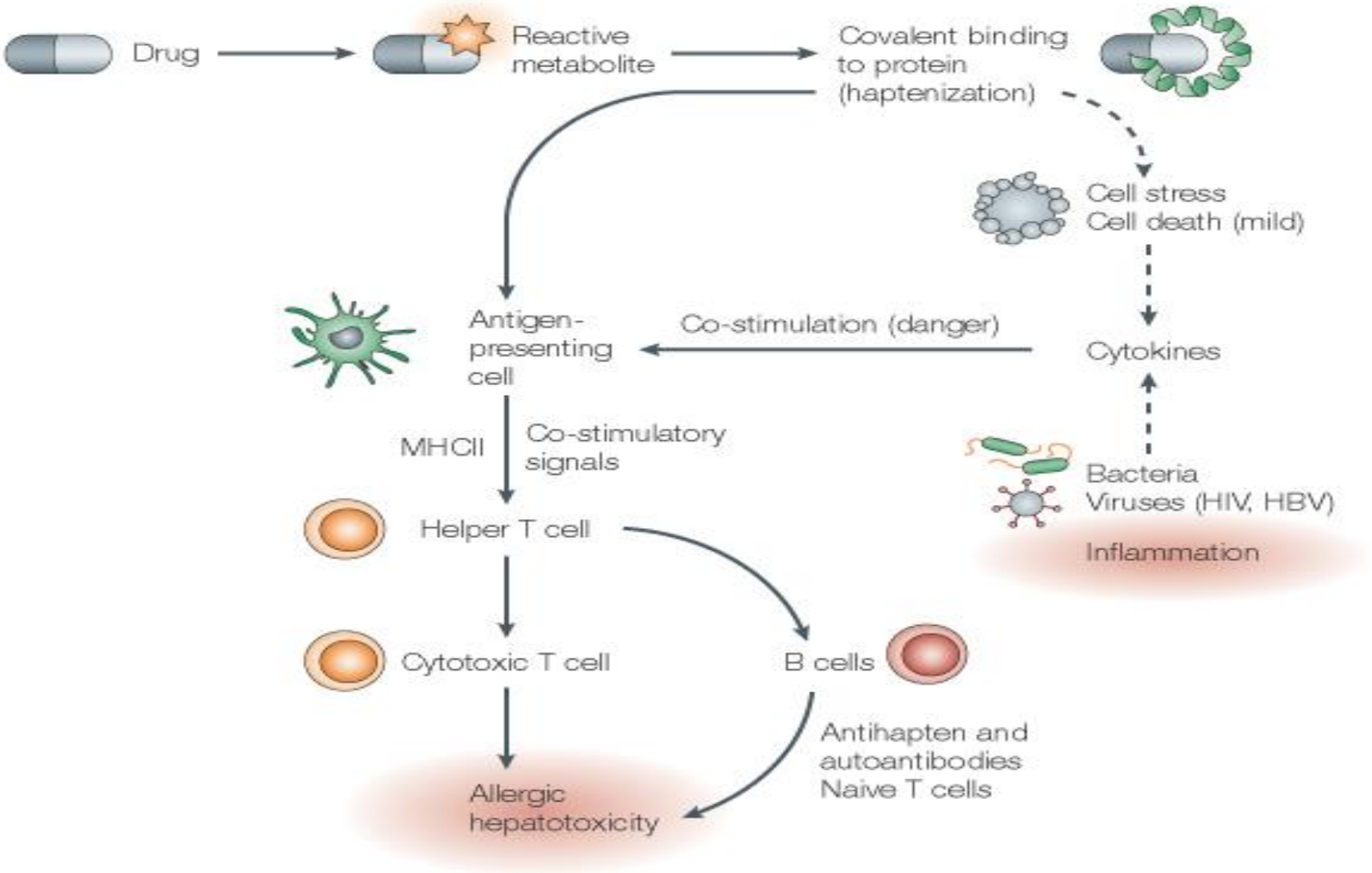
CAUSES

- **The patient**
- **The drug** ; therapeutic index, allergy, ingredients, compatibility, salts
- **The prescriber**; type C, D, E, interactions
- **The environment**; pollution, weather, smoking

