Core Curriculum Outline and Reading List

Last Reviewed:May 2011

The Allergy and Immunology Training Program Directors' (TPD) Core Curriculum Outline and Reading List serves as a guide for:

- TPD and trainees in meeting the requirements of the Residency Review Committee
- The Reading List Subcommittee
- The In-Training Examination Subcommittee.

This document provides a framework for training programs to design an individualized course of study that supplements the diverse strengths and weaknesses of each fellowship training program and faculty. It is updated every three years, and is consistent with the requirements of the Residency review Committee for training in allergy and immunology.

In an effort to keep the materials as current as possible, email Mariana Duran at mduran@aaaai.org with supplemental inforamtion. Suggestions will be reviewed at the end of each calendar year.

Allergy and Immunology Training Program Directors' Core Curriculum Outline and Reading List

Click on any of the Core Curriculum topics to view the citation and abstract of the reading(s) or activities selected for each Core Curriculum topic.

Strategies and resources for acquiring the body of knowledge within the Basic Science Core Curriculum might include structured didactic programs, TPD-recommended textbooks, TPD reading list, and regional or national seminars. The knowledge obtained through the basic science curriculum serves as the foundation for diagnosis and therapy for immunologic and allergic disorders.

I. Basic Immunology

A. Overview of the Immune System

1. Organization and Functions of the Immune System

REVIEW:
Cahalan MD. Gutman GA.
The sense of place in the immune system.
Nat Immunol. 2006;7:329-32
This series of reviews examines the effect of differing tissue environments on the activity and functional capacity of cells in the immune system. From their origins as hematopoietic stem cells, throughout their development and as mature cells, cells of the immune system find themselves in distinct and highly specialized niches, and contact with antigen or inflammatory signals changes their phenotype, activity and trafficking. Two-photon microscopy has provided the first direct observations of living cells and their activation choreography in the tissue environment and will no doubt continue to provide greater understanding of cellular dynamics and immune function.

a. Thymic development and shaping peripheral systemic T-cell immunity

REVIEW:
Zuniga-Pflucker JC.
T-cell development made simple.
Nat Rev Immunol 2004;4:67-72.
The thymus is the primary site of T-cell lymphopoiesis. However, the precise molecular interactions that enable the thymus to carry out this function are only recently being elucidated. Although several important molecular players have been identified, including soluble factors, extracellular matrix components, and integral membrane receptors and their ligands, the precise role of these molecules in thymocyte differentiation has yet to be fully characterized. In this regard, the advent of a simple and efficient culture system for the generation of T cells from stem cells, as discussed here, should greatly facilitate the study of T-cell development.

REVIEW:
Hayday AC.
Key factors in the organized chaos of early T cell development.
Nat Immunol. 2007;8:137-44
A fundamental issue in T cell development is what controls whether a thymocyte differentiates into a gammadelta T cell or an alphabeta T cell, each defined by their distinct T cell receptor. Most likely, lessons learned in studying that issue will also provide insight into how the thymus produces T cell subsets with distinct functional and regulatory potentials. Here we review recent experiments, focusing on three factors that regulate thymocyte differentiation up to and including the expression of the first products of antigen receptor gene rearrangements. Those factors are the archetypal developmental regulator Notch, intrinsic signals emanating from antigen-receptor complexes, and trans conditioning, which reflects communication between different subsets of thymocytes. We also review new findings on the positive selection of gammadelta T cells and on extrathymic T cell development.

RESEARCH FRONTIER:
Rothenberg EV.
Cell lineage regulators in B and T cell development.
Nat Immunol. 2007;8:441-4, 2007
This special issue highlights a pivotal set of regulatory molecules that have emerged as central controllers of cell-type identity in the immune system. Each in its own way has been considered as a kind of 'master' regulator of a particular cell fate choice, but the actual modes of action of these factors vary widely. The comparison among them sheds light on the different ways that an essential regulatory input can affect cellular identity.

b. Cutaneous Immunity

REVIEW:
Berger CL.
Langerhans cells: mediators of immunity and tolerance.
Int J Biochem Cell Biol. 38(10):1632-6, 2006.
Langerhans cells provide the epidermis with a surveillance network that samples the external environment influencing the decision between immunity and tolerance. Langerhans cells are immature dendritic cells acquiring antigens from foreign invaders as well as damaged native tissue for display to the immune response. The current paradigm suggests that the state of maturity of Langerhans cells, defined by the display of molecules that provoke immune responses (histocompatibility, co-stimulators, adhesion and homing receptors), determines whether emigration of the Langerhans cell to lymph nodes signals immunity or tolerance. Other factors such as type of immunogen ingested, environmental danger signals and the level of cell death may also play a role in tipping the balance towards immunity or immunosuppression. As modulators of the immune response, Langerhans cells play a role in cutaneous autoimmunity in lupus and in cancers that have an affinity for the epidermis such as cutaneous T cell lymphoma

c. Intestinal/Mucosal Immunity

REVIEW:
Teitelbaum JE
The development of mucosal immunity.
Eur J Gastro Hepatol 2005;17:1273-8.
The development of the intestinal immune system is a complex sequence of events that begins in utero under various genetic influences, but continues after birth, being modified by factors such as bacteria, hormones and feeds. This review discusses what is known about the ontogeny of each aspect of the mucosal immune system so as to provide a better understanding of how aberrations in the system might lead to systemic disease.

REVIEW:
Dubois B.
Oral tolerance and regulation of mucosal immunity.
Cell Mol Life Sci 2005 62(12):1322-32.
Regulated mechanisms sustain the ability of the gut immune system to discriminate harmless food antigens (Ag) and commensal bacteria from pathogenic microorganisms, resulting in tolerance versus protective immunity, respectively. Antigens of the gut commensals are not simply ignored, but rather trigger an active immunosuppressive process, more commonly known as oral tolerance,

which prevents the outcome of immunopathology. Both intrinsic properties of the gut microenvironment and cellular actors, as well as peripheral events induced by systemic dissemination of oral Ag, promote the induction of regulatory mechanisms that ensure maintenance of gut homeostasis. The aim of this review is to provide a synthetic update on the mechanisms of oral tolerance, with particular emphasis on the complex interplay between regulatory CD4+ T cells, dendritic cells and the gut microenvironment.

d. Primary Immune Function of Cellular Elements of the Immune System

i. T-cells

REVIEW:
Jiang H.
Regulation of Immune Responses by T cells
N Engl J Med 2006;354:1166-76

The T-cell branch of the immune system can respond to a virtually infinite variety of antigens, in part because it includes a very large repertoire of T-cell clones, each with a unique receptor for antigen. It is inevitable that this diverse repertoire contains T cells with receptors that can recognize the body's own antigens — self-reactive T cells — and instigate harmful autoimmunity. For this reason, a means of restraining such T cells is essential. The controls depend on two mechanisms that not only avert autoimmunity but also maintain protective immunity: shaping of the T-cell repertoire in the thymus and regulation of T cells in the periphery. The proposal that peripheral regulatory mechanisms have a key role in the immune response, advanced more than three decades ago by Richard Gershon, was based on two concepts — homeostasis and the potential for autoimmunity.1 The immune system is indeed a homeostatic organization that must regulate itself to avert insufficient immunity and suppress excessive responses. Protective immunity has a considerable potential for error because it entails the production of potent proinflammatory molecules and killer cells that can destroy not only invading microorganisms and cancer cells but also normal cells. To ensure effective immunity to foreign antigens but avert pathogenic autoimmunity in the periphery, the immune system must control the magnitude and class of immune responses but also discriminate self from nonself. The control of magnitude and class is accomplished by intrinsic homeostatic mechanisms, whereas self–nonself discrimination is mediated largely by suppressor T cells, a term originally coined by Gershon1 These two immunoregulatory mechanisms have direct clinical relevance to autoimmune diseases, allograft rejection, responses to pathogens, and antitumor immunity. It is likely that an understanding of the molecular and cellular mechanisms of immune regulation will generate new ways of preventing and treating immune-mediated diseases. How T cells mediate these mechanisms is the topic of this review.

