

Master Answers for the Atopy and Allergy Small Group Session

The introductory vignette illustrates what the IgE response was originally designed for: parasite control

Master Answer for Case 1a & 1b

Atopy and Allergy

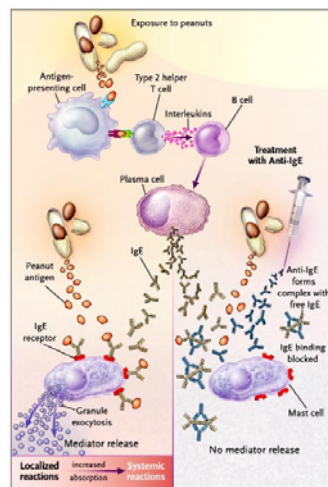
*Bees have a multi-antigen venom that is highly allergenic in genetically predisposed individuals. Class II APC presentation of these allergens by basophils, mast cells or DC to Th-2 cells and subsequent vigorous production of anti-venom protein IgE sets the stage for subsequent, occasionally severe/fatal allergic reactions. Often the individual does not recall the sensitizing event (usually in childhood). Subsequent injection of the venom by stinging leads to allergen binding to anti-bee venom IgE bearing mast cells resident in the skin. These cells degranulate and release extremely potent vasoactive mediators such as histamine, serotonin, complement cleaving enzymes, and pro inflammatory cytokines. The dissemination of these vasoactive substances and bee venom allergens by the systemic circulation to distant sites dictate the clinical response. If the distant site is gut, vasoactive and spasmogenic compounds are activated that lead to bloating, cramping and diarrhea. If the distant binding site is the pulmonary submucosa, severe bronchial asthma hypoxemia can develop. If the site is skin, diffuse urticaria (hives) and vasodilatation with erythema can develop. If the patient is intensely sensitized, systemic vasodilatation and severe hypotension ensues. In Case 1a, the nurse and patient both knew the rapid use of epinephrine (adrenaline), a drug with strong alpha and beta-adrenergic actions (more about this in another course!) would block the vasoactive responses that generate the anaphylactic reaction. Any individual sensitized to bee venom should have ready access to epinephrine, the **only** drug that will block the anaphylactic (immediate) reaction. Corticosteroids, potent hormones that can inhibit nuclear activation of genes that produce factors that up regulate pro inflammatory cytokines, will block or blunt the **late** reaction but will have no **effect** on the immediate, potentially fatal one. In vitro detection of IgE bee venom antibody formation by RAST is feasible, but unfortunately RAST reactively does not always predict in vivo pathophysiologic reactions to the same allergen. In vitro skin testing, while theoretically attractive, can be extremely dangerous and the skin tester better be prepared for an immediate infusion/injection of epinephrine to block a potential fatal reaction. The clinical strategy that uses of repeated intradermal or intramuscular injections of bee venom extracts mimics what occurs in beekeepers after repeated stings and is thought to elicit an expansion of bee venom specific DC4,25 Tregs that reroute the immune response to Th-2 helper T-cell responses and appropriate IgG (weirdly it usually is IgG4, a subclass no one really knows much about) formation and away from a predominant Th-2 response with exuberant production of IgE responses.*

In 1b, a peanut protein derivative acts as a potent allergen in the genetically predisposed individual who, by virtue of certain MHC conformations of antigen presented by Class 2 MHC, has a strong Th-2 cell response and exuberant formation of

IgE in lieu of IgG to peanut antigens. The child is a member of an atopic family that increases the likelihood of atopy. Skin exposure (dendritic cell), respiratory (pulmonary macrophages) and gut mucosa APCs can initiate the sensitization. Subsequent skin or gut exposure, where highly “armed” mast cells reside, can produce severe, sometimes fatal, reactions.

Peanut allergy is estimated to cause 30-40 deaths per year in the United States. Of great interest is the report that an oral vaccine composed of a DNA construct that encodes the production of the peanut allergen Arah-2 and encapsulated in a protected carbohydrate that enables it to migrate through the stomach has been successful in preventing IgE sensitization in mice. This DNA vaccine increases mucosal IgA levels, initiates a Th-1 response and vaccinated mice do not produce IgE antibody to the allergen.

Unfortunately, at the current time, this vaccine would probably only work on an individual who had not had **prior exposure** to peanut allergens but it's a start. As noted in your allergy lecture, the use of a monoclonal anti-IgE that inhibits mast cell activation by allergen may be useful for treatment. Interestingly, a clinical trial looking at this concept had to be halted recently because a requirement for entry into the trial was documentation of peanut allergy by skin tests and several children had severe reactions to the skin tests.