PATHOPHYSIOLOGY




Blood
Tissue
Lymph Node
G
Mast Cell
FcεRI Receptor
Histamine
IL-4
Degranulation
H
IgE
F
Plasma Cell
IL-4
A
B Cell
D
Allergen
Antigen Presenting Cell
B
T Cell
T Cell Receptor
Presented Antigen
MHC II
B7
CD28
C
Antigen
B Cell Receptor
CD40
CD40L
IL-4
Th2 Cell
E



Nature Reviews | Drug Discovery

IMMUNOLOGICAL….

MANIFESTATIONS

- Urticarial rash and angioedema
- Non Urticarial rashes
- Lymphoid; Infectious mononucleosis
- Anaphylactic shock
- Pneumonitis, interstitial fibrosis, asthma
- Serum sickness syndrome

IMMUNOLOGICAL….

MANIFESTATIONS…….

- Blood disorders; thrombocytopenia, granulocytopenia, aplastic anemia, hemolysis
- Fever; interleukin-1, PG-E 1
- Collagen disease; SLE (isoniazid, hydralazine)
- Hepatitis and cholestatic jaundice
- Nephropathy

ROLE OF DESENSITISATION!!!!!!!!

Table 1. **Summary of Definitions Relevant to Drug-Related Harm**

Term	Definition*	Example
Harm occurred		
Adverse event	Harm in a patient administered a drug but not necessarily caused by a drug (16)	Traumatic death while taking lovastatin
Adverse drug reaction	Harm directly caused by a drug at normal doses† (16) *Unexpected adverse drug reaction:* *An adverse drug event whose nature or severity is not consistent with the product information (17)*	Congestive heart failure from metoprolol
Adverse drug event	Harm caused by the use of a drug (4, 18) *Effective definition in common practice:* *Harm caused by a drug or the inappropriate use of a drug*	Hematoma from tirofiban overdose
Harm may have occurred		
Medication error	Inappropriate use of a drug that may or may not result in harm (19)	Failure to renew prednisone order on transfer to medical ward
Side effect	A usually predictable or dose-dependent effect of a drug that is not the principal effect for which the drug was chosen; the side effect may be desirable, undesirable, or inconsequential (17)	(This term should be avoided when considering adverse events)
Harm did not occur		
Potential adverse drug event	Circumstances that *could* result in harm by the use of a drug but *did not* harm the patient	Receipt of roommate's felodipine but no resulting hypotension

* Definitions are abstracted from cited sources. See text for original definitions.

† The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use recently dropped the dose limits for adverse drug reactions, but it is not clear whether or when the U.S. Food and Drug Administration will adopt these revised definitions (20).

ADVERSE DRUG REACTIONS

- **Adverse reactions** = harmful effects occurring at doses intended for therapeutic effects
- **Toxicity** = higher doses, carcinogenicity, mutagenicity, teratogenicity
- **Secondary effects** = following prolonged antibiotic therapy, diuretic use with digoxin

ADVERSE DRUG REACTIONS

- **Intolerance** = low threshold to a normal pharmacodynamic action, individual variations
- **Idiosyncracy** = inherent qualitative abnormality
- **Degrees of conviction** = definitive, probable, possible, conditional, doubtful
- **Drug induced illness** = drug fever, pseudomembraneous colitis

CLASSIFICATION(CLINICAL)

- **Type A (Augmented)**

ACE inhibitors, oral anti diabetics, diuretics, β blockers, warfarin

- **Type B (Bizarre)**

Idiosyncrasy, allergy, penicillin, halothane, chloramphenicol

- **Type C (Chronic)**

NSAIDs, neuroleptics, Levodopa, Cushing syndrome, laxatives

- **Type D (Delayed)**

Carcinogenicity, mutagenicity, Extrapyramidal syndrome:

- **Type E (Ending of use)** =

Steroids, morphine, β blockers, phenytoin

ALLERGIC DRUG REACTIONS

- **Type 1** = immediate, anaphylaxis,
  Develop within minutes, lasts 1-2 hours
- **Type 2** = antibody dependant cytotoxic
  Non self, autoimmune, hemolytic anemia
- **Type 3** = immune complex mediated; vasculitis, glomerulonephritis, serum sickness
- **Type 4** = lymphocyte mediated; contact dermatitis, tuberculin test

Table 1. **Relationship of Clinical Symptoms to Drug Reactivity***

Extended Coombs and Gell Classification†	Type of Immune Response‡	Pathologic Characteristics	Clinical Symptoms‡	Covalent and Noncovalent Drug Binding§	Cell Type
Type I	IgE‖	Mast-cell degranulation	Urticaria, anaphylaxis	Covalent drug binding	B cells/Ig
Type II	IgG and FcR‖	FcR–dependent cell destruction	Blood cell dyscrasia	Covalent drug binding	B cells/Ig
Type III	IgG and complement or FcR‖	Immunocomplex deposition	Vasculitis	Covalent drug binding	B cells/Ig
Type IVa	Th 1 (IFN-γ)	Monocyte activation	Eczema	Covalent and noncovalent drug binding	T cells
Type IVb	Th 2 (IL-5 and IL-4)	Eosinophilic inflammation	Maculopapular exanthema, bullous exanthema	Covalent and noncovalent drug binding	T cells
Type IVc	CTL (perforin and granzyme B)	CD4- or CD8-mediated killing of cells (i.e., keratinocyte)	Maculopapular exanthema, eczema, bullous exanthema, pustular exanthema	Covalent and noncovalent drug binding	T cells
Type IVd	T cells (IL-8)	Neutrophil recruitment and activation	Pustular exanthema	Covalent and noncovalent drug binding	T cells

* CTL = cytotoxic T cells; FcR = Fc receptor; IFN = interferon; Ig = immunoglobulin; IL = interleukin; Th = T helper.

† Based on reference 10.

‡ Only the dominant reaction is shown. In maculopapular exanthema, type IVb and IVc reactions can occur together; in pustular exanthema, type IVb, IVc, and IVd can occur together; and in bullous exanthema, type IVc with IVb, IVa, or both can occur together. In most instances, 1 type predominates clinically (type IVc in maculopapular and bullous exanthema, type IVd in pustular exanthema). See text.

§ Covalent binding can elicit both T-cell– and B-cell–mediated immune reactions, while noncovalent presentation may elicit exclusive T-cell reactions. See text.

‖ T-cell help for Ig (e.g., IL-4, IL-5, IFN-γ).

Type of hypersensitivity	Immune effector mechanism	Clinical manifestation	Remarks
Type 1 (immediate or anaphylactic)	IgE bound to surface of mast cells or basophils. antigen (Ag) binding causes mast cell degranulation, release of histamine and other mediators	Urticaria/angioedema, asthma, anaphylaxis	Skin/prick test and intradermal test (with 15-min response) will detect it except in pseudo-allergic types
Type 2 (cytotoxic)	Antibodies (Abs) to Ag determinants on cell surface are target for IgG/IgM Abs. Cells/ tissues damaged by activated complement or by binding to cells through Fcr receptors, and activate cytotoxic killing, e.g., by K cells	Pemphigus, neutropenia, thrombocytopenia, hemolysis	Skin manifestation is rare and mainly as pemphigus
Type 3 (immune complex)	Circulating immune complex deposited in vascular beds or on tissue surfaces, complement is activated, neutrophils attracted and their products damage tissues	Hypersensitivity vasculitis, Henoch-Schonlein purpura	Skin tests are of no value
Type 4 (delayed type)	T-lymphocytes (CD4 or CD8) producing different patterns of cytokines and/or cytotoxic factors		Can be elicited by patch testing or intradermal test read after 48 h
Type 4a	Th1-Tc1 cells: IFN-g, TNF-a	Contact dermatitis, tuberculin reaction	
Type 4b	Th2 cells: IL-4/-13, IL-5, Eosinophils	Maculopapular rash, exanthema with eosinophilia	
Type 4c	Cytotoxic T-cells: Perforin, Granzyme-B, Granulysin	Contact dermatitis, maculopapular drug rash, Stevens-Johnson syndrome, Toxic epidermal necrosis	
Type 4d	T-cells: CXCL-8, GM-CSF, neutrophils	Acute generalized exanthematous pustulosis	

