HISTAMINE & ANTIHISTAMINICS

Dr. Nashwa Aborayah

Associate professor of clinical and experimental pharmacology

Mu‘tah University- Faculty of Medicine

OBJECTIVES

- What is an antihistaminic?
- What causes allergies and what are they?
- What is histamine?
- Classes of antihistaminics
- Clinical uses of antihistaminics
- Adverse effects of antihistaminics

WHAT IS AN ANTIHISTAMINIC?

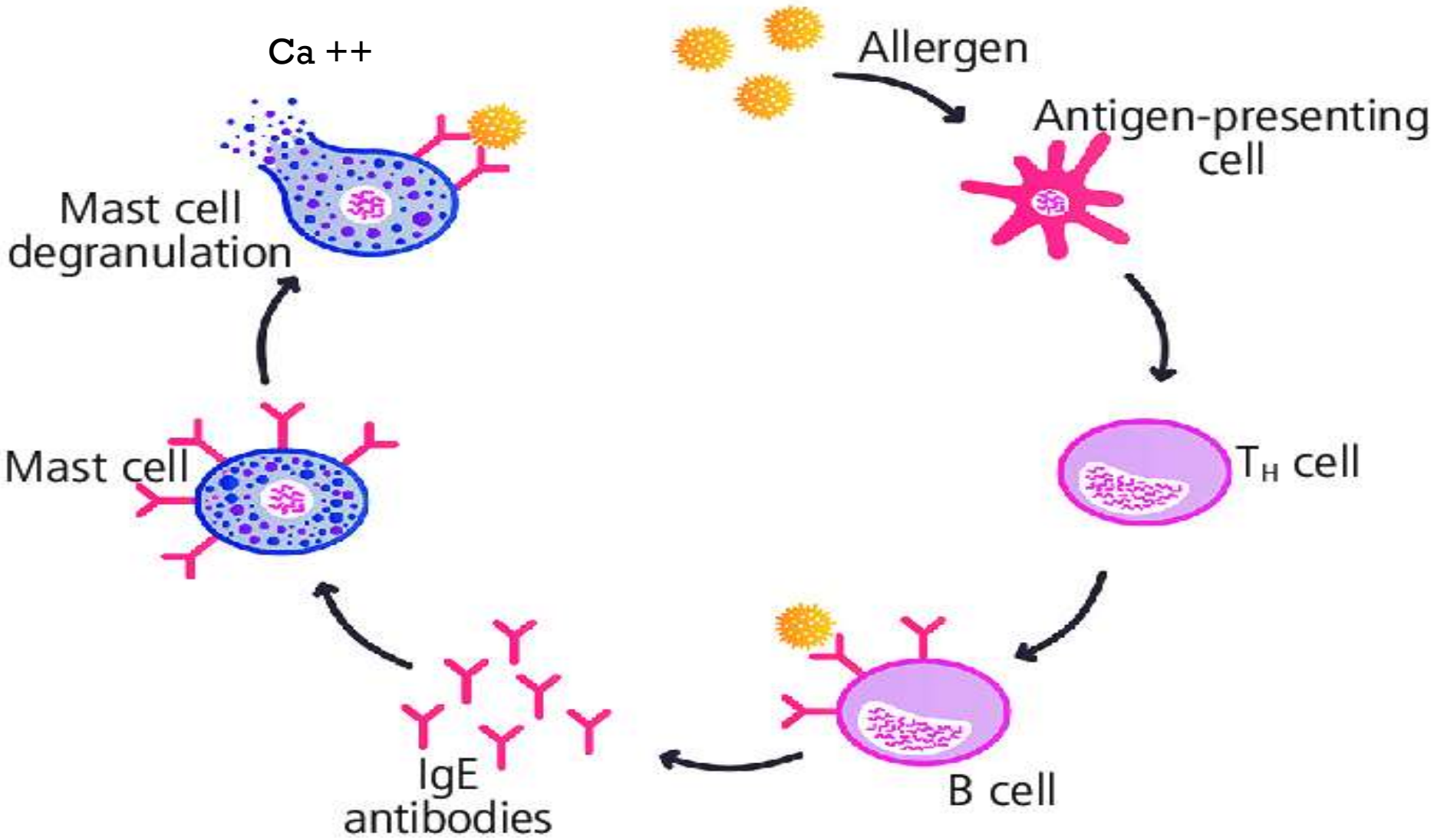
- A drug that reduces or eliminates the effects mediated histamine
- The term antihistamine **only refers to H_1 receptor antagonists**
- Antihistamines compete with histamine for binding sites at the receptors
- Antihistamine cannot remove the histamine if it is already bound
- More effective in preventing the actions of histamine rather than reversing them
- Should be given early in treatment, before all the histamine binds to the receptors

