Client Questions

- When I was young, none of our dogs were allergic. Why are allergies so common now?
- There were 7 other puppies in the litter. Why is this the only one with allergies?
- Do you think that all those vaccinations cause more dogs to be allergic?

Answers

- I know what you mean. It is hard and frustrating ($) to care for an allergic pet. I feel bad for pet and caregiver
- Genetic and environmental differences are interesting and confusing factors
- Your dog’s immune system is a life saver! I have seen dogs dogs that did not get their vaccinations on time come down with distemper, have seizures and die. I have cut a dogs head off to check for rabies.
- My dogs get whatever vaccinations that their veterinarian says they should get.
- Lets talk about some short and long term options

Reality: Private Practice

- Grand Dad: “Don’t tell me more than I need to know”
- Two parts of the immune system
- Workers (reactive part): protects us from infections (bacteria, viruses and parasites)
- Regulators (supervisory part): keeps the workers on right track (do the right job at the right time)
- Allergies: supervisor is not doing the job correctly. This allows workers to overact against stuff (pollens) that they should just leave alone.
- Workers have “OCD” and Supervisor: “ADD”
Epidermal Barrier Function: “New” school

- Not just anatomical “bricks and mortar’
- The bricks and mortar are very physiologically and chemically active
- Abnormal barrier function increases contact of allergens with epidermal immune cells and leads to a Th2 immune response (allergy).
- Causes allergen exposure, abnormal IgE and other Ig in susceptible patients

General Immune System

- Innate immunity: native, natural & non specific
  - PAMPs: Pathogen Associated Molecular Patterns
    - Self vs non self (macrophages, dendritic cells=APC and neutrophils)
  - DAMPs: Damage Associated Molecular Pattern
    - Pathogens vs non pathogens (macrophages, APC and neutrophils)
  - PAMPs + DAMPs = Innate immune system becomes activated = local inflammation and initiate “Adaptive immunity”
- Adaptive immunity: acquired & specific (T cells & neuts)
  - Traditional classification: Humoral (antibody-mediated)
  - Traditional classification: Cell-mediated (T-cell mediated)
  - Activation Signals (PAMP<DAMP) = Tcells respond & work

T lymphocyte Classification “1980s”

- **TH1 cell**: CD4+ Tcells function by activating macro-phages and cytotoxic Tcells (activate CMI)
- **TH2 cell**: CD4+, activate eosinophils, basophils and mast cells (Type 1 hypersensitivity) and defend especially against migrating larva in tissue as well as helminth parasites in general (humoral factors influenced by and cause “cellular actions”
T Lymphocytes Class “current”

- **TH1**: activate macrophages and cytotoxic T cells
- **TH2**: activate eosinophils, basophils and mast cells
- **TH17**: Recruit & activate neuts & monocytes, important in clearance of extracellular pathogens
- **TFH**: “Follicular-helper cells,” migrate into the B-cell follicles & assist B cells with antibody production
- **TREG**: “Regulatory T cells,” Suppress immune responses. Most inhibit activated dendritic cells or inhibit activation of T lymphocytes. (Supervisors)
- **TC**: Cytotoxic, CD8+, kill infected host cells-intracellular infections (patterns of cytokines further differentiate)

T Lymphocyte Class: Depends on antigen induced cytokines

- Antigen Dose
- Affinity of the T-cell receptor for antigen
- Cytokine millieu
  - Affected by PAMPs and DAMPs associated with the introduction of a foreign antigen
- State of activation of the dendritic APC
  - Affected by PAMPs and DAMPs associated with the introduction of a foreign antigen
- Helminth antigens = ^cytokines favoring TH2 T cells

Dendritic Cells

- Capture externally created antigens
  - APC for primary immune response & B cells are APC for secondary immune response
- Phagocytose process and present extracellular antigens
  - Exogenous antigen presenting pathway
  - Bind with MHC class II molecules & present on cell surface
- Allow antigen recognition by CD4+ helper T cells which orchestrate the “adaptive immune response”
- Migrate from tissue to lymph: B,T cell clonal expansion
FYI: MHC class I molecules bind with endogenously created antigens (Intracellular organisms)