Modified after Friedman and Ardern-Jones.[3] Abs: Antibodies, TNF-α: Tumor necrosis factor-α,

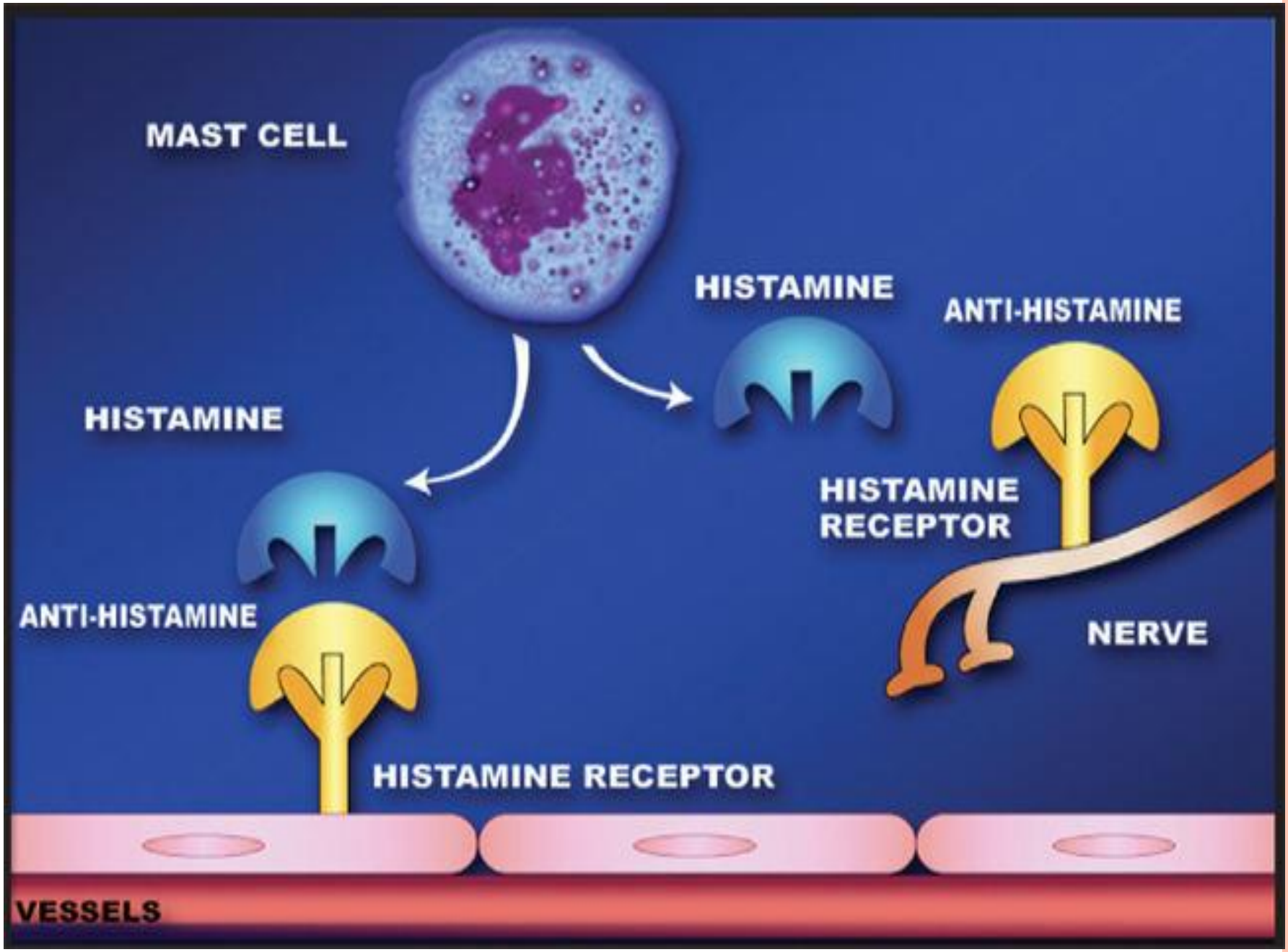
