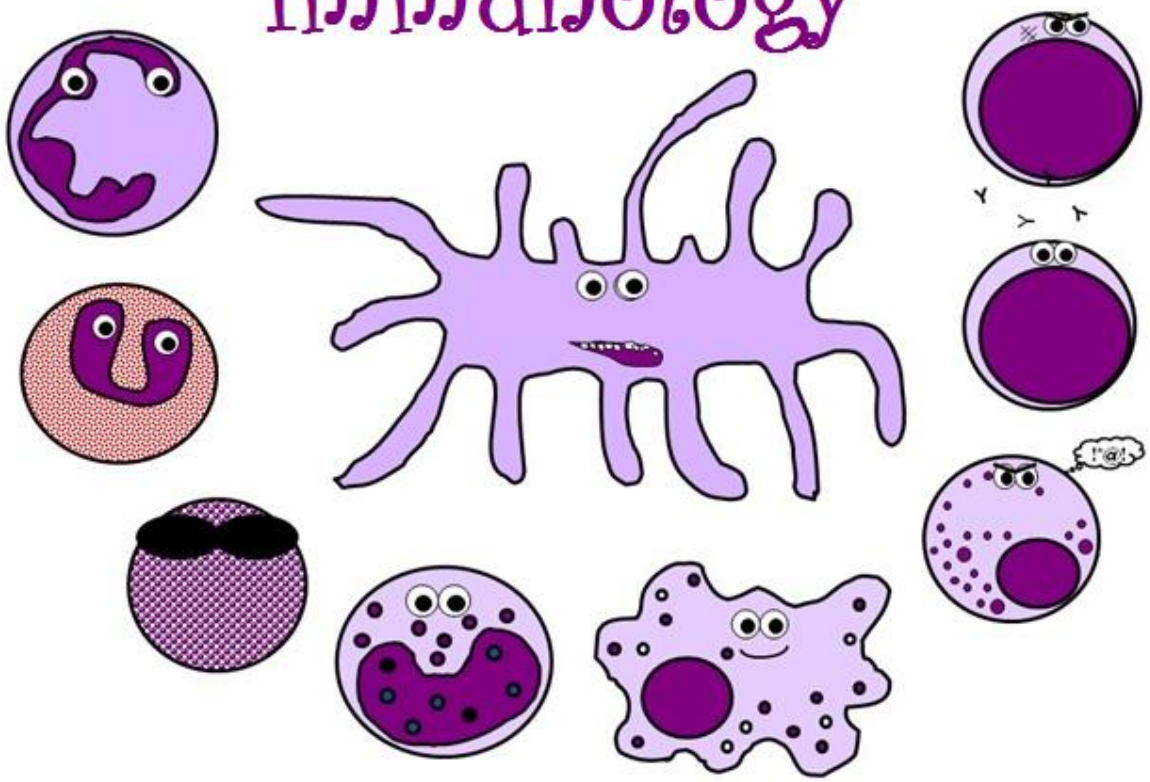
Immunology



Sheet Slides

Number: 17

Subject: Acute Systemic Anaphylaxis

Done by: *Omar Saffar*

Corrected by: John Doe

Doctor: Issa Abu-Dayyeh

CASE 49 Acute Systemic Anaphylaxis

A life-threatening immediate hypersensitivity reaction to peanuts.

Adaptive immune responses can be elicited by antigens that are not associated with infectious agents. Inappropriate immune responses to otherwise innocuous foreign antigens result in allergic or hypersensitivity reactions, and these unwanted responses can be serious. Allergic reactions occur when an already sensitized individual is reexposed to the same innocuous foreign substance, or allergen. The first exposure generates allergen-specific antibodies and/or T cells; reexposure to the same allergen, usually by the same route, leads to an allergic reaction.