THE HISTAMINE RECEPTORS

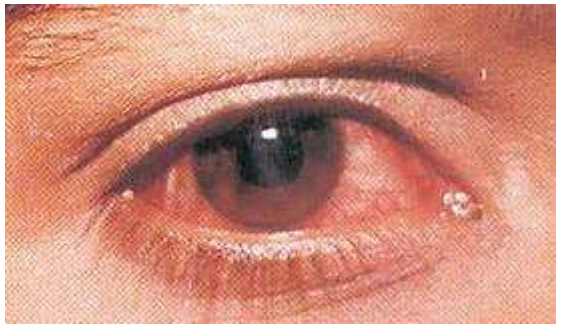
	Location	Type of receptor	Effect	Treatment
H1	Throughout the body, specifically in smooth muscles, on vascular endothelial cells, CNS, exocrine glands, nerve endings	G-protein coupled, linked to intercellular Gq	smooth muscle relaxation VD- Sedation- increase exocrine secretions- itching	Allergies, nausea, sleep disorders
H2	gastric parietal cells, heart	G-protein coupled, linked to intercellular Gs	Increases the release of gastric acid Increase cardiac contractility	Stomach ulcers
H3	Found mostly in the CNS, in small intestine, testis and prostate.	G-protein coupled, possibly linked to intercellular Gi	Neural presynaptic receptor: release control	Unknown
H4	They were recently discovered in 2000. They are widely expressed in the immune system such as the spleen, thymus and leukocytes.	Unknown, most likely also G-protein coupled	Unknown	In addition to benefiting allergic conditions, research in the h4 receptor may lead to the treatment of autoimmune diseases. (rheumatoid arthritis and IBS)

WHAT ARE ALLERGIES?

- Allergies are caused by a hypersensitivity reaction of the antibody class **IgE** (which are located on mast cells in the tissues and basophils in the blood)
- When an allergen is encountered, it binds to IgE, which excessively activates the mast cells or basophils, leading them to release massive amounts of histamines.
- These histamines lead to inflammatory responses ranging from runny nose to anaphylactic shock