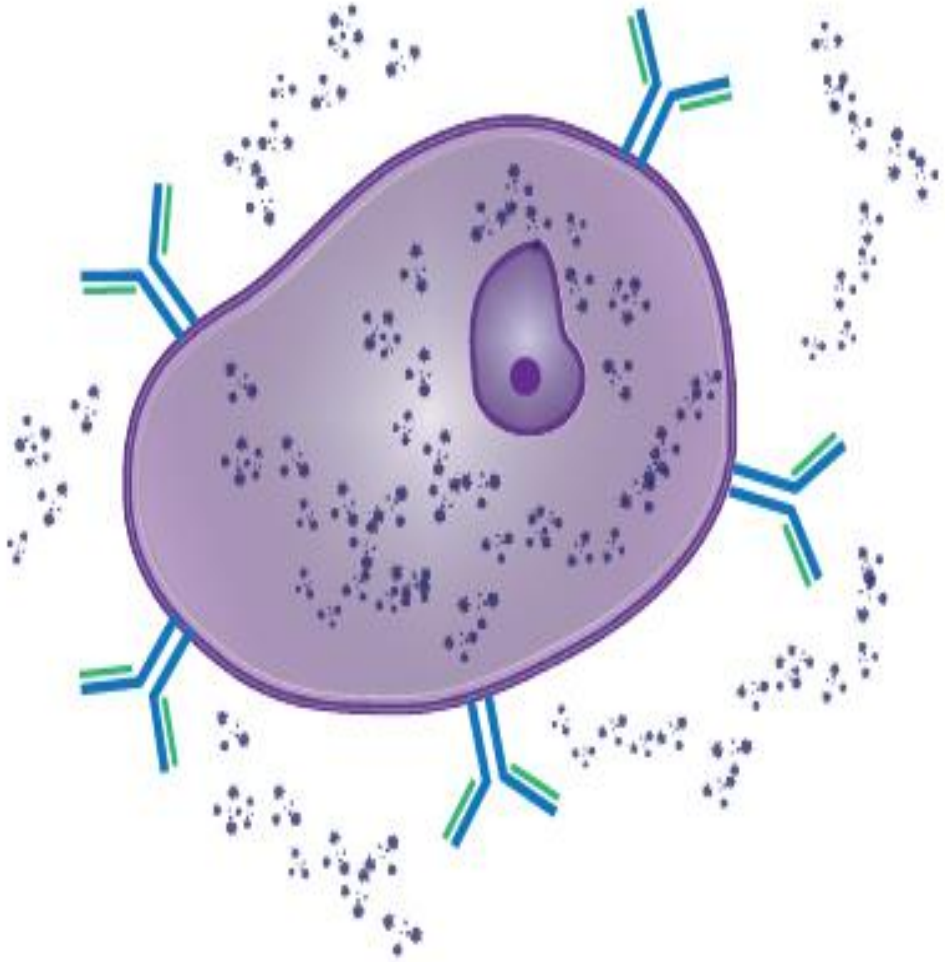
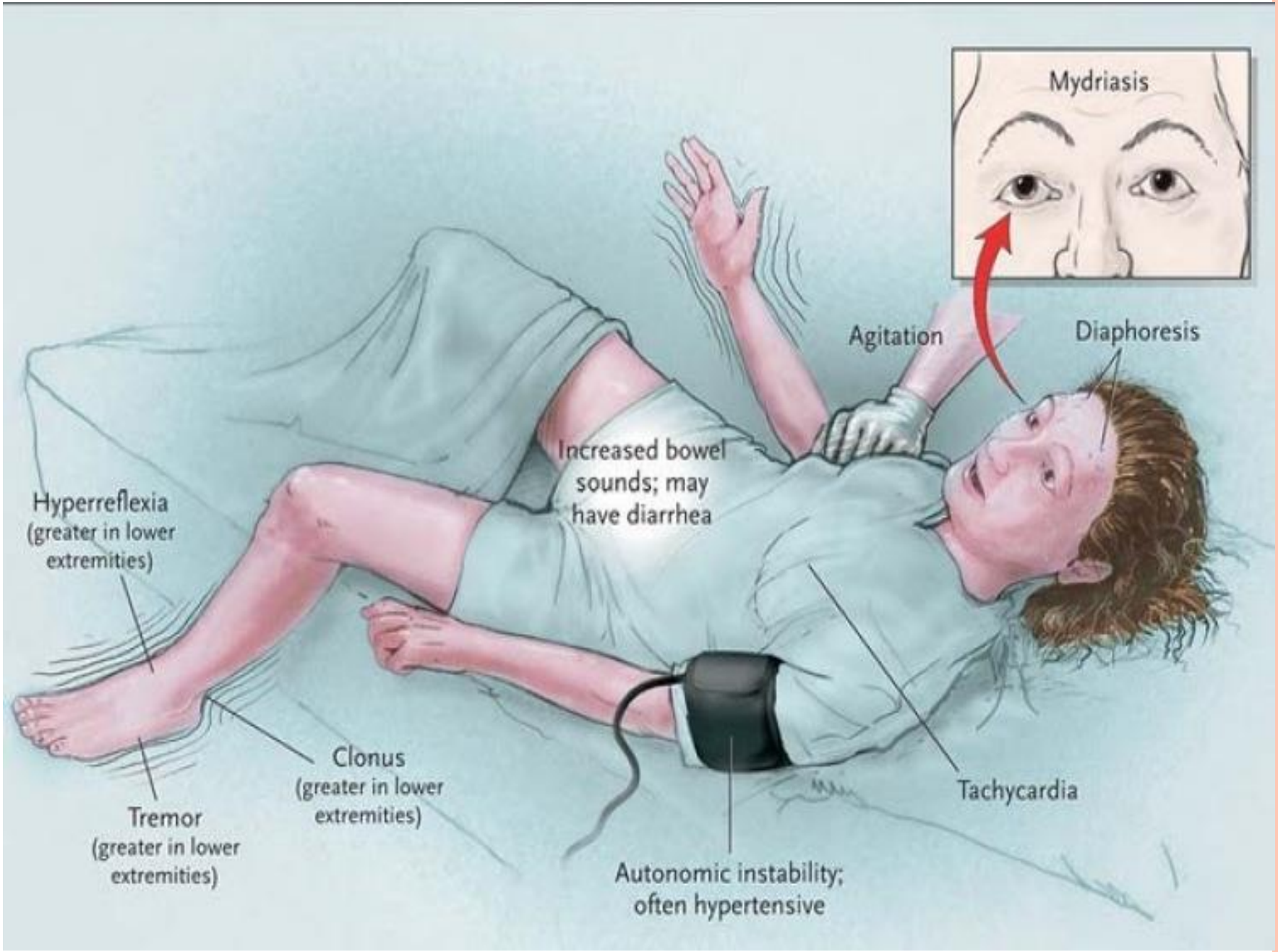