Peanut allergy

Merz, B. N Engl J Med 2003;348:975-976



Master Answer for Case 2

Atopy and Allergy

The patient may have had an exposure to penicillin as a child when treated for her “sore throat” or been exposed to it in bovine milk. Cows have been treated with penicillin for udder infections and the penicillin is excreted in the milk or cutaneously in the areas of udder inflammation. If the patient had breakdown of her skin on her fingers while milking the herd, she was exposed. Ok, unless you grew up on a dairy farm, you wouldn’t know this but I put it in to emphasize there are many ways a patient can get sensitized to a drug.

Penicillin is hydrolyzed in aqueous medium to a group of major and minor antigenic determinants; the latter can stimulate anaphylactic reactions. These very small molecules are usually ignored by the immune system but when they combine with self proteins they can act as haptens, become allergenic and incite an IgE response. Prior to the availability of the large array of non-chemically/structural related antibiotics, penicillin allergy was a significant clinical problem. She had a severe anaphylactic reaction to the penicillin in the infusion and almost died.

The lucky bracelet is a different type of hypersensitivity. Here, the divalent nickel ion leached out of the bracelet, diffused through her epidermis and combined with dermal proteins. The nickel-protein complex was then taken up by DC and presented as an antigen that induced Th1 cells that caused TMMI driven inflammation that manifested itself as a rash. Some of you, no doubt, are now wondering about poison ivy. This plant has a chemical in its leaves that diffuses through the skin and elicits a CD8 cytotoxic response to cells that have taken it up. The bottom line is that although there are at least 3 different ways to react to low molecular weight chemicals, only the one that elicits IgE can kill the patient.

Master Answer for Case 3

Atopy and Allergy

This individual developed not only in situ (pulmonary) IgE formation but also systemic IgE and IgG antibodies to repetitively inhaled allergens (fungal) during the repotting procedure with moist composted material. One component of the pulmonary reaction is a classic allergenic one with severe bronchospasm and wheezing. One might view this as regional malfunction of T regulatory cells. But this patient has a bi-isotypic response and also forms large amounts of antifungal IgG also. Thus, other component is an arthus like reaction caused by complexing of fungal antigens with the anti-fungal IgG. The precipitating IgG antibodies can be detected in a gel diffusion assay in which fungal antigens migrate in a gel toward patient serum Ig and precipitate at areas of equivalence. Preventing respiratory exposure to the fungal antigens will lead to a corresponding decrease in IgE and IgG. The allergic syndrome is treated by standard methods discussion in Cases 1-3.

The crudely drawn gel diffusion with explanation is shown below. The precipitin band with the upper label tells you that there is IgG in the patient serum and that the rabbit has made antibody to human IgG heavy chain. The precipitin band with lower label tells you that the patient has IgG antibody to aspergillus antigens. How do you know it is IgG? Because the band merges with, but does not cross over, the IgG band generated by rabbit anti-IgG. If the patient had made IgA or M or E antibody to aspergillus antigens, a specific immunological reaction with an antisera to IgG (the rabbit antisera) would not be possible and no band would form. The merged bands simply tell you that the antibody forming the aspergillus reaction has an identical heavy chain to the generic IgG band formed by the rabbit antiserum to all the IgG in the patient serum.

Agar Gel Immunoprecipitin assay

(SEE NOTES FOR TECHNIQUE)



Master Answer for Case 4

Atopy and Allergy

*Fate favors the prepared. The epidemiologic evidence strongly suggested that this gut autoimmune disease was found almost exclusively in highly developed societies. This led many to ponder whether these patients had a Th1/Th2 imbalance that is **opposite** that found in allergy patients. In Crohn's, uncontrolled Th1 driven inflammation led to destruction of the bowel mucosa and worse. [As you might suspect, it has very recently been shown that The Th1 cells are actually Th17 cells and the predominant cytokine is IL-23].*

The prepared mind works thus: some astute investigators realized that very few people in underdeveloped countries get Crohn disease or asthma. They were also aware that worm infestation of the bowel is epidemic in underdeveloped countries and that some children develop asthma after being "dewormed". They decided to "reset" Th1/Th2 balance of patients with Crohn and disease (should work with asthma also) with a worm infection! Harvesting ova from the feces of whipworm infested pathogen-free pigs, the investigators fed them to patients with Crohn's. That must have been some consent process! In any event, the patients clearly responded and it was found that not only was there a decrease in gut inflammatory cytokines but that the patients had expanded and "reset" their CD4,25, FoxP3 regulator T cell compartment. Infection with whipworms has recently controlled severe ulcerative colitis (another inflammatory bowel disease) in another patient. We are going to see a lot more clinical research in this area and it may also support the concept of becoming a "dirtier" country...