Dendritic Cells
- Langerhans cells and Dermal dendritic cells
- Both express same receptors for IgE as mast cells
- Langerhans cells in steady state express inhibitory molecules that maintain a state of tolerance to antigens
- Dermal dendritic cells in atopic humans are found in disproportionate high numbers
  - Promote both TH1 and TH2 lymphocytes
  - Supervisor not doing its job correctly

Miscellaneous Immunology
- Allergens bind to same receptors as PAMPs
- Half of all allergens are lipid-binding proteins:
  - may serve as intrinsic adjuvants
- Dust mite allergen (Der p 2), when complexed with bacterial Lipopolysaccharide
  - could activate dendritic cells directly
- Late-Phase reaction (some of Immediate Type 1 hypersensitivity reactions): TH2 early TH1 later

Miscellaneous Immunology
- Genetics of allergies
  - Anatomic: Abnormal barrier function (Filaggrin)
  - Phenotype: Predisposition to TH2 responses
- Hygiene Hypothesis
  - Inverse relationship between allergies and hygiene
  - However, some childhood viral infections increase risk of allergic asthma
  - However, Helminths (TH2) decreases risk of allergy
  - However, IBD & Autoimmunity (TH1) increasing
Emerging View (R. Smith)

- Common saprophytic organisms and helminths need to be accepted, or tolerated, by the immune system.

- Although some may be harmful, greater morbidity and more severe disease results from an immune response than from the agents themselves.

- "TREG down-regulation" or "Old Friends Hypothesis:" Exposure promotes a TREG lymphocyte bias which may be established by dendritic cells that take on a regulatory phenotype and release cytokines favorable to TREG development. Such regulatory dendritic cells continuously sample antigens (potential allergens) from the gut, respiratory tract and skin and bias the response.

- Set point: Says Dunny

Emerging View (A Dunny compares to a day in veterinary practice)

- Common saprophytic organisms and helminths need to be accepted, or tolerated, by the immune system.

- Most clients and patients need to be accepted or at least tolerated by the veterinary practice (including the staff).

Emerging View

- Although some organisms may be harmful, greater morbidity and more severe disease results from an immune response than from the agents themselves.

- Although some clients or patients may be harmful, bigger problems and more severe issues result from inappropriate response (non welcoming response) by staff towards all clients than from the clients or patients themselves.

Emerging View

- "TREG down-regulation" or "Old Friends Hypothesis:" Exposure promotes a TREG lymphocyte bias which may be established by dendritic cells that take on a regulatory phenotype and release cytokines favorable to TREG development. Such regulatory dendritic cells continuously sample antigens (potential allergens) from the gut, respiratory and skin and bias the response.

- A Dunny’s Hypothesis. Exposure to VARIOUS ideas & clients early in employment promote a supervisor (Vet and manager) (bias is influenced by the support staff) that interacts with old and new clients/patients and figures out how to best handle and deal with them for the health of
the practice. So immune systems and veterinarians need a relatively normal and adaptive environment in which to do their job properly. Abnormal experiences can permanently mess you up for the rest of your life (unless you push the restart button)

The American College of Veterinary Dermatology Task force on Canine Atopic Dermatitis

- Veterinary Immunology & Immunopathology: Vol. 81
- Thierry Olivry (NCSU); Doug Deboer (University of Wisconsin); Craig Griffin (San Diego); Richard Halliwell and Peter Hill ((Edinburgh); Andrew Hillier (OSU); Rosanna Marsella (UF), Candice Sousa (Sacramento)

Clinical Approach: Allergic Dermatitis

- Veterinarian educates self and client: Manage (rarely cure)
- Patient has chronically abnormal cutaneous and general immune system: Anatomy & Physiology
- Client education: Permanent underlying abnormality with variety of manifestations which often manifest as an inappropriate immune response and overgrowth of normal organisms