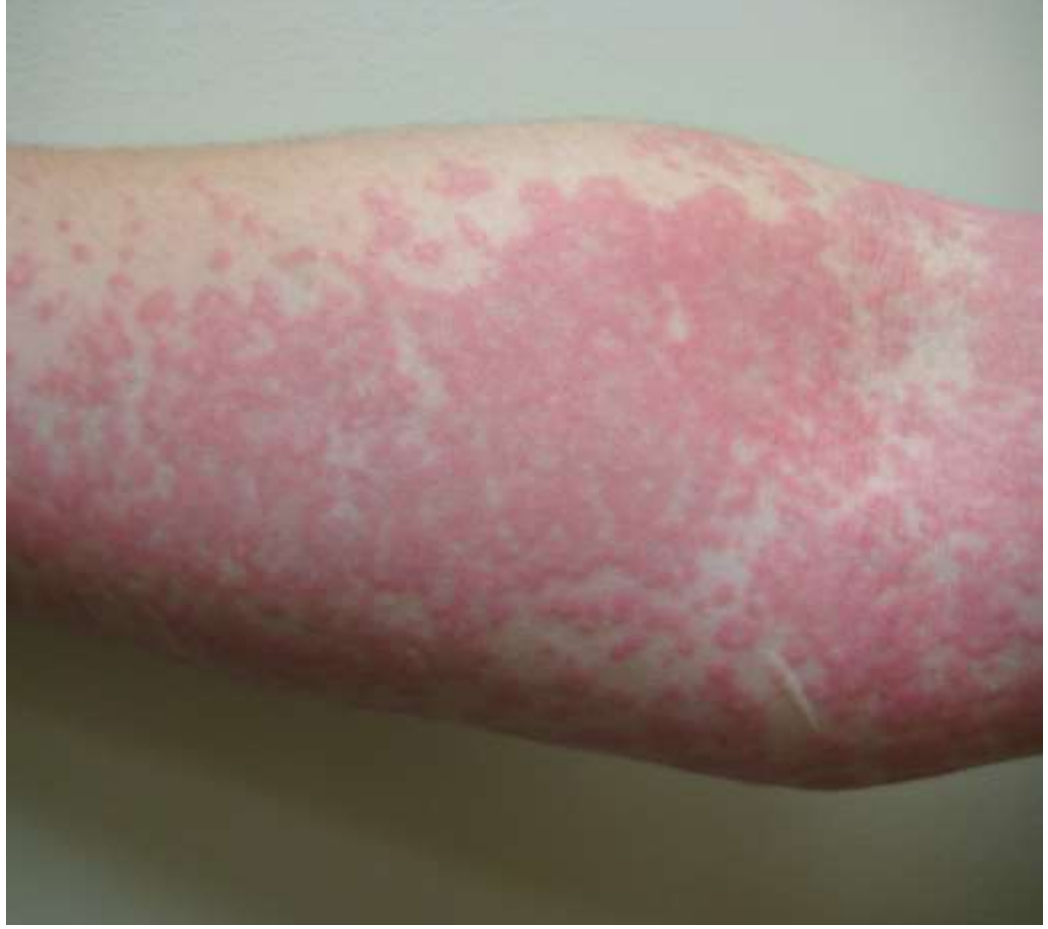

Ca ++
Allergen
Antigen-presenting cell
Mast cell degranulation
Mast cell
T_H cell
IgE antibodies
B cell