Acute systemic anaphylaxis is a type I IgE-mediated hypersensitivity reaction (Fig. 49.1) that is rapid in onset and can cause death. There is typically involvement of at least two organ systems, including the skin, respiratory, gastrointestinal, cardiovascular, or central nervous systems. As with any type I hypersensitivity reaction, the first exposure to the allergen generates allergen-specific IgE antibodies, which become bound to Fc receptors (FcεRI) on the surface of mast cells. On repeat exposure to allergen, cross-linking of IgE bound to FcεRI on mast cells and basophils leads to degranulation, with the release of preformed mediators such as histamine and tryptase and the synthesis and release of other mediators such as prostaglandins and leukotrienes. Histamine is a major mediator of the immediate effects of anaphylaxis, causing multiple symptoms including increased permeability of blood vessels, which can cause life-threatening hypotension. The mast-cell mediators important for anaphylaxis, and the clinical consequences of their release, are illustrated in Fig. 49.2.

Allergens introduced systemically are most likely to cause a serious anaphylactic reaction through the activation of sensitized connective tissue mast cells. The disseminated effects on the circulation and on the respiratory system are the most dangerous, and localized swelling of the upper airway can cause suffocation. Ingested antigens cause a variety of symptoms through their action on mucosal mast cells.

Any protein allergen can provoke an anaphylactic reaction, but those that most commonly cause acute systemic anaphylaxis are foods, medications, and insect venoms (Fig. 49.3). Proteins in food, most commonly milk, soy beans, eggs, wheat, peanuts, tree nuts, and shellfish, can also cause systemic anaphylaxis. Contact with protein antigens found in latex, a common

This case was prepared by Raif Geha, MD, in collaboration with Lisa Bartnikas, MD.

Topics bearing on this case:
Class I hypersensitivity reactions
Allergic reactions to food
Mast-cell activation via IgE

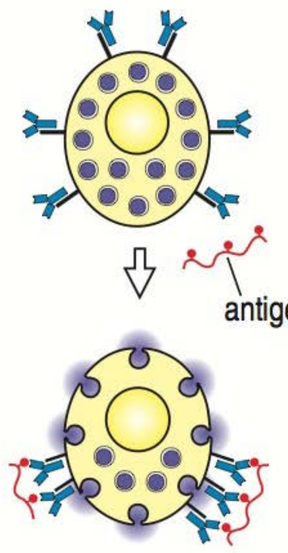
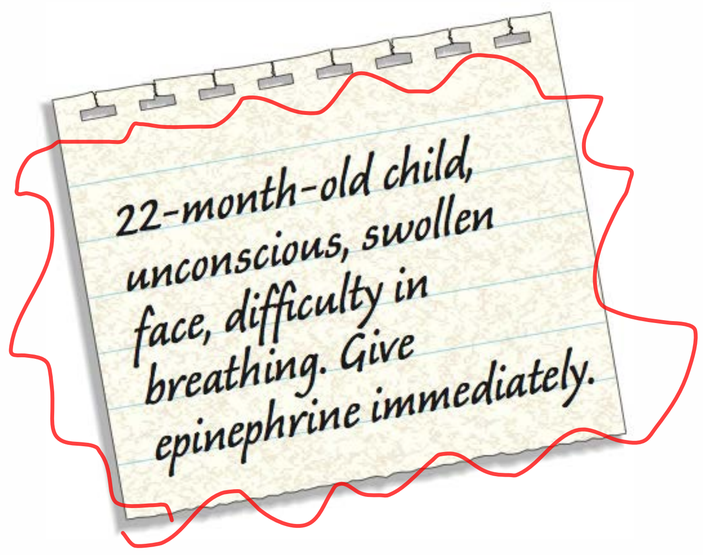
Type I immune-mediated tissue damage	
Immune reactant	IgE antibody
Antigen	Soluble antigen
Effector mechanism	Mast-cell activation
	
Example of hypersensitivity reaction	Allergic rhinitis, allergic asthma, systemic anaphylaxis

Fig. 49.1 Type I immunological hypersensitivity reactions. Type I hypersensitivity reactions involve IgE antibodies and the activation of mast cells (see also Case 50).



constituent of rubber gloves, is also known to cause anaphylaxis. In addition, small-molecule antibiotics such as penicillin can act as haptens, binding to host proteins.