MAST CELL
HISTAMINE
ANTI-HISTAMINE
HISTAMINE
HISTAMINE
RECEPTOR
ANTI-HISTAMINE
NERVE
HISTAMINE RECEPTOR
VESSELS

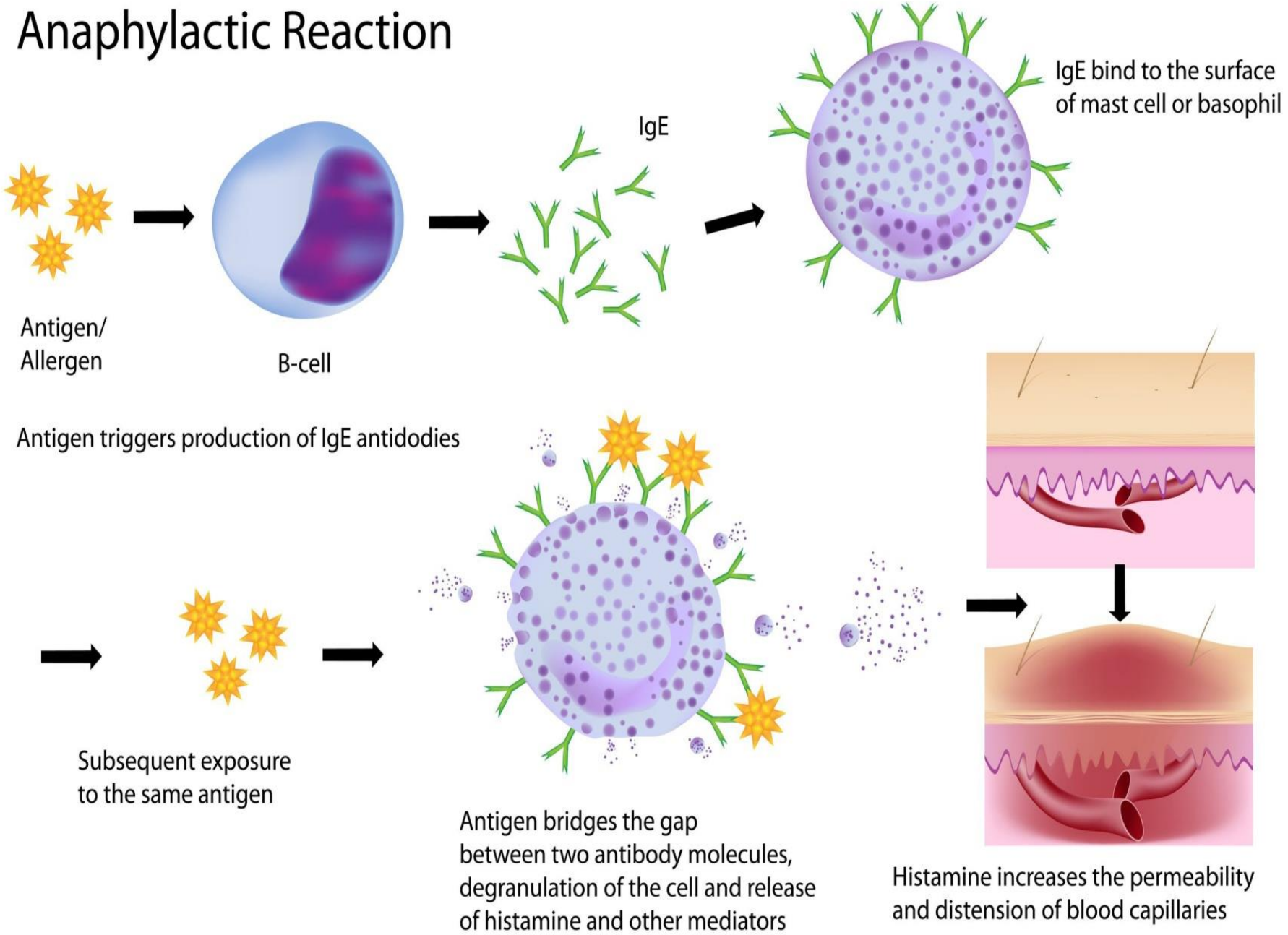
Figure 2: *Mast cell*

Ig-E antibodies on the surface of mast cells, when activated by a medication, cause the mast cell to release chemical mediators into the tissue and blood.



