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INTRODUCTION: ATOPIC DERMATITIS

Atopic dermatitis (AD) is a complex, multifaceted disease with many possible manifestations, and many possible treatment modalities. Modern research continually reveals new findings about the pathogenesis of AD, which is incompletely understood even in man. It is important to understand what is known about the pathogenesis of AD in order to understand the logical diagnosis and treatment of this disease. The objective of this lecture is to review new findings about AD, particularly regarding epidermal barrier function, and to discuss how these findings affect how we approach management of AD.

ATOPIC DERMATITIS: INSIDE-OUTSIDE?

Historically, AD was considered to be caused by an IgE-mediated, immediate-type hypersensitivity response to an inhaled allergen – “allergic inhalant dermatitis.” The IgE produced would sensitize cutaneous mast cells; the mast cells degranulate upon further allergen exposure, with subsequent mediator release causing clinical signs. Taking one step backwards, we emphasized that the important factor underlying this hypersensitivity response was a basic alteration in the immune response, caused by a combination of genetic and environmental factors. There was an alteration in lymphocyte responses to antigens, such that there was a change from IgG production (the “normal” defense response – the one we hope to evoke with, for example, routine vaccination) to IgE production (the “allergy” response). When an animal’s immune system encounters a foreign substance, and an antibody response is evoked, whether the IgG or IgE response predominates is controlled by cytokines released by different subsets of helper T-lymphocytes. If the IgE response predominates, this is an abnormal response, and sets the stage for allergy. Many things can potentially influence which response predominates. Modulating the IgG/IgE “balance” and returning it towards the “normal” IgG bias is the target of treatments such as allergen-specific immunotherapy.

Thus, we viewed AD as a disease that began on the “inside” of the individual – the immune system – and that following this, “outside” influences such as allergens, irritants, bacteria, and yeast would cause development and worsening of symptoms (“inside-outside”). Many years and thousands of research studies focused on defining the abnormalities in the “inside” - the immune system and inflammatory response. Our diagnostic approach was focused on evaluating the immunologic IgE and immediate hypersensitivity response, and our treatment approach consisted mostly of attempting to modify the immune system and inflammatory response.

ATOPIC DERMATITIS: OUTSIDE-INSIDE?

More recently, this “inside-outside” view has come into some question, and a different view is evolving. For example, we began to recognize that atopic dermatitis may not always be IgE-mediated, or at least we could not prove this in some patients. Some authorities even theorized that the presence of IgE was merely an ‘epiphenomenon’ or marker of the true underlying disorder. In humans, about 70-80% of patients with AD have demonstrable allergen-specific IgE in serum or are positive on “allergy tests”; 20-30% do not and are NOT positive on these tests...we can find no “inside” abnormality! Therefore, it seemed that other mechanisms were clearly involved, at least in some patients.

Some examples of other mechanisms that were shown to be important in human AD, and which came under investigation in animal allergy, include (1) decreased epidermal barrier function, resulting in higher permeability of the skin to allergens and irritants; (2) reduced production of antimicrobial peptides by epidermal cells, leading to greater propensity for skin infections; (3) augmentation of the inflammatory response by substances secreted by micro-organisms on the skin, such as staphylococcal exotoxins; (4) identification of genetic polymorphisms highly associated with AD and allergy, some of which involved genes coding for structural proteins of the epidermis; and (5) recognition that environmental conditions can affect or modify development of the allergic response in a genetically-predisposed individual...the “hygiene hypothesis.”

It was thus noted that many of the factors being discovered involved the epidermis itself and “outside” influences, and a new view developed – perhaps AD may begin first as a defect in the “outside”...
– for example, in the epidermal barrier – and following this, the barrier function problems result in development of an altered immune response and inflammatory cascade. Thus, the “outside-inside” view came into being. For clinicians, the importance of all this discussion is that we now recognize that AD has a very complex pathogenesis. We can now see clearly how diagnosis and treatment will be more difficult than we used to think!

THE EPIDERMAL BARRIER

Because many of the abnormalities recently identified in AD patients involved some aspect of the epidermal barrier, it is useful to examine this concept more closely. The “epidermal barrier” is primarily a function of the stratum corneum, the uppermost layer of the epidermis consisting of dead, keratinized cells held tightly together by intercellular “glue” consisting of a complex mixture of lipid and protein. This structure has often been compared to a wall made of “bricks and mortar.”

The stratum corneum is formed by the process of cornification (or keratinization), which is an extremely complex process of cell division, maturation, and differentiation during which dozens of new proteins are synthesized to produce tough, resistant, fully mature corneocytes (‘bricks’) and the intercellular material (“mortar”) that holds them together and prevents passage of material into or out of this tough barrier. The intercellular material is produced by the corneocytes themselves. Within the cells, lipid-rich “lamellar bodies” form, which are then transported to the cell surface and ejected out into the intercellular space to form a regular, layered structure of “lipid lamellae” which act as physical gaskets between the cells.