Type I allergic responses are characterized by the activation of allergen-specific CD4 helper cells (T_H2 cells) and the production of allergen-specific IgE antibody. The allergen is captured by B cells through their antigen-specific surface IgM and is processed so that its peptides are presented by MHC class II molecules to T-cell receptors of antigen-specific T_H2 cells. The interleukins IL-4 and/or IL-13 produced by the activated T_H2 cells induce a switch to the production of IgE, rather than IgG, by the B cell (see Fig. 2.4). However, allergen-specific IgE antibodies can exist without the occurrence of anaphylaxis, suggesting that factors other than IgE may be required.

This case concerns a child who suffered from life-threatening systemic anaphylaxis caused by an allergy to peanuts.

The case of John Mason: a life-threatening immune reaction.

John was healthy until the age of 22 months, when he developed swollen lips while eating cookies containing peanut butter. The symptoms disappeared in about an hour. A month later, while eating the same type of cookies, he started to vomit, became hoarse, had great difficulty in breathing, started to wheeze and developed a swollen face. He was taken immediately to the emergency room of the Children's Hospital, but on the way there he became lethargic and lost consciousness.

On arrival at hospital, his blood pressure was catastrophically low at 40/0 mmHg (normal 80/60 mmHg). His pulse was 185 beats min^{-1} (normal 80–90 beats min^{-1}), and his respiratory rate was 76 min^{-1} (normal 20 min^{-1}). His breathing was labored. An anaphylactic reaction was diagnosed and John was immediately given an intramuscular injection of 0.15 ml of a 1:1000 dilution of epinephrine (adrenaline). An intravenous solution of normal saline was infused as a bolus. The antihistamine Benadryl (diphenhydramine hydrochloride) and the anti-inflammatory corticosteroid Solu-Medrol (methylprednisolone) were also administered intravenously. A blood sample was taken to test for histamine and the enzyme tryptase.

Mediators of anaphylaxis		
Mediator	**Action**	**Signs/symptoms**
Histamine	Vasodilation, bronchoconstriction	Pruritus, swelling, hypotension, diarrhea, wheezing
Leukotrienes	Bronchoconstriction	Wheezing
Platelet-activating factor*	Bronchoconstriction, vasodilation	Wheezing, hypotension
Tryptase	Proteolysis	Unknown

Fig. 49.2 Mediators released by mast cells during anaphylaxis and their clinical consequences. *Platelet-activating factor is not released by mast cells but by neutrophils, basophils, platelets, and endothelial cells.

IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs Serum Venoms	Intravenous (either directly or following oral absorption into the blood)	Edema Vasodilation Tracheal occlusion Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Insect bites Allergy testing	Subcutaneous	Local increase in blood flow and vascular permeability
Allergic rhinitis (hay fever)	Pollens (ragweed, timothy, birch) Dust-mite feces	Inhaled	Edema of nasal mucosa Irritation of nasal mucosa
Allergic asthma	Danders (cat) Pollens Dust-mite feces	Inhaled	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Shellfish Milk Eggs Fish Wheat	Oral	Vomiting Diarrhea Pruritus itching Urticaria (hives) Anaphylaxis (rarely)

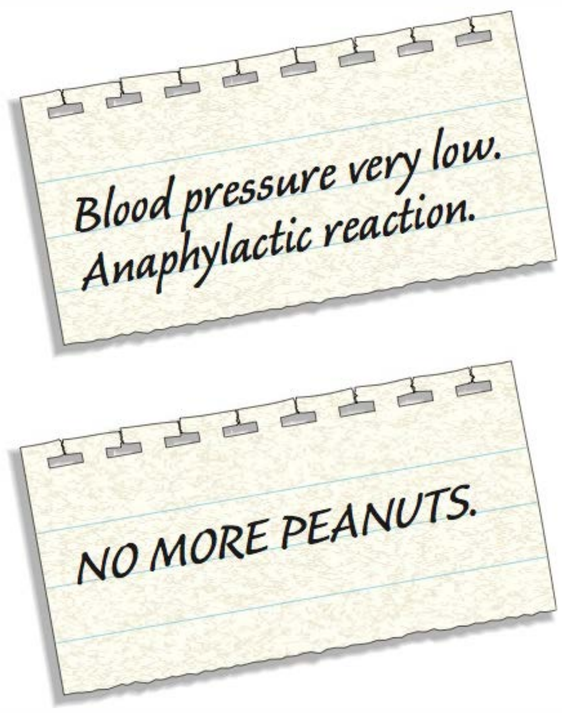
Fig. 49.3 IgE-mediated reactions to extrinsic antigens. All IgE-mediated responses involve mast-cell degranulation, but the symptoms experienced by the patient can be very different depending on whether the allergen is injected, inhaled, or eaten, and depending on the dose of the allergen.