Atopy: Pathophysiology: (Thank you Dr. Rosanna Marsella)

- Tradition: Type 1 hypersensitivity (IgE). Allergens attach to IgE (which has previously affixed to mast cells in the skin) = mast cell degranulation and release of inflammatory mediators such as histamine and others
- Previously accepted definition and dogmas are only part of the process
- Complex, Variable and dynamic nature

Pathophysiology: New (Thank you R. Marsella and T. Olivery)

- IgE mediated reactions play an important role in the capture and processing of allergens, but additional factors are significant. (Epidermal v Serum IgE)
- Epidermal Barrier function is likely abnormal and allow allergens into the skin
- T-lymphocyte cell imbalances: Helper T-cells (Th1 and Th2)
Pathophysiology:

- **Early stage Atopy**: elevated numbers of Th2 cells (compared to Th1)
- Th2 cells help induce IgE production and interleukins (IL-4, IL-5 and IL-10)
- These interleukins stimulate mast cell and eosinophil activation and proliferation
- “Allergic March” or “Cycle” or “Cascade” contributes to progression and eventual switch from primarily TH2 to both TH1 and TH2 with chronic disease
- By then, the Dermal APC are already geared up in a bad way

Allergen Specific Immunotherapy (Humans)

- Inhibits both immediate-phase and late-phase responses after allergen challenge (humans)
- Affects effector inflammatory cells and secretion of mediators
- Changes concentration of allergen-specific immuno-globulins (slow decline of IgE, blunting of seasonal increase of IgE and large increases in IgG1 & IgG4)
- Shift in favor of Type 1 response to allergen vs type 2 response. Change T-cell function & cytokine production
- Allergen specific anergy of peripheral T-cells
- Dunny says “Helps allergic patients immune system treat allergens as “old friends” or at least family (that we tolerate)”

Allergen Specific Immunotherapy

- Significant increase in allergen specific IgG after 6 months (canine)
- Immunoglobulin changes may not correlate with clinical improvement (canine and human) (Why?)
- Increased efficacy associated with (human)
  - Higher doses of allergen
  - Hypersensitivity to one or few allergens
  - Commencement of ASIT at young age
  - Commencement before chronic inflammatory change
Humans w Allergic rhinitis, bronchitis, conjunctivitis: Advantages of early ASIT

- Prevention of chronic inflammatory changes
- Prevent further development of severe disease
- Prevent development of new hypersensitivities
- Possible reduction of adverse reactions due to a lower state of hypersensitivity
- May prevent the natural progression of further allergic disease in other organs

Immunotherapy Proposal (K9) ACVD Task Force (Olivry, Sousa)

- Potential to result in partial or complete remission
- Demonstrable and clinically relevant allergen-specific IgE antibodies
- Allergen contact is unavoidable
- Symptoms respond poorly to antipruritic drugs or cost/side effects are unacceptable
- Clients: time, expense and technical aspects
- Need: validated controlled experiments
- IDST and ASIT Protocols: Extremely variable. Best left up to someone with training and experience
- Allergen diluted from 40,000 PNU to IDST strength (1,000 PNU) every 2 weeks and stored in glass. IDST strength stored for < 48 hours in plastic syringes
- Gradual build up for 1-200 PNU to 1-2,000 to 10-20,000 every 2-3 days, then maintained at 0.25-1.0cc every 3-31 days. The standard is 1.0cc every 10-14 days.
- ASIT protocol based on patient and client

Allergy workup v Medical Therapy

- Help clients think long term & short term
- Medically: Safe steroids equates to approx 3-4 months a year. I am ok with this if not progressing or often secondary infections
- Long term non steroidal maintenance medical therapy is almost always more expensive than ASIT. Remember cost of drug, monitoring and side effects.
Immunodermatology: Case Report

- Bubba, 2.5 year neutered male Labrador Retriever