The epidermal barrier has many functions, including protection against mechanical trauma and ultraviolet radiation, prevention of water loss through the skin, and preventing entry of external substances (toxins, drugs, irritants, allergens…) into the body. A recent view is to consider the epidermal barrier to consist of two basic elements: a physical permeability barrier, as described above, but also an antimicrobial barrier. It is now recognized that the epidermis and associated glandular structures are also very active in secreting a wide variety of substances involved in defense against cutaneous micro-organisms. These substances include antimicrobial lipids and specific immunoglobulins, as well as antimicrobial peptides such as the defensins and cathelicidins. Together with the tough mechanical structure of the stratum corneum, these molecules provide a formidable defense against colonization and infection…or at least, they will provide this in normal individuals!

There is no question that the epidermal barrier functions are abnormal in atopic people. Early research on morphologic evaluations (as performed by electron microscopy), analysis of lipid components of the epidermis, and functional evaluations (as performed by the technique of transepidermal water loss) consistently showed that the stratum corneum in atopic human beings is defective or “leaky” compared with normal people. As research progressed, it was determined that not only the permeability barrier, but also the antimicrobial barrier was defective – the skin of atopic people produces much less antimicrobial peptide than normal. More recently, genetic analysis has revealed specific genetic defects in critical functional proteins in the epidermis. Most notably, a mutation in the gene coding for the epidermal protein filaggrin was recently shown to be highly associated with allergy in certain groups of people. In fact, the more the concept of “barrier function” is examined, the more it becomes obvious that barrier function is abnormal in AD, and this is a critical part of the pathogenesis of the disease.

Do these same concepts extend to allergy in animals? Early morphologic studies showed remarkable differences in the intercellular lamellar lipid structure between normal and atopic dogs. Studies on lipid composition and functional evaluations are in their beginning stages, but as results become available, it appears that the situation will likely parallel exactly what is seen in human beings. Some groups of investigators are also beginning to evaluate antimicrobial peptides, filaggrin, and other possible specific defects in canine skin.

From a clinician’s standpoint, the obvious question becomes “can we improve clinical signs of AD by somehow improving barrier function?” This is actually two questions in one: (1) can we somehow modify barrier function through therapy? and (2) if so, does such modification result in clinical benefit? In human AD, application of emollient preparations to the skin is an important and basic element of treatment, and unquestionably helps relieve symptoms over time. In dogs, studies have shown that the lipid composition of the stratum corneum can be modified by either dietary or topical means. Manipulation of the diet by altering its fatty acid composition affects the composition of skin lipids. A series of studies of micronutrients demonstrated convincingly that certain nutrients can stimulate production of barrier
components and can measurably enhance barrier function in dogs. Some of these studies suggested that the modifications in epidermal composition were accompanied by relief of allergy clinical signs.

Topical modification of barrier function is an active area of research in veterinary medicine. Early research has shown that application of topical lipid emulsion preparations can result in “normalization” of the intercellular lipid lamellar structure and composition. If these therapies result in remission of clinical signs, they will become an important and necessary part of the therapy of AD. To summarize experience to date, barrier function can indeed be modified through dietary or topical means. Modifying barrier function is an important and effective part of treatment in human AD, and may become a mainstay of therapy in animals in the near future.

TREATING AD: AN INTEGRATED APPROACH

With recognition of the complexity of the pathogenesis of AD, we now also recognize that treatment approaches must be individualized and flexible, must combine several modes of therapy, and must be aimed at both the primary disease and at secondary complications, to maximize success and client satisfaction. Within this “integrated approach,” we see each of the potential therapy possibilities as “tools.” Our goal with each patient is to find just the right combination of tools to provide lifelong therapy that is effective, affordable, convenient, and with as few adverse effects as possible.

Historically, management of AD has been aimed at the “end process” of the disease, in other words, focused on anti-inflammatory therapies. “Managing inflammation” has been the first goal of therapy. Our new view demands that we take a much broader approach. Important elements of this “new approach” include:

- Elimination of allergens (avoidance) where possible
- Augmenting the permeability barrier, to reduce entry of allergens and irritants
- Control of secondary infections, which contribute to discomfort and augment the allergic and inflammatory responses
- Augmenting the antimicrobial barrier, to reduce the frequency of these secondary infections
- Modification of the immunologic response through allergen immunotherapy
- Management of any remaining inflammatory response that persists despite the above measures.

This new approach will also require renewed efforts at educating clients about treatment of AD. Therapies such as repair of barrier function and modification of the immune response are “proactive treatments” that are aimed at correcting the underlying pathogenesis of the disease. These treatments will not work instantly, as do the “reactive treatments” such as anti-inflammatory drugs. They are not expected to produce immediate improvement, but rather, prolonged improvement over a longer time period. Owners must be educated that this “preventive approach” represents our best chance of controlling this lifelong disease with minimal use of drugs that may be detrimental over the long term.

New facts about AD produce important changes in our thinking about how this disease works in pets, and will form the basis for exciting new approaches to treatment in the future.