Within minutes of the epinephrine injection, John's hoarseness improved, the wheezing diminished, and his breathing became less labored (Fig. 49.4). His blood pressure rose to 50/30 mmHg, the pulse decreased to 145 beats min^{-1} and his breathing to 61 min^{-1}. Thirty minutes later, the hoarseness and wheezing got worse again and his blood pressure dropped to 40/20 mmHg, his pulse increased to 170 beats min^{-1} and his respiratory rate to 70 min^{-1}.

John was given another intramuscular injection of epinephrine and was made to inhale nebulized albuterol (a β_2-adrenergic agent). This treatment was repeated once more after 30 minutes. One hour later, he was fully responsive, his blood pressure was 70/50 mmHg, his pulse was 116 beats min^{-1} and his respiratory rate had fallen to 46 min^{-1}. John was admitted to the hospital for further observation.

Treatment with Benadryl and methylprednisolone intravenously every 6 hours was continued for 24 hours, by which time the facial swelling had subsided and John's blood pressure, respiratory rate, and pulse were normal. He had stopped wheezing and when the doctor listened to his chest with a stethoscope it was clear.

He remained well and was discharged home with an Epi-Pen. His parents were instructed to avoid giving him foods containing peanuts in any form, and were asked to bring him to the Allergy Clinic for further tests.



Acute systemic anaphylaxis.

Anaphylaxis presents a medical emergency and is the most urgent of clinical immunologic events; it requires immediate therapy. It results from the generation and release of a variety of potent biologically active mediators and their concerted effects on a number of target organs. John showed classic rapid-onset symptoms of anaphylaxis, starting with vomiting and swelling of the

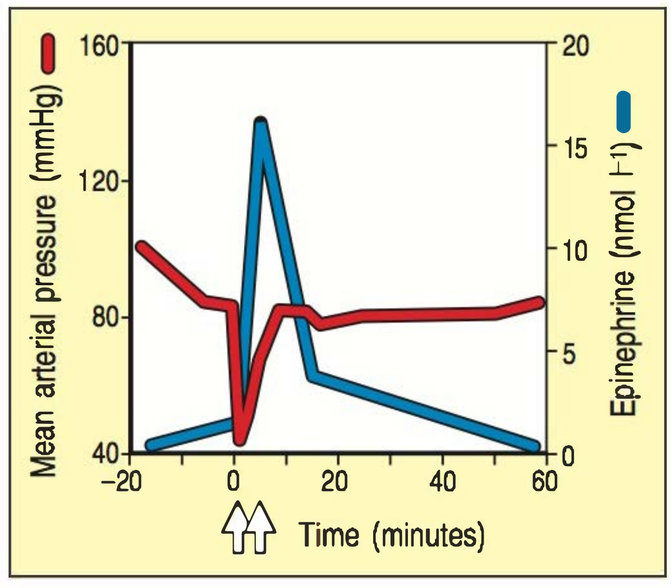


Fig. 49.4 Mean arterial pressure and epinephrine levels in a representative patient with insect-sting anaphylactic shock. Time 0 indicates the onset of the anaphylactic reaction as reported by the patient. The arrows indicate administration of antihistamines and epinephrine.

face and throat, and constriction of the bronchial smooth muscle, which led to his difficulty in breathing. This was soon followed by a catastrophic loss of blood pressure, due to leakage of fluid from the blood vessels. Anaphylaxis can also cause urticaria (hives), heart arrhythmias, and myocardial ischemia, and gastrointestinal symptoms such as nausea, vomiting, and diarrhea. All these signs and symptoms can occur singly or in combination.