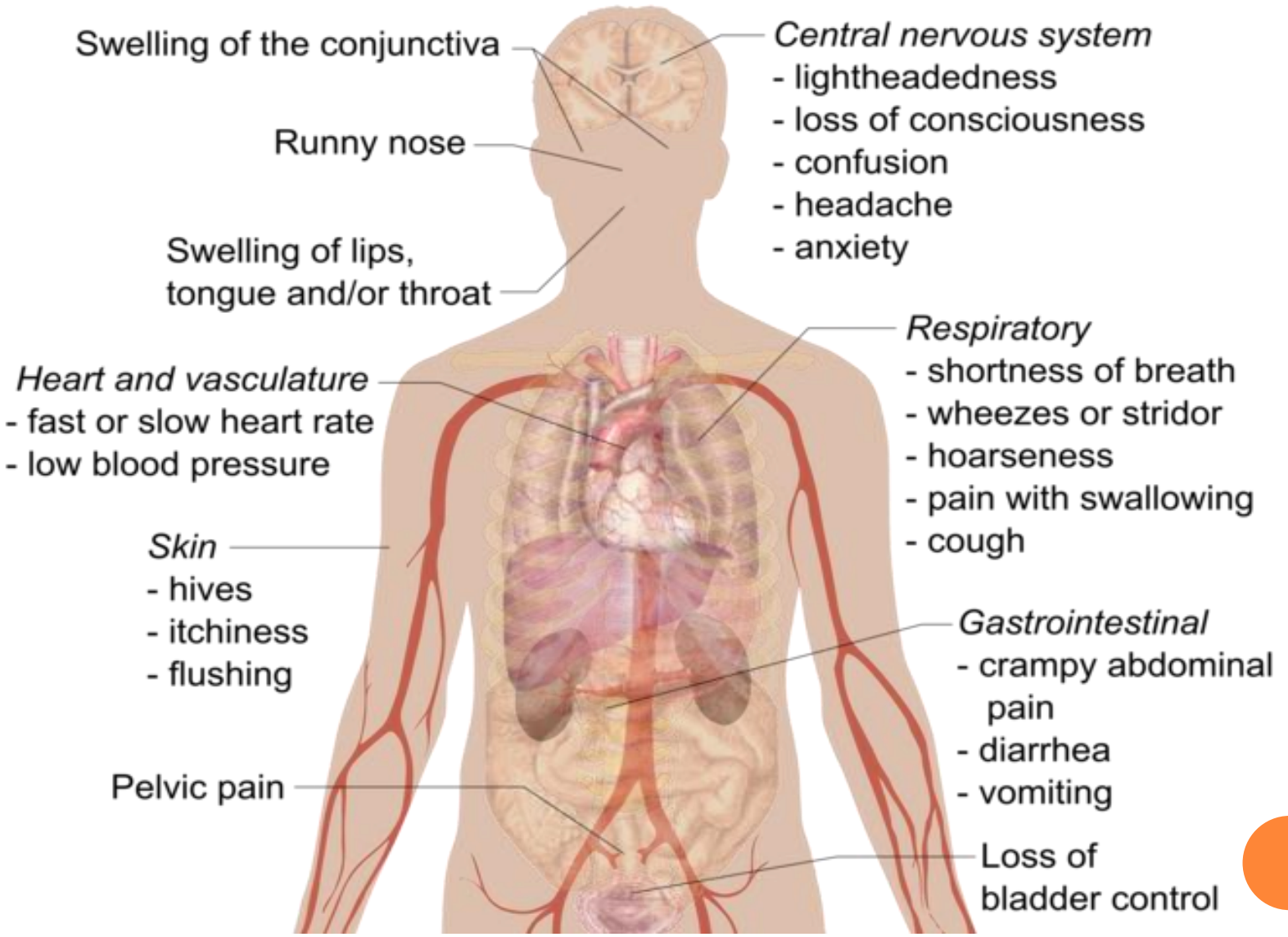

Mydriasis
Agitation
Diaphoresis
Increased bowel sounds; may have diarrhea
Hyperreflexia (greater in lower extremities)
Clonus (greater in lower extremities)
Tremor (greater in lower extremities)
Tachycardia
Autonomic instability; often hypertensive

Anaphylactic Reaction



Signs and symptoms of

Anaphylaxis



TREATMENT OF ANAPHYLAXIS

- **Adrenaline;**

  0.5 ml of 1 in 1000 solution; S/C or I/V (not the nor adrenaline)

- **Anti histamine**;

  Chlorpheniramine, 10-20 mg

- **Hydrocortisone;**

  100-300 mg, within 30 min:

- **Colloid solutions** (not crystalloids)
- **Oxygen and artificial ventilation**

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