REVIEW:
Bacchetta R.
The role of regulatory T cells and FoxP3 in human disease
J Allergy Clin Immunol 2007;120:227-235

Immune regulation and tolerance are specific functions of the immune system, meaning at prevention or limitation of effector immune responses against inner and external insults. Regulatory T (Treg) cells are crucial players in this immune balance network. Research over the last 10 years has significantly contributed to characterizing Treg cell features, their mechanisms of

function, and their role in human pathologies. The discovery of FOXP3 as an essential transcription factor not only for differentiation and function of naturally occurring Treg cells but also for regulation of intracellular molecules related to effector T-cell responses has provided new insights into the pathogenesis of immune-mediated diseases. Interestingly, there is increasing evidence that the individual signature of genes relevant for immune regulation definitely influences the final outcome of an immune response.

ii. B cells

REVIEW:
Vascotto F.
Antigen presentation by B lymphocytes: how receptor signaling directs membrane trafficking.
Curr Opin Immunol 2007; 19:354-64.
Antigen capture and presentation onto MHC class II molecules by B lymphocytes is mediated by their surface antigen receptor - the B-cell receptor (BCR). The BCR must therefore coordinate the transport of MHC class II- and antigen-containing vesicles for them to converge and ensure efficient processing. Recently, progress has been made in understanding which and how these vesicular transport events are molecularly linked to BCR signaling. In particular, recent studies have emphasized the key roles of membrane microdomains and the actin cytoskeleton in regulation of membrane trafficking upon BCR engagement.

REVIEW:
McHeyzer LJ
Antigen-specific memory B cell development
Ann Rev Immunol 2005;23:487-513
Helper T (Th) cell–regulated B cell immunity progresses in an ordered cascade of cellular development that culminates in the production of antigen-specific memory B cells. The recognition of peptide MHC class II complexes on activated antigen-presenting cells is critical for effective Th cell selection, clonal expansion, and effector Th cell function development (Phase I). Cognate effector Th cell–B cell interactions then promote the development of either short-lived plasma cells (PCs) or germinal centers (GCs) (Phase II). These GCs expand, diversify, and select high-affinity variants of antigen-specific B cells for entry into the long-lived memory B cell compartment (Phase III). Upon antigen rechallenge, memory B cells rapidly expand and differentiate into PCs under the cognate control of memory Th cells (Phase IV). We review the cellular and molecular regulators of this dynamic process with emphasis on the multiple memory B cell fates that develop in vivo.

REVIEW:
Mizoguchi, A.
A case for regulatory B cells
J Immunol 2006;176:705-10
B cells are typically characterized by their ability to produce Abs, including autoantibodies. However, B cells possess additional immune functions, including the production of cytokines and the ability to function as a secondary APC. As with T cells, the B cell population contains functionally distinct subsets capable of performing both pathogenic and regulatory functions. Recent studies indicate that regulatory B cells develop in several murine models of chronic

inflammation, including inflammatory bowel disease, rheumatoid arthritis, and experimental autoimmune encephalomyelitis. The regulatory function may be directly accomplished by the production of regulatory cytokines IL-10 and TGF-beta and/or by the ability of B cells to interact with pathogenic T cells to dampen harmful immune responses. In this review, we make a case for the existence of regulatory B cells and discuss the possible developmental pathways and functional mechanisms of these B cells.

iii. Neutrophils

REVIEW:
Wang Q.
Neutrophils in Innate Immunity
Semin Respir Crit Care Med 2004; 25: 33-41
Neutrophils are an important component of innate immunity in the lungs. During bacterial pneumonia, neutrophils are recruited from the capillaries of the pulmonary circulation in the gas-exchanging regions of the lungs. This process requires the coordinated activation of many cells within the lungs, including neutrophils and capillary endothelial cells. Cellular activation during innate immune responses is mediated in part by tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1-initiated signaling through their receptors, activation of nuclear factor kappa B (NF-κB) and downstream gene transcription, endothelial cell signaling initiated by neutrophil adherence to intercellular adhesion molecule (ICAM)-1, and binding of leukocyte adhesion molecules to cellular and matrix ligands. These events are essential to effective host defense during pneumonia

REVIEW:
Burg ND, Pillinger MH.
The Neutrophil: Function and Regulation in Innate and Humoral Immunity.
Clin Immunol 2001;99:7-17
The neutrophil is a critical effector cell in humoral and innate immunity and plays vital roles in phagocytosis and bacterial killing. Discussed here are the neutrophil components necessary for these processes and the diseases in which these components are either lacking or dysfunctional, illustrating that normal neutrophil function is vital for health.

REVIEW:
Segal AW.
How neutrophils kill microbes
Ann Rev Immmunol 2005;23;197-223
Neutrophils provide the first line of defense of the innate immune system by phagocytosing, killing, and digesting bacteria and fungi. Killing was previously believed to be accomplished by oxygen free radicals and other reactive oxygen species generated by the NADPH oxidase, and by oxidized halides produced by myeloperoxidase. We now know this is incorrect. The oxidase pumps electrons into the phagocytic vacuole, thereby inducing a charge across the membrane that must be compensated. The movement of compensating ions produces conditions in the vacuole conducive to microbial killing and digestion by enzymes released into the vacuole from the cytoplasmic granules.

RESEARCH FRONTIER:

Appelberg R
Neutrophils and intracellular pathogens: beyond phagocytosis and killing.
Tr Microbiol 2007;15:87-92.
Neutrophils are not simply scavenging phagocytes that clear extracellular spaces of rapidly proliferating microbes; they are also active in the control of infections by intracellular pathogens. Several mechanisms for nonphagocytic roles of neutrophils in protective immunity have been put forth over the years but further evidence has recently been accumulating at an increasing pace. In this review, I present the evidence that suggests neutrophils are involved in pathogen shuttling into the lymphoid tissues, in antigen presentation, and in early T cell recruitment and initiation of granuloma organization. Also, a clearer view on the antimicrobial molecules that can be acquired by macrophages to enhance their antimicrobial activity is now emerging. Finally, neutrophils can adversely affect immunity against certain parasites by causing immune deviation.

iv. Eosinophils

REVIEW:
Lee JJ
Eosinophil degranulation: an evolutionary vestige or a universally destructive effector function?
Clin Exp Allergy 2005; 35:986–994
The goal of this review is to examine the importance of eosinophil degranulation from a 'thinking outside of the box' perspective in an attempt to shed new light on an old problem. In particular, we will pose and answer the questions'What is the evolutionary origin of eosinophils and degranulation and why is degranulation viewed as the ultimate eosinophil effector function?' More importantly, 'Does the available data support an alternative to the prevailing hypothesis that degranulation is a destructive effector function?' We do not expect to adequately answer these questions and many of our answers may eventually be shownto be incorrect. However, as noted by the 19th centurynaturalist Charles Darwin: 'False views, if supported by some evidence, do little harm, for everyone takes salutary pleasurein proving their falseness!'

REVIEW:
Klion AD, Nutman TB
The role of eosinophils in host defense against helminth parasites.
J Allergy Clin Immunol 2004;113:30-37
The precise function of eosinophils in parasitic infection in vivo remains poorly understood despite eosinophils having been shown to be potent effectors in killing parasites in vitro. Although it has long been held that the primary function of the eosinophil is protection against helminth parasites, there are little data to prove this unequivocally. Moreover, eosinophils are responsible for a considerable amount of inflammatory pathology accompanying helminth infections. This article will provide an overview of our current knowledge about eosinophils and their role, both protective and pathogenetic, in parasitic helminth infections.

v. Mast cells

REVIEW:
Mekori, YA
The mastocyte" the "other" inflammatory cell in immunopathogenesis
J Allergy Clin Immunol 2004;114:52-7

It is becoming increasingly evident that the contribution of mast cells to both physiologic and pathologic processes extends far beyond their accepted role in allergic disease. The accumulation and activation of lesional mast cells as observed in several chronic inflammatory and fibrotic processes such as multiple sclerosis, rheumatoid arthritis, sarcoidosis, Crohn's disease, chronic graft-versus-host disease, and scar tissue suggest their involvement.[Several morphologic and functional features of mast cells enable them to contribute to nonallergic inflammatory processes. Mast cells are strategically poised at perivascular sites to regulate inflammatory responses. They are also located for optimal interaction with the environment and for their putative functions in host defense. Their predilection to occupy tissues that interface the external environment including the skin and respiratory and gastrointestinal tracts places them in a unique position to encounter invading organisms and orchestrate a response. Their close physical proximity with T cells in inflamed tissues has led investigators to propose a functional relationship between these 2 cell populations that might facilitate the immune response.

REVIEW:
Boyce JA.
Mast Cells: Beyond IgE.
J Allergy Clin Immunol 2003;111:24-32
Mast cells, historically known for their involvement in type I hypersensitivity, also serve critical protective and homeostatic functions. They directly recognize the products of bacterial infection through several surface receptor proteins, releasing proteases, cytokines, and eicosanoid mediators that recruit neutrophils, limit the spread of bacterial infection, and facilitate subsequent tissue repair. In vitro studies suggest that the spectrum of microbes capable of initiating mast cell activation is broad and extends to common respiratory viruses, mycoplasma, and even products of tissue injury, such as nucleotides. TH2-polarized inflammation elicits a reactive hyperplasia of mast cells at the involved mucosal surfaces in both mice and human subjects. Several recombinant TH2 cytokines (IL-3, IL-4, IL-5, and IL-9) act synergistically with stem cell factor to facilitate proliferation of nontransformed human mast cells in vitro. IL-4 induces the expression of critical inflammationassociated genes by human mast cells, such as those encoding leukotriene C4 synthase, Fc RI, and several cytokines. Consequently, priming with IL-4 not only amplifies classical Fc RI-dependent mast cell activation but also dramatically alters the product profile of mast cells activated by innate signals and by chemical mediators of inflammation. Strikingly, IL-4 induces an activation response by mast cells to cysteinyl leukotrienes, which act through a receptor shared with uridine diphosphate to induce cytokine generation without exocytosis. It is possible that alterations in mast cell phenotype by the TH2 milieu of allergy permits otherwise trivial infections or homeostatic chemical signals to initiate harmful inflammatory cascades and sustain tissue pathology. Drug development must take these nonclassical mast cell activation pathways into account without compromising the beneficial and protective functions of mast cells.

vi. Basophils

REVIEW:
Gibbs BF
Human basophils as effectors and immunomodulators of allergic inflammation and innate immunity.
Clin Exp Med. 2005 Jul;5(2):43-9.
Basophils have often stood in the shadow of their tissue-fixed mast cell counterparts which share

some, common features, such as high-affinity IgE receptor expression and the ability to release histamine. That rodent mast cells produce a variety of pro-allergic and inflammatory cytokines has further added to the deception that basophils only play a minor role in allergic inflammation. Surprisingly, in humans, basophils, but not mast cells, appear to be the prime early producers of the Th2-type cytokines IL-4 and IL-13, which perform several crucial functions in initiating and maintaining allergic responses. This putative immunomodulatory role of basophils is supported further by their ability to express CD40 ligand, which, together with IL-4 and IL-13, serve as inductors of B-cell proliferation and class switching to IgE and IgG4. Moreover, human basophils are the main cellular source for rapid IL-4 generation, a mandatory requirement for the development of Th2 responses. Recent specific staining techniques have localized basophils in various tissues affected by allergic diseases and it appears likely, but remains to be proven, that the interaction ofbasophils, T cells and B cells at these sites propagate pro-allergic immune responses. Additionally, basophil activation is not restricted to antigen-specific IgE crosslinking but can be caused in nonsensitised individuals by parasitic antigens, plant lectins and viral superantigens binding to nonspecific IgEs. Finally, the presence of novel IgE-independent receptor targets that cause trafficking and Th2 cytokine release from basophils further underlines their potential role in innate as well asadaptive immunity.

vii. Antigen presenting cells

REVIEW:
Rossi, M
Human dendritic cells: potent antigen-presenting cells at the crossroads of innate and adaptive immunity.
J Immunol 2005;175:1373-81
Dendritic cells (DCs) are specialized, bone marrow-derived leukocytes that are critical to the development of immunity. Investigators have emphasized the role of DCs in initiating adaptive or acquired MHC-restricted, Ag-specific T cell responses. More recent evidence supports important roles for DCs in the onset of innate immunity and peripheral tolerance. Progress in the generation of DCs from defined hemopoietic precursors in vitro has revealed the heterogeneity of these APCs and their attendant divisions of labor. This review will address these developments in an attempt to integrate the activities of different DCs in coordinating innate and adaptive immunity.

REVIEW:
Schuurhuis DH
Ins and outs of dendritic cells
Int Arch Allergy Immunol 2006;140:53-72
Dendritic cells (DC) are professional antigen-presenting cells which are strategically positioned at the boundaries between the inner and the outside world, in this way bridging innate and adaptive immunity. DC can initiate T cell responses against microbial pathogens and tumors due to their capacity to stimulate naive T cells. The development of DC occurs in distinct stages. DC precursors develop in the bone marrow and home to a large variety of tissues. Immature DC capture antigen (Ag) and, following proinflammatory signals, migrate to the lymphoid organs where, after maturation, they present captured Ag to naive T cells, thereby inducing differentiation of naive T cells into effector T cells. An important cognate event in the development of cell-mediated immunity is the interaction between CD40 and CD40 ligand. Ligation of CD40 on DC by its ligand results in maturation of the DC. In addition to CD40 ligand (expressed by activated

Th cells), inflammatory cytokines, bacterial components or Ag-Ab immune complexes can induce maturation of DC. Maturation of DC is crucial for the priming of efficient T cell responses and is characterized by a decreased Ag processing capacity, an increased cell surface expression of MHC and costimulatory molecules, and rearrangement of cytoskeleton, adhesion molecules, and cytokine receptors. Mature DC migrate from peripheral tissues to secondary lymphoid organs, where T cell priming occurs. DC are not only critical in initiating T cell immunity, they also play a role in the induction of T cell tolerance and the regulation of the type of T cell response that is induced. Here we give an overview of the dendritic cell system.

RESEARCH FRONTIER:
Liu YJ
Thymic stromal lymphopoietin and OX40 ligand pathway in the initiation of dendritic cell mediated allergic inflammation.
J Allergy Clin Immunol 2007;128:238-244
It was demonstrated 5 years ago that thymic stromal lymphopoietin (TSLP), a IL-7–like cytokine produced by epithelial cells, could strongly activate human myeloid dendritic cells to induce an inflammatory TH2 response characterized by high TNF-a and little IL-10 production, distinct from the regulatory TH2 responses characterized by low TNF-a and high IL-10 production. TSLP was found highly expressed by keratinocytes of skin lesions of atopic dermatitis and associated with dendritic cell activation in situ. This suggests for the first time that TSLP represents a master switch of allergic inflammation at the epithelial cell and dendritic cell interface. During the last several years, the evidence for the association of TSLP with human asthma was revealed. The direct link between TSLP expression with the pathogenesis of atopic dermatitis and asthma in vivo was demonstrated. In addition, OX40 ligand was found to be the TSLP-induced molecule on dendritic cells that triggers inflammatory TH2 differentiation in the absence of IL-12. TSLP was also demonstrated to direct the innate phase of allergic immune responses through activating mast cells. Therefore, TSLP and OX40 ligand may represent important targets for intervention of the initiation of allergic inflammatory responses.

viii. Natural Killer Cells

REVIEW:
Lodoen MB, Lanier LL.
Natural Killer Cells as an initial defense against pathogens
Curr Opin in Immunol 2006, 18:391-398
Natural killer (NK) cells serve as a crucial first line of defense against tumors and a diverse range ofpathogens. Recognition of infection by NK cells is accomplished by the activation of receptors onthe NK cell surface, which initiate NK cell effector functions. Many of the receptors and ligands involved in NK cell antimicrobial activity have been identified, and we are beginning to appreciate how they function during infection. In addition, NK cells are activated by cytokines (e.g. interleukin12 and type I interferons), which are products of activated macrophages and dendritic cells. Inresponse to these activating stimuli, NK cells secrete cytokines and chemokines and lyse targetcells. Recent studies have focused on the mechanisms by which NK cells recognize and respond to viruses, parasites and bacteria, and on the unique role of NK cells in innate immunity to infection.

ix. NKT cells

REVIEW:
Van Kaer. L
NKT cells: T lymphocytes with innate effector functions
Curr Opin Immunol 200719:354-64

Natural killer T (NKT) cells are innate-like T lymphocytes that recognize glycolipid antigens in the context of the MHC class I-related glycoprotein CD1d. Recent studies have identified multiple ways in which NKT cells can become activated during microbial infection. Mechanisms of CD1d-restricted antigen presentation are being unraveled, and a surprising connection has been made to proteins that control lipid metabolism and atherosclerosis. It appears that several microorganisms have developed strategies to interfere with the CD1d antigen-presentation pathway. New studies have also provided important insight into the mechanisms that control effector cell differentiation of NKT cells and have revealed specialized functions of distinct NKT cell subsets. Finally, there is continued enthusiasm for the development of NKT cell-based therapies of human diseases.

x. Platelets

REVIEW:
von Hundelshausen, P
Platelets as Immune Cells
Circ Res 2007;100:27 - 40

Beyond an eminent role in hemostasis and thrombosis, platelets are characterized by expert functions in assisting and modulating inflammatory reactions and immune responses. This is achieved by the regulated expression of adhesive and immune receptors on the platelet surface and by the release of a multitude of secretory products including inflammatory mediators and cytokines, which can mediate the interaction with leukocytes and enhance their recruitment. In addition, platelets are characterized by an enormous surface area and open canalicular system, which in concert with specialized recognition receptors may contribute to the engulfment of serum components, antigens, and pathogens. Platelet-dependent increases in leukocyte adhesion may not only account for an exacerbation of atherosclerosis, for arterial repair processes, but also for lymphocyte trafficking during adaptive immunity and host defense. This review compiles a selection of platelet-derived tools for bridging inflammation and vascular disease and highlights the molecular key components governing platelet-mediated mechanisms operative in immune surveillance, vascular remodeling, and atherosclerosis.

REVIEW:
Elzey BD, Tian J, Jensen RJ, et al.
Platelet-Mediated Modulation of Adaptive Immunity. A Communication Link between Innate and Adaptive Immune Compartments
Immunity 2003;19:9-19

Platelets are highly reactive components of the circulatory system with well-documented hemostatic function. Recent studies extend platelet function to modulation of local inflammatory events through the release of chemokines, cytokines, and a number of immunomodulatory ligands, including CD154. We hypothesized that platelet-derived CD154 modulates adaptive immunity. The data reported herein demonstrate that platelets, via CD154, induce dendritic cell maturation, B cell isotype switching, and augment CD8+ T cell responses both in vitro and in vivo. Platelet

transfusion studies demonstrate that platelet-derived CD154 alone is sufficient to induce isotype switching and augment T lymphocyte function during viral infection, leading to enhanced protection against viral rechallenge. Additionally, depletion of platelets in normal mice results in decreased antigen-specific antibody production.

xi. Epithelium

REVIEW:
Schleimer R
Epithelium: At the interface of innate and adaptive immune responses
J Allergy Clin Immunol 2007;120:1279-84
Several diseases of the airways have a strong component of allergic inflammation in their cause, including allergic rhinitis, asthma, polypoid chronic rhinosinusitis, eosinophilic bronchitis, and others. Although the roles played by antigens and pathogens vary, these diseases have in common a pathology that includes marked activation of epithelial cells in the upper airways, the lower airways, or both. Substantial new evidence indicates an important role of epithelial cells as both mediators and regulators of innate immune responses and adaptive immune responses, as well as the transition from innate immunity to adaptive immunity. The purpose of this review is to discuss recent studies that bear on the molecular and cellular mechanisms by which epithelial cells help to shape the responses of dendritic cells, T cells, and B cells and inflammatory cell recruitment in the context of human disease. Evidence will be discussed that suggests that secreted products of epithelial cells and molecules expressed on their cell surfaces can profoundly influence both immunity and inflammation in the airways.

B. Immune Mechanisms

1. Innate versus adaptive immunity

REVIEW:
Tosi MF
Innate Immune Responses to Infection
J Allergy Clin Immunol 2005;116:241-9
The human host survives many infectious challenges in the absence of preexisting specific (adaptive) immunity because ofthe existence of a separate set of protective mechanisms that do not depend on specific antigenic recognition. These antigenindependent mechanisms constitute innate immunity. Antimicrobial peptides are released at epithelial surfaces and disrupt the membranes of many microbial pathogens. Toll-like receptors on epithelial cells and leukocytes recognize a range of microbial molecular patterns and generate intracellular signals for activation of a range of host responses. Cytokines released from leukocytes and other cells exhibit a vast array of regulatory functions in both adaptive and innate immunity. Chemokines released from infected tissues recruit diverse populations of leukocytes that express distinct chemokine receptors. Natural killer cells recognize and bind virus-infected host cells and tumor cells and induce their apoptosis. Complement, through the alternative and mannose-binding lectin pathways, mediates antibody-independent opsonization, phagocyte recruitment, and microbial lysis. Phagocytes migrate from the microcirculation into infected tissue and ingest and kill invading microbes. These innate immune mechanisms and their interactions in defense against infection provide the host with the time needed to mobilize the more slowly developing mechanisms of adaptive immunity, which might protect against subsequent challenges.

LANDMARK PUBLICATION:
Krieg AM, Yi A, Matson S et al
CpG motifs in bacterial DNA trigger B-cell activation.
Nature 1995;374:546-549.
Unmethylated CpG dinucleotides are more frequent in the genomes of bacteria and viruses than of vertebrates. We report here that bacterial DNA and synthetic oligodeoxynucleotides containing unmethylated CpG dinucleotides induce murine B cells to proliferate and secrete immunoglobulin in vitro and in vivo. This activation is enhanced by simultaneous signals delivered through the antigen receptor. Optimal B-cell activation requires a DNA motif in which an unmethylated CpG dinucleotide is flanked by two 5' purines and two 3' pyrimidines. Oligodeoxynucleotides containing this CpG motif induce more than 95 percent of all spleen B cells to enter the cell cycle. These data suggest a possible evolutionary link between immune defence based on the recognition of microbial DNA and the phenomenon of `CpG suppression' in vertebrates. The potent immune activation by CpG oligonucleotides has implications for the design and interpretation of studies using `antisense' oligonucleotides and points to possible new applications as adjuvants.

RESEARCH FRONTIER:
Drenth JPH
The Inflammasome – A Linebacker of Innate Defense
N Engl J Med 2006;355:730-733
Three articles recently published in Nature now suggest that by discovering cryopyrin, the researchers stumbled on the Rosetta stone of innateimmunity: a highly conserved and specific response system that detects the presence of microorganisms.

RESEARCH FRONTIER:
Schjetne, KW, Thompson KM, Nilsen N, et al.
Link between innate and adaptive immunity: Toll-like receptor 2 internalizes antigen for presentation to CD4+ T cells and could be an efficient vaccine target.
J Immunology 2003;171:32-36
An ideal vaccine for induction of CD4+ T cell responses should induce local inflammation, maturation of APC, and peptide loading of MHC class II molecules. Ligation of Toll-like receptor (TLR) 2 provides the first two of these three criteria. We have studied whether targeting of TLR2 results in loading of MHC class II molecules and enhancement of CD4+ T cell responses. To dissociate MHC class II presentation from APC maturation, we have used an antagonistic, mouse anti-human TLR2 mAb (TL2.1) as ligand and measured proliferation of a mouse C -specific human CD4+ T cell clone. TL2.1 mAb was 100-1000 times more efficiently presented by APC compared with isotype-matched control mAb. Moreover, TL2.1 mAb was internalized into endosomes and processed by the conventional MHC class II pathway. This novel function of TLR2 represents a link between innate and adaptive immunity and indicates that TLR2 could be a promising target for vaccines.

a. Complement and the innate immune response

REVIEW:
Molina H
Complement and immunity

Rheum Dis Clin North Am. 2004;30:1-18
Our body is in constant interaction with the environment. Some of the interactions involve the recognition and disposal of foreign substances that may harm the delicate balance between health and disease. The foreign elements, or antigens, include infectious organisms and lifeless macromolecules. The ability of the body to recognize what is dangerous and what is inconsequential, and to refrain from damaging what is perceived as self, are the main functions of the immune system. One important component of the innate immune response is the complement system. This article describes the different mechanisms of how complement is activated and the consequence of this activation, followed by a characterization of the complement's role in inflammation and autoimmunity, and the therapeutic considerations emanating from these studies.

REVIEW:
Walport MJ.
Complement: Parts 1&2.
N Eng J Med 2001;344:1058-1066 & 1140-1144.
Complement is part of the innate immune system and underlies one of the main effectormechanisms of antibody-mediated immunity. It has three overarching physiologic activities (Table 1): defending against pyogenic bacterial infection, bridging innate and adaptive immunity, and disposing of immune complexes and the products of inflammatory injury. In this review, each of these activities will be placed in a clinical context. Complement was first identified as a heat-labile principle in serum that complemented" antibodies in the killing of bacteria.
Outline…
Complement and the Defense against Infection
Pyogenic Infections
Complement Deficiency and Neisserial Infections
Mannose-Binding Lectin Deficiency
Complement and the Pathogenesis of Infectious Disease
Abnormalities of Complement Regulation
Activation of C3 C3 Nephritic Factors
Factor H Deficiency
C1 Inhibitor Deficiency
Paroxysmal Nocturnal Hemoglobinuria

REVIEW:
Kemper C and Atkinson J.
T-cell regulation: with complements from innate immunity.
Nature Reviews Immunology 2007;7:9-18.
The complement system was traditionally known as an effector arm of humoral immunity. Today we also recognize it as a main element of the innate immune system. In blood and other body fluids complement is a first line of defense against pathogens, because it becomes fully active within seconds. Active complement fragments attach to the invading pathogen to promote opsonization and lysis, triggering a local inflammatory response. This review focuses on the evolving role of the complement system in the regulation of T-cell responses, from directing the initiation phase, through driving lineage commitment, to regulating the contraction phase.

RESEARCH FRONTIER:

Yalcindag A
The complement component C3 plays a critical role in TH1 and TH2 responses to antigen
J Allergy Clin Immunol 2006;117:1455-61
BACKGROUND: Complement component C3 is synthesized by keratinocytes and is activated after skin injury. C3 is also synthesized by peritoneal macrophages, which are activated by the adjuvant alum. OBJECTIVE: We sought to investigate the role of C3 in inciting allergic skin Inflammation and systemic immune responses after epicutaneous sensitization or intraperitoneal sensitization with antigen. METHODS: C3-deficient (C3-/-) mice and wild-type (WT) control animals were subjected to epicutaneous sensitization with the antigen ovalbumin (OVA) on shaved and tape-stripped skin or intraperitoneal immunization with OVA in alum. RESULTS: Skin Infiltration by eosinophils and expression of mRNA encoding the TH2 cytokines IL-4 and IL-5 in OVA-sensitized skin sites was impaired in C3-/- mice. Splenocytes from epicutaneously sensitized C3-/- mice secreted less IL-4, IL-5, IL-13, and IFN-gamma in response to OVA stimulation than splenocytes from WT control animals. The defect in cytokine secretion by splenocytes was also observed after intraperitoneal immunization of C3-/- mice. C3-/- mice had impaired IgG1, IgG2a, and IgE antibody responses after both epicutaneous and intraperitoneal immunization. The defect in cytokine secretion of C3-/- mice was not due to defective proliferation to antigen, was not observed after anti-CD3 stimulation, and was corrected by the addition of purified C3 protein. CONCLUSION: These results suggest that C3 plays an important role in both the TH1 and TH2 response to antigen in vivo. CLINICAL IMPLICATIONS: The complement pathway might be a potential target in the therapy of allergic diseases.

b. Pattern Recognition Receptors

REVIEW:
Iwasaki A. Medzhitov R
Toll-like receptor control of the adaptive immune responses
Nature Immunol. 2004;5:987-95
Recognition of microbial infection and initiation of host defense responses is controlled by multiple mechanisms. Toll-like receptors (TLRs) have recently emerged as a key component of the innate immune system that detect microbial infection and trigger antimicrobial host defense responses. TLRs activate multiple steps in the inflammatory reactions that help to eliminate the invading pathogens and coordinate systemic defenses. In addition, TLRs control multiple dendritic cell functions and activate signals that are critically involved in the initiation of adaptive immune responses. Recent studies have provided important clues about the mechanisms of TLR-mediated control of adaptive immunity orchestrated by dendritic cell populations in distinct anatomical locations.

REVIEW:
Kaisho T and Akiro S.
Toll-like receptor function and signaling.
J Allergy Clin Immunol 2006; 117:979-987.
Mammals sense pathogen invasion through pattern-recognition receptors. A group of transmembrane proteins, Toll-like receptors (TLRs), play critical roles as pattern-recognition receptors. They are mainly expressed on antigen-presenting cells, such as macrophages or dendritic cells, and their signaling activates antigen-presenting cells to provoke innate immunity and to establish adaptive immunity. Each TLR has common effects, such as inflammatory cytokine

induction or upregulation of costimulatory molecule expression, but also has its specific function, exemplified by type I IFN-inducing ability. These immunoadjuvant effects are not only critical in antimicrobial immunity but are also involved in manifestations of autoimmunity. Furthermore, some TLR agonists are now promising therapeutic tools for various immune disorders, including allergy. Therefore understanding molecular mechanisms on TLRs should be quite useful in the development of therapeutic maneuvers against allergy and autoimmune diseases.

REVIEW:
Gearing A.
Targeting toll-like receptors for drug development: a summary of commercial approaches.
Immunol Cell Biol 2007;85:490-94.
Toll-like receptors (TLRs) are essential mediators of both innate and adaptive immunity by recognizing and eliciting responses upon invasion of pathogens. The response of TLRs must be stringently regulated as exaggerated expression of signalling components as well as pro-inflammatory cytokines can have devastating effects on the host, resulting in chronic inflammatory diseases, autoimmune disorders and aid in the pathogenesis of TLR-associated human diseases. Therefore, it is essential that negative regulators act at multiple levels within TLR signalling cascades, as well as through eliciting negative-feedback mechanisms in order to synchronize the positive activation and negative regulation of signal transduction to avert potentially harmful immunological consequences. This review explores the various mechanisms employed by negative regulators to ensure the appropriate modulation of both immune and inflammatory responses.

REVIEW:
Lang T and Mansell A.
The negative regulation of Toll-like receptor and associated pathways.
Immunol Cell Biol 2007;85:425-34
Toll-like receptors (TLRs) are essential mediators of both innate and adaptive immunity by recognizing and eliciting responses upon invasion of pathogens. The response of TLRs must be stringently regulated as exaggerated expression of signaling components as well as pro-inflammatory cytokines can have devastating effects on the host, resulting in chronic inflammatory diseases, autoimmune disorders and aid in the pathogenesis of TLR-associated human diseases. Therefore, it is essential that negative regulators act at multiple levels within TLR signaling cascades, as well as through eliciting negative-feedback mechanisms in order to synchronize the positive activation and negative regulation of signal transduction to avert potentially harmful immunological consequences. This review explores the various mechanisms employed by negative regulators to ensure the appropriate modulation of both immune and inflammatory responses.

RESEARCH FRONTIER:
LeibundGut-Landmann S, Gross O, et al.
Syk- and CARD9-dependent coupling of innate immunity to the induction of T helper cells that produce interleukin 17.
Nat Immunol 2007; 8:630-38.
Initial demonstration that the Dectin-1-CARD9 signaling pathway is critical for the development of Th17 cells during *C. albicans* infection.

c. Natural Antimicrobial Agents

i. reactive oxygen species

REVIEW:
Lambeth JD
NOX enzymes and the biology of reactive oxygen
Nature Reviews. Immunology 2004;4:181-9
Professional phagocytes generate high levels of reactive oxygen species (ROS) using a superoxidegenerating NADPH oxidase as part of their armoury of microbial mechanisms. The multicomponent phagocyte oxidase (Phox) which has been well characterized over the past tree decades, includes the catalytic subunit gp91phox. The discovery of a family of superoxide-generating homologues of gp91phox has led to the concept that ROS are "intentionally" generated in these cells with distinctive cellular functions related to innate immunity, signal transduction and modification of the extracellular matrix.

ii. releasable granule proteins

REVIEW:
Logan MR. Odemuyiwa SO. Moqbel R
Understanding exocytosis in immune and inflammatory cells: the molecular basis of mediator secretion
J Allergy Clin Immunol 2003;111:923-32
Inflammatory cells secrete proteins from intracellular vesicles or granules by a process referred to either as exocytosis or as degranulation, which is common to all cell types. Exocytosis is a precise term that describes the process of granule or vesicular fusion with the plasma membrane and is accompanied by release of granule/vesicle contents to the cell exterior. This process is of particular significance with respect to tissue damage and remodeling in inflammatory diseases, inasmuch as these changes are the consequences of inflammatory cell activation and mediator elaboration. Despite its unifying importance to all inflammatory cell types, little is known about the precise molecular and intracellular mechanisms that regulate mobilization of secretory granules/vesicles and, ultimately, secretion of mediators from immune and inflammatory cells. This article reviews the mechanisms and molecules currently implicated at distal stages of exocytosis from eosinophils, neutrophils, mast cells, platelets, and macrophages. Conserved molecules identified among inflammatory cell types indicate a convergence of pathways leading to mediator secretion. The identification of essential molecules in the cascade of events leading to exocytosis is critical in the search for novel therapeutic targets aimed at modulating mediator secretion from these cell types.

REVIEW:
Radek K
Antimicrobial peptides: natural effectors of the innate immune system.
Sem Immunopath 2007;29:27-43
Antimicrobial peptides (AMPs) are an evolutionarily conserved component of the innate immune system that defend against invading bacteria, viruses, and fungi through membrane or metabolic disruption. The efficiency of host defense via AMPs derives from the ability of these peptides to quickly identify and eradicate foreign pathogens through precise biochemical mechanisms. Recent advances in this field have expanded the repertoire of activities for AMPs to include

immunostimulatory and immunomodulatory capacity as a catalyst for secondary host defense mechanisms. Further scrutiny of the biochemical and regulatory mechanisms of AMPs will lead to novel alternative approaches to the treatment of human pathogenic disorders.

LANDMARK PUBLICATION:
Ong P
Endogenous Antimicrobial Peptides and Skin Infections in Atopic Dermatitis
N Engl J Med 2002; 347:1151-1160

Background The innate immune system of human skin contains antimicrobial peptides known as cathelicidins (LL-37) and β-defensins. In normal skin these peptides are negligible, but they accumulate in skin affected by inflammatory diseases such as psoriasis. We compared the levels of expression of LL-37 and human β-defensin 2 (HBD-2) in inflamed skin from patients with atopic dermatitis and from those with psoriasis. *Methods* The expression of LL-37 and HBD-2 protein in skin-biopsy specimens from patients with psoriasis, patients with atopic dermatitis, and normal subjects was determined by immunohistochemical analysis. The amount of antimicrobial peptides in extracts of skin samples was also analyzed by immunodot blot analysis (for LL-37) and Western blot analysis (for HBD-2). Quantitative, real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays were used to confirm the relative expression of HBD-2 and LL-37 messenger RNA (mRNA) in the skin-biopsy specimens. These peptides were also tested for antimicrobial activity against *Staphylococcus aureus* with the use of a colony-forming assay. *Results* Immunohistochemical analysis confirmed the presence of abundant LL-37 and HBD-2 in the superficial epidermis of all patients with psoriasis. In comparison, immunostaining for these peptides was significantly decreased in acute and chronic lesions from patients with atopic dermatitis (P=0.006 and P=0.03, respectively). These results were confirmed by immunodot blot and Western blot analyses. Real-time RT-PCR showed significantly lower expression of HBD-2 mRNA and LL-37 mRNA in atopic lesions than in psoriatic lesions (P=0.009 and P=0.02, respectively). The combination of LL-37 and HBD-2 showed synergistic antimicrobial activity by effectively killing *S. aureus*. *Conclusions* A deficiency in the expression of antimicrobial peptides may account for the susceptibility of patients with atopic dermatitis to skin infection with *S. aureus*.

2. Major histocompatibility complex – molecular structure and function

REVIEW:
Al-Daccak R, Mooney N, Charron D.
MHC class II signaling in antigen presenting cells.
Curr Opin Immunol 2004;16:108-113

The MHC class II molecules have been recognized as signaling receptors for more than a decade, and recent work has revealed the importance of their signaling for the immune response. Today, we know that the function of MHC class II molecules on antigen presenting cells (APCs) is not limited to their role as antigen-presenting structures; they are flexible receptors that, by triggering a variety of signaling pathways, can regulate APC activities from proliferation and maturation to apoptosis. Recent advances have provided insights into how these molecules might accommodate such regulation.

REVIEW:
Thorsby E

MHC Structure and Function.
Transplant Proc 1999: 31:713-716
It was Peter A. Gorer who in 1937 was the first to demonstrate a histocompatibility antigen, [1] which led to the discovery of the H-2 complex of histocompatibility antigens in mice. Later a similar complex was found in man, called HLA (first defined on human leukocytes, hence the name human leukocyte antigens), and in many other animals. Together they are called the major histocompatibility complex (MHC) because the corresponding antigens are major histocompatibility antigens (ie, they induce strong alloimmune responses and are mainly responsible for rejection of allografts). It became quickly accepted that the MHC antigens were not created to embarrass transplantation surgeons. Their biological function remained, however, an enigma until the early 1970s, when their important role in antigen recognition by T cells was discovered, particularly through the work of Doherty and Zinkernagel.[2] When the peptide-binding cleft of MHC molecules was first visualized a little more than 10 years ago, [3] their immunobiological role as informers for T cells was fully revealed. A short summary of our present knowledge of the structure and function of the peptidepresenting ("classical") MHC molecules is given here. No attempt will be made to cover the vast amount of literature in this area.

3. Immunogenetics – Gene rearrangements in the generation of immune system diversity

REVIEW:
Rooney S
The role of the non-homologous end-joining pathway in lymphocyte development
Immunol Rev 2004;200:115-131
One of the most toxic insults a cell can incur is a disruption of its linear DNA in the form of a double-strand break (DSB). Left unrepaired, or repaired improperly, these lesions can result in cell death or neoplastic transformation. Despite these dangers, lymphoid cells purposely introduce DSBs into their genome to maximize the diversity and effector functions of their antigen receptor genes. While the generation of breaks requires distinct lymphoid-specific factors, their resolution requires various ubiquitously expressed DNA-repair proteins, known collectively as the non-homologous end-joining pathway. In this review, we discuss the factors that constitute this pathway as well as the evidence of their involvement in two lymphoid-specific DNA recombination events.

REVIEW:
Spicuglia S
Regulation of V(D)J recombination
Curr Opin Immunol 2006;18:158-163
Adaptive immunity is intimately linked to the expression of antigen-specific immunoglobulin and T cell receptor genes and their recombination assembly from germline V, D and J gene segments. This developmentally regulated process relies on the activity of the Rag1–Rag2 recombinase, on accessibility of target gene segments and on monoallelic gene activation. Recent studies have revealed new mechanisms that, along with recombinase activity and locus accessibility, are likely to contribute to the control of V(D)J recombination, including target-site bias by the recombinase, RNA processing and chromosome positioning.

REVIEW:

Nossal GJ,
The Double helix and Immunology.
Nature 2003;421:440-4
The immune system can recognize and produce antibodies to virtually any molecule in the Universe. This enormous diversity arises from the ingenious reshuffling of DNA sequences encoding components of the immune system. Immunology is an example of a field completely transformed during the past 50 years by the discovery of the structure of DNA and the emergence of DNA technologies that followed.

LANDMARK PUBLICATION:
Jerne NK
The somatic generation of immune regulation
Eur J Immunology 1971;1:1-9

4. Antigen-presenting cells – processing and presentation of conventional and superantigens

REVIEW:
Sundberg EJ
TCR recognition of peptide/MHC class II complexes and superantigens
Semin Immunol 2007;19:262-71
Major histocompatibility complex (MHC) class II molecules display peptides to the T cell receptor (TCR). The ability of the TCR to discriminate foreign from self-peptides presented by MHC molecules is a requirement of an effective adaptive immune response. Dysregulation of this molecular recognition event often leads to a disease state. Recently, a number of structural studies have provided significant insight into several such dysregulated interactions between peptide/MHC complexes and TCR molecules. These include TCR recognition of self-peptides, which results in autoimmune reactions, and of mutant self-peptides, common in the immunosurveillance of tumors, as well as the engagement of TCRs by superantigens, a family of bacterial toxins responsible for toxic shock syndrome.

REVIEW:
Rossi, M
Human dendritic cells: potent antigen-presenting cells at the crossroads of innate and adaptive immunity.
J Immunol 2005;175:1373-81
Dendritic cells (DCs) are specialized, bone marrow-derived leukocytes that are critical to the development of immunity. Investigators have emphasized the role of DCs in initiating adaptive or acquired MHC-restricted, Ag-specific T cell responses. More recent evidence supports important roles for DCs in the onset of innate immunity and peripheral tolerance. Progress in the generation of DCs from defined hemopoietic precursors in vitro has revealed the heterogeneity of these APCs and their attendant divisions of labor. This review will address these developments in an attempt to integrate the activities of different DCs in coordinating innate and adaptive immunity.

REVIEW:
Petersson K, Fossberg G, Walse B.
Interplay between superantigens and immunoreceptors

Scand J Immunol 2004;59:345-55.
Superantigens (SAGs) cause a massive T-cell proliferation by simultaneously binding to major histocompatibility complex (MHC) class II on antigen-presenting cells and T-cell receptors (TCRs) on T cells. Despite a common overall three-dimensional fold of these SAGs, they have been shown to bind to MHC class II in different ways. Recently, it has also been shown that SAGs have individual preferences in their binding to the TCRs. They can interact with various regions of the variable ß-chain of TCRs and at least one SAG seems to bind to the a-chain of TCRs. In this review, different subclasses of SAGs are classified based upon their binding mode to MHC class II, and models of trimolecular complexes of MHC–SAG–TCR molecules are described in order to reveal and understand the complexity of SAG-mediated T-cell activation.

RESEARCH FRONTIER:
Llewelyn M
HLA class II polymorphisms determine responses to bacterial superantigens.
J Immunol. 2004;172:1719-26.
The excessive immunological response triggered by microbial superantigens has been implicated in the etiology of a wide range of human diseases but has been most clearly defined for the staphylococcal and streptococcal toxic shock syndromes. Because MHC class II presentation of superantigens to T cells is not MHC-restricted, the possibility that HLA polymorphisms could influence superantigenicity, and thus clinical susceptibility to the toxicity of individual superantigens, has received little attention. In this study, we demonstrate that binding of streptococcal and staphylococcal superantigens to HLA class II is influenced by allelic differences in class II. For the superantigen streptococcal pyrogenic exotoxin A, class II binding is dependent on DQ alpha-chain polymorphisms such that HLA-DQA1*01 alpha-chains show greater binding than DQA1*03/05 alpha-chains. The functional implications of differential binding on T cell activation were investigated in various experimental systems using human T cells and murine Vbeta8.2 transgenic cells as responders. These studies showed quantitative and qualitative differences resulting from differential HLA-DQ binding. We observed changes in T cell proliferation and cytokine production, and in the Vbeta specific changes in T cell repertoire that have hitherto been regarded as a defining feature of an individual superantigen. Our observations reveal a mechanism for the different outcomes seen following infection by toxigenic bacteria.

5. Gell and Coombs Classification of Immune Responses

REVIEW:
Sell S.
“Immunopathology”
In Rich RR, Fleisher TA, Schwartz BD et al editors;
Clinical Immunology: Principles and Practice. 1996 pp 449-477

LANDMARK PUBLICATION:
Coca AF, Cooke RA
On the classification of the phenomenon of hypersensitiveness.
J Immunol 1923;8:163-182

RESEARCH FRONTIER:
van Wijk F, Hoeks, Nierkens S et al

CTLA-4 Signaling Regulates the Intensity of Hypersensitivity Responses to Food Antigens, but is Not Decisive in the Induction of Sensitization
J Immunol 2005;174:174-179
Although food allergy has emerged as a major health problem, the mechanisms that are decisive in the development of sensitization to dietary Ag remain largely unknown. CTLA-4 signaling negatively regulates immune activation, and may play a crucial role in preventing induction and/or progression of sensitization to food Ag. To elucidate the role of CTLA-4 signaling in responses to food allergens, a murine model of peanut allergy was used. During oral exposure to peanut protein extract (PPE) together with the mucosal adjuvant cholera toxin (CT), which induces peanut allergy, CTLA-4 ligation was prevented using a CTLA-4 mAb. Additionally, the effect of inhibition of the CTLA-4 pathway on oral exposure to PPE in the absence of CT, which leads to unresponsiveness to peanut Ag, was explored. During sensitization, anti-CTLA-4 treatment considerably enhanced IgE responses to PPE and the peanut allergens, *Ara h 1*, *Ara h 3*, and *Ara h 6*, resulting in elevated mast cell degranulation upon an oral challenge. Remarkably, antagonizing CTLA-4 during exposure to PPE in the absence of CT resulted in significant induction of Th2 cytokines and an elevation in total serum IgE levels, but failed to induce allergen-specific IgE responses and mast cell degranulation upon a PPE challenge. These results indicate that CTLA-4 signaling is not the crucial factor in preventing sensitization to food allergens, but plays a pivotal role in regulating the intensity of a food allergic sensitization response. Furthermore, these data indicate that a profoundly Th2-biased cytokine environment is insufficient to induce allergic responses against dietary Ag.

a. Type I –Immediate Hypersensitivity Response

REVIEW:
Platts-Mills TA
The role of immunoglobulin E in allergy and asthma
Am J of Respir Crit Care Med;2001 164:S1-5
Abstract: It has been nearly a century since the first suggestion that a soluble factor in plasma or serum might be responsible for the symptoms of allergic disease and asthma, and more than 30 yr since immunoglobulin E (IgE) was identified as the key molecule in mediating what are now described as type 1 hypersensitivity reactions (allergic asthma, allergic rhinitis, food allergy, atopic dermatitis, some forms of drug allergy, and insect sting allergy). Since that time, many of the details of the inflammatory cascade
underlying allergy and asthma have been elucidated, and IgE is now known to play a key upstream role. The goals of this report are to review the cellular and molecular events set in motion by IgE and to examine the evidence for its participation in both the immediate allergic response and the late-phase or chronic inflammatory response in the skin and lungs.

i. IgE binding and signal transduction

REVIEW:
Siraganian RP
Mast cell signal transduction from the high-affinity IgE receptor
Cur Opin Immunol;2003:15:639-46
Antigen-mediated aggregation of IgE bound to its high-affinity receptor on mast cells or basophils initiates a complex series of biochemical events, resulting in the release of mediators that cause allergic inflammation and anaphylactic reactions. Recent progress has defined the molecular

pathways that are involved in stimulating these cells and has shown the importance of protein tyrosine kinases in the subsequent reactions. The activation pathways are regulated both positively and negatively by the interactions of numerous signaling molecules.

RESEARCH FRONTIER:
Cendron AC
An FcgammaRIIa-binding peptide that mimics the interaction between FcgammaRIIa and IgG.
Mol Immunol. 2008;45:307-19
A disulphide-constrained peptide that binds to the low affinity Fc receptor, FcgammaRIIa (CD32) has been identified and its structure solved by NMR. Linear (7-mer and 12-mer) and disulphide-constrained (7-mer) phage display peptide libraries were panned on recombinant soluble FcgammaRIIa genetically fused to HSA (HSA-FcgammaRIIa). Peptides were isolated only from the constrained peptide library and these contained the consensus sequence, CWPGWxxC. Phage clones displaying variants of the peptide consensus sequence bound to FcgammaRIIa and the strongest binding clone C7C1 (CWPGWDLNC) competed with IgG for binding to FcgammaRIIa and was inhibited from binding to FcgammaRIIa by the FcgammaRIIa-blocking antibody, IV.3, suggesting that C7C1 and IgG share related binding sites on FcgammaRIIa. A synthetic disulphide-constrained peptide, pep-C7C1 bound to FcgammaRIIa by biosensor analysis, albeit with low affinity (K(D) approximately 100muM). It was significant that the FcgammaRIIa consensus peptide sequence contained a Proline (Pro(3)), which when substituted with alanine abrogated FcgammaRIIa binding, consistent with Pro(3) contributing to receptor binding. Upon binding of IgG and IgE to their respective Fc receptors (FcgammaRs and FcvarepsilonRI) Pro(329) in the Fc makes a critical interaction with two highly conserved Trp residues (Trp(90) and Trp(113)) of the FcRs. The NMR structure of pep-C7C1 revealed a stabilizing type II beta-turn between Trp(2) and Trp(5), with Pro(3) solvent exposed. Modelling of the pep-C7C1 structure in complex with FcgammaRIIa suggests that Pro(3) of C7C1 binds to FcgammaRIIa by inserting between Trp(90) and Trp(113) of FcgammaRIIa thereby mimicking the molecular interaction made between FcgammaRIIa and IgG.

ii. Preformed and newly synthesized mediator release

REVIEW:
Marone G. Casolaro V. Patella V, et al.
Molecular and cellular biology of mast cells and basophils.
Int Arch Allergy Immunol;1997 114:207-17
In all mammalian species investigated so far, mast cells and basophils are the only cells that synthesize histamine and express plasma membrane receptors that bind IgE with high affinity (Fc epsilonRI). Human basophils and mast cells derive from distinct precursors that originate in the bone marrow and fetal liver and probably circulate in peripheral blood. There is extensive evidence that mast cells and basophils and their mediators are primary effectors of allergic inflammation. Immunologically activated human basophils release two cytokines: IL-4 and IL-13. Expression of several cytokines has been documented in a number of experimental models of human and rodent mast cells. However, to date few studies have analyzed the mechanisms of gene expression in human Fc epsilonRI+ cells. Some of these studies imply a role for NFAT and GATA family members in the IgE-mediated activation of cytokine gene transcription in basophils and

mast cells. Studies of human basophils and mast cells isolated from different anatomic sites have established the different profiles of eicosanoids released by these cells. Recently, the characterization of arachidonic acid pools and the identification of novel enzymes involved in arachidonate remodeling and mobilization clarified in part how eicosanoid productions is regulated in mast cells and basophils. In addition to histamine, human mast cell secretory granules contain the neutral proteases tryptase, chymase and carboxypeptidase that possess several biochemical properties. In particular, tryptase may play a role as a fibrogenic factor and