Fatal allergic reactions to the venoms in bee and wasp stings have been recognized for at least 4500 years and account today for roughly 40 deaths each year in the United States. In 1902, Portier and Richet reported that a second injection of a protein from a sea anemone caused a fatal systemic reaction in dogs that had been injected previously with this protein. Because this form of immunity was fatal rather than protective, it was termed 'anaphylaxis' to distinguish it from the 'prophylaxis' (protection) generated by immunization.

Anaphylaxis requires a latent period for sensitization after the first introduction of antigen followed by reexposure to the sensitizing agent, which can be any foreign protein or a hapten. In the early part of the 20th century, the most frequent cause of systemic anaphylaxis was horse serum, which was used as a source of antibodies to treat infectious diseases.

In many cases, the presentation of food allergy occurs on the first known ingestion, suggesting that routes other than the oral one may be important in sensitization. For example, epidemiologic data suggest that sensitization to peanut protein may occur in children through the application of peanut oil to inflamed skin. A recent study demonstrated that the incidence of peanut allergy in children who avoided peanut ingestion correlated with the level of peanut consumption in their homes, which is consistent with the skin's being an important route of allergen sensitization. At present there is no cure for food allergy. Current therapy relies on allergen avoidance and the treatment of severe reactions with epinephrine.

Anaphylaxis is increasing in prevalence and is a frequent cause of visits to the emergency room, with 50–2,000 episodes per 100,000 persons, or a lifetime prevalence of 0.05–2.0%. The rate of fatal anaphylaxis from any cause is estimated at 0.4 cases per million individuals per year. Although in John's case the reaction was brought on by eating a food, an antigen administered by subcutaneous, intramuscular, or intravenous injection is more likely to induce a clinical anaphylactic reaction than one that enters by the oral or respiratory route.

Questions.

1 *Anaphylaxis results in the release of a variety of chemical mediators from mast cells, such as histamine and leukotrienes. Angioedema (localized swelling caused by an increase in vascular permeability and leakage of fluid into tissues) is one of the symptoms of anaphylaxis. With the above in mind, why did John get hoarse and why did he wheeze?*

2 *When his parents brought John back to the Allergy Clinic, a nurse performed several skin tests by pricking the epidermis of his forearm with a shallow plastic needle containing peanut antigens. John was also tested in a similar fashion with antigens from nuts as well as from eggs, milk, soy, and wheat. Within 5 minutes John developed a wheal, 10 mm × 12 mm*

in size, surrounded by a red flare, 25 mm × 30 mm (see Fig. 50.5), at the site of application of the peanut antigen. No reactions were noted to the other antigens. A radioallergosorbent test (RAST) was performed on a blood sample to examine for the presence of IgE antibodies against peanut antigens. It was positive. What would you advise John's parents to do?

3 Why was John treated first with epinephrine in the emergency room?

4 Why was John given a blood test for histamine and the enzyme tryptase?

5 Why was the skin testing for peanuts not done in the hospital immediately after John had recovered, instead being done at a later visit?

6 The incidence of peanut allergy is increasing. Why?

7 John's parents want to know whether there are therapies that might cure him of his peanut allergy. What do you tell them?

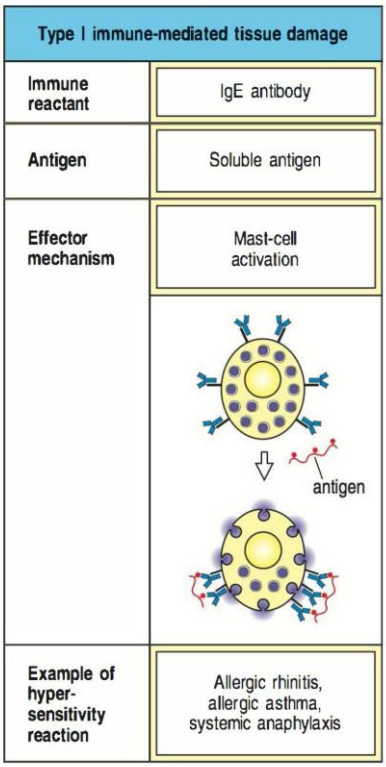
بسم الله الرحمن الرحيم

Doctor Notes

❁ Anything written in italic is extra information

We have 4 types of hypersensitivity:

I. **Type 1 IgE mediated** e.g. Anaphylaxis which could be fatal if not treated
II. **Type 2 related to antibodies**, and antibody dependent cytotoxicity ADCC
III. **Type 3 related to antibody-antigen complex**, the body should clear this complex yet in this condition these complexes accumulate in the body and cause problems e.g. SLE
IV. **Type 4 related to cell mediated immunity** "the only type not related to antibodies" e.g. delayed type hypersensitivity



Anaphylaxis

- The special characteristic about anaphylaxis is that it involves at least two organs.
- Like the GI system "if the antigen is ingested orally", the respiratory system & the CVS and these three are involved in our case,
- And other organs like the skin and sometimes the CNS etc…

Remember: in order for the mast cell to be activated it has to be exposed to the antigen two times, the first exposure will make the IgE load on its surface, and the second one will activate it to the maximum and the anaphylactic effect will show up →release of histamine which causes HTN and bronchoconstriction *and we will see these symptoms in our case*

*Also leukotrienes play a role in bronchoconstriction!

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Platelet-activating factor*	Bronchoconstriction, vasodilation	Wheezing, hypotension
Tryptase	Proteolysis	Unknown

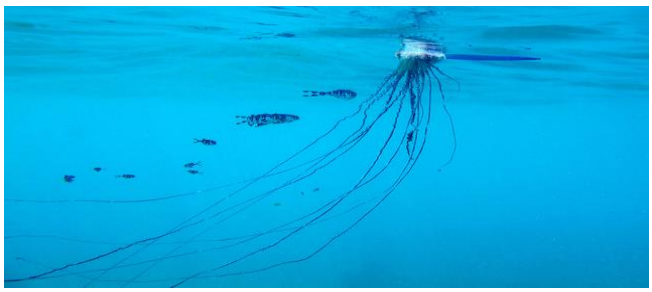
Etymology of the word "Anaphylaxis"

Anaphylaxis X Prophylaxis

- Ana- means against , -phylaxis means protect
- So anaphylaxis means "against protection → no protection "

How was it discovered?

- a study was don on the "Portuguese man of war" (a jelly fish), its sting is very dangerous and can cause anaphylactic shock1
- So a French doctor named Richet *"with dr. portier"* studied the animal's sting poison effect on dogs and found that it's the opposite to the normal sensitivity reactions,
- By applying a certain dose for the first time an allergic reaction would occur, but a second exposure to the same dose or even less would kill all the dogs instead of developing prophylaxis,
- His researches on anaphylaxis got him a noble prize in the end



- So systemic anaphylaxis occurs mainly through an IV, subcutaneous or intramuscular administration of the antigen *(e.g. bee, scorpion, snake)* to produce the anaphylactic shock (most potent routes)
- Yet other routes also possible like respiratory tract or oral administration like this case which was due to ingestion of peanuts

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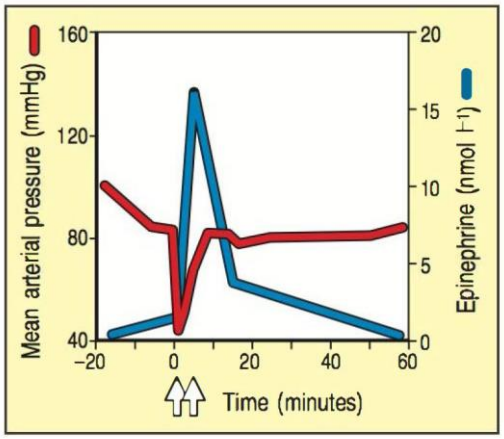
The Case

- John Mason, 22 months old baby,
- Ate peanuts and had a swollen lips on first exposure
- The Second time of eating peanuts he started to vomit, had hoarse voice, wheezing and all the other symptoms which indicates a more sever reaction.
- IgM, IgG, IgA were all elevated
- most important symptom of these is the very low blood pressure, which makes this condition very dangerous , and it happens due to loss of fluids which produces hypovolemia
- Main treatment this anaphylactic shock is **epinephrine shot!!** Which will return the blood pressure to normal immediately
- This case is similar to some extent to the case of hereditary angioedema which at that time we said at the emergency room we should give epinephrine because we were not sure that the patient is having anaphylactic shock or angioedema!
- We gave the baby anti-histamines, anti-inflammatory corticosteroids, β2-agonist "by inhalation" (albuterol).
- Blood tests for histamine and tryptase were taken
- Discharged with epi-pen, with restriction of eating peanuts.
- And asked to come back after few days for immunologic test



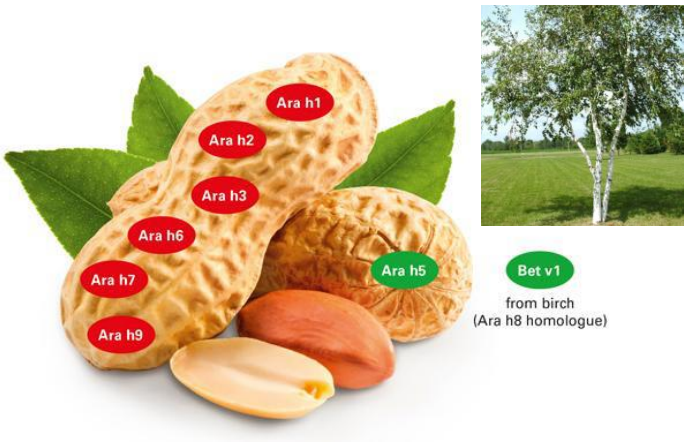
- Latest research shows that not all peanuts allergy are the same!

Statistically nuts are the main food allergens…

Ara h1, h2, h3, h6, h7, h9 are intense and strong antigens!

Ara h5 is similar to an antigen called **Bet v1** which is found in a pollen from birch tree, this similarity produces **cross-reaction** between these two, yet this cross-reaction is not as strong as the reaction occurs from the previous mentioned strong antigens.

Cross reaction may also occur between different kinds of food, *like Cinnamon!*



QUESTIONS!

1. Explain the hoarseness of voice and wheeze?

Hoarseness= Angioedema of vocal cord, may also be due to inflammation or even a tumor!

Wheeze= histamine and leukotrienes causing smooth muscle constriction of bronchial tubes.

2. Skin Prick and specific IgE blood tests revealed peanut allergy only, advice patient?

Avoid any foods containing peanuts, read food labels, ask in restaurants.

Avoid Peas! Wear bracelet, and Keep Epi-Pen injection at home or when traveling. Peas should be avoided due to high incidence of cross reaction!

3. What other drug were given to John?

Albuterol (β2-adrenergic agent) by inhalation → bronchodilation & vasoconstriction,

and also corticosteroids

4. Why was John's blood tested for histamine and tryptase?

Released by mast cells, indication of anaphylactic shock

5. Why was Skin Prick test delayed a few days and not done on the spot in the hospital?

Immediately after Anaphylactic shock, patient is unresponsive to skin prick test,

6. why?

Tachyphylaxis (lasts 72-96 hours following anaphylaxis), due to depletion of histamine and leukotrienes from mast cells and basophils

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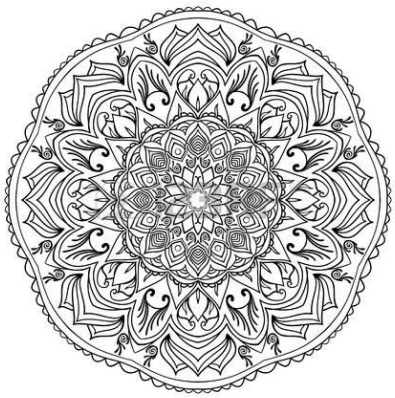

Le Fin.

"You have to go wholeheartedly into anything in order to achieve anything worth having." - Frank Lloyd Wright

Omar Saffar