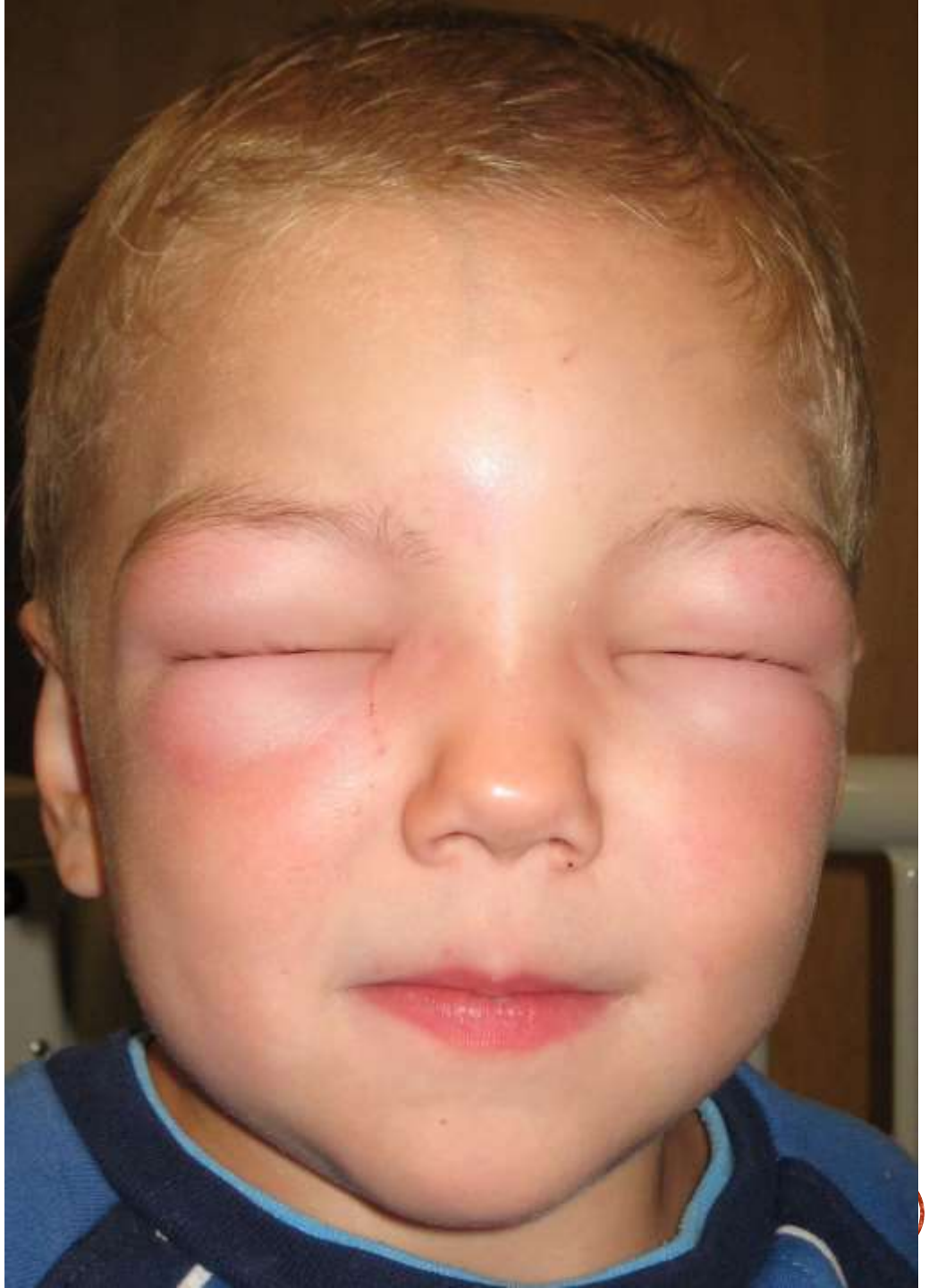
CLINICAL USES OF ANTIHISTAMINES



- **1- Allergy**:
- Allergic rhinitis (common cold)
- Allergic conjunctivitis (pink eye)
- Allergic dermatological conditions:
- A- Urticaria (hives)
- B- Angioedema (swelling of the skin)
- C- Pruritus (atopic dermatitis, insect bites)
- Anaphylactic reactions (severe allergies)

- **2- Motion sickness, vertigo** (first generation H_1-antihistamines)
- 3- **Carcinoid syndrome**: cyproheptadine





HISTAMINE VS. ANTIHISTAMINE EFFECTS

Cardiovascular (small blood vessels)

- Histamine effects:
  - Dilation and increased permeability (swelling, redness)
- Antihistamine effects:
  - Prevent dilation of blood vessels
  - Prevent increased permeability

HISTAMINE VS. ANTIHISTAMINE EFFECTS

Smooth Muscle (on exocrine glands)

- Histamine effects:
  - Stimulate salivary, gastric, lacrimal, nasal and bronchial secretions
- Antihistamine effects:
  - Prevent salivary, gastric, lacrimal, nasal and bronchial secretions

HISTAMINE VS. ANTIHISTAMINE EFFECTS

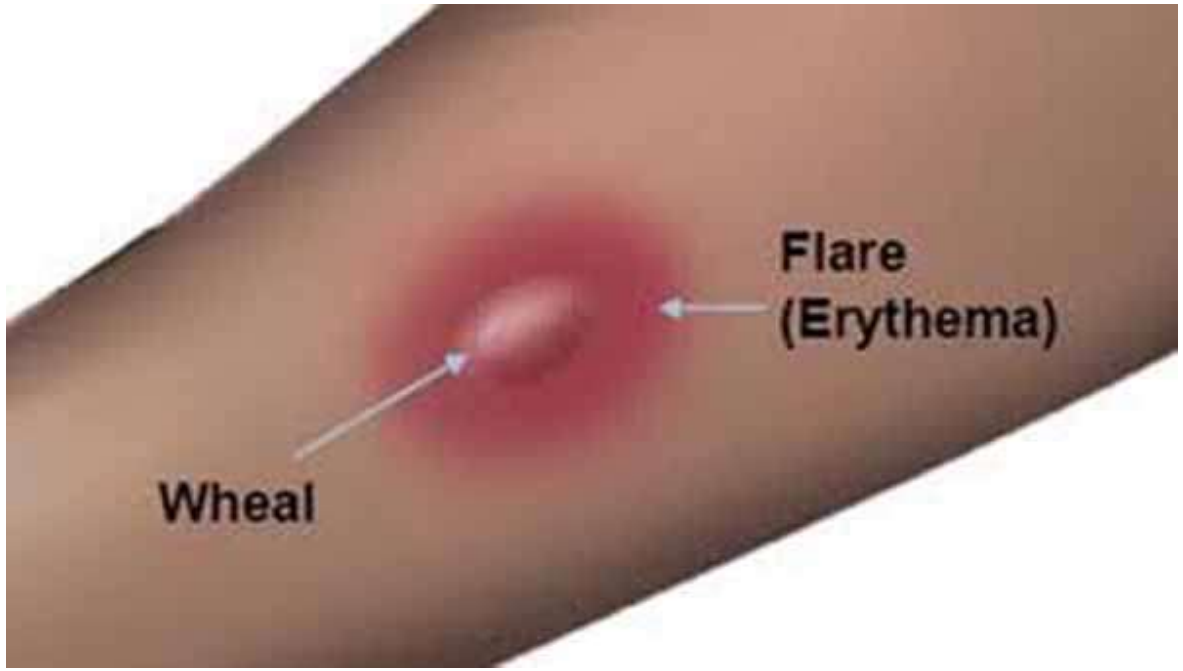
Immune System

(Release of substances commonly associated with allergic reactions)

- Histamine effects:
  - Mast cells release histamine and other substances, resulting in allergic reactions.
- Antihistamine effect:
  - Binds to histamine receptors, thus preventing histamine from causing a response.

ANTIHISTAMINES: OTHER EFFECTS

- Wheal-and-flare formation, itching
- **Anticholinergic?**
- **Sedative**?



HOW TO ANTAGONIZE HISTAMINE EFFECTS?

- 1- Physiologic antagonism
- 2- Receptor antagonism
- 3- Mast cell stabilizers
- 4- Immunotherapy

ADVERSE SIDE EFFECTS

- **Associated with the first generation H_1-antihistamines and due to their lack of selectivity for the H_1 receptor and anti-cholinergic activity.**
- **Sedation:** due to CNS depression
- **EXCITATION** in children under 6 years age (atropine-like)
- Blurred vision, dry mouth, urine retention (esp. old age), glaucoma (old age), tachycardia **(atropine-like action)**
- **Alpha blocking action**: orthostatic hypotension
- **Serotonin blocker** (cyproheptadine): weight gain, dry mouth, drowsiness
- Newer second generation H1-antihistamines are more selective for the peripheral histamine receptors and have less side effects, BUT
- **Serious types of arrhythmias(fatal)**: prolongation of QT-interval: astemizole

FIRST GENERATION H_1 RECEPTOR ANTAGONIST

- **1- Ethylenediamines**: mepyramine
- **2- Ethanolamines**: Diphenhydramine: Oldest and most effective antihistamine on the market
- Available over the counter
- Because it induces sedation, it's used in nonprescription sleep aids
- Dimenhydrinate: Anti-emetic
- **3- Alkylamines**: chlorphenramine
- **4-Piperazines**: cyclizine: motion sickness
- Cetirizine (Zyrtec): allergies and is safe to use in children as young as 2
- **5- Tricyclics**: Promethazine (Phenegran): It was originally used as an antipsychotic, however now it is most commonly used as a sedative or antiemetic drug (also severe morning sickness) and requires a prescription

SECOND GENERATION H_1-RECEPTOR ANTAGONISTS

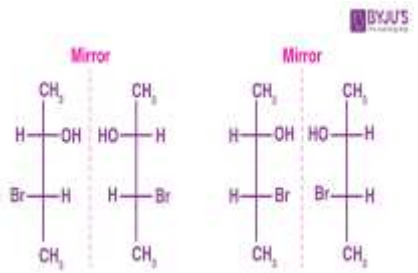
- These are the newer drugs and they are much more selective for the peripheral H1-receptors involved in allergies than to the H1-receptors in the CNS
- Therefore, these drugs provide the same relief with many fewer adverse side effects
- They are less lipophilic than the first generation drugs, therefore they do not cross the BBB as readily

SECOND GENERATION H_1-RECEPTOR ANTAGONISTS

- Astemizole:
- it has been taken off the market in most countries because of adverse interactions with erythromycin and grapefruit juice(microsomal enzyme inhibitors)
- Loratidine:
- It is the only drug of its class available over the counter
- It has long lasting effects and does not cause drowsiness because it does not cross the BBB

1st generation	2nd generations
• Short to intermediate action	• Long acting
• BBB cross	• Poor penetration
• Sedative action	• No
• Produce anti muscurnic side effects	• No
• Also block auonomic receptors	• No
• Cheap	• Relatively expensive

THIRD GENERATION H_1-RECEPTOR ANTAGONISTS



- These drugs are derived from second generation antihistamines
- They are either the active enantiomer or metabolite of the second generation drug designed to have increased efficacy and fewer side effects

Levocetirizine (Zyzal)

- This drug is the active enantiomer of cetirizine
- Also it is not metabolized and is likely to be safer than other drugs due to a lack of possible drug interactions.
- It does not cross the BBB and does not cause significant drowsiness

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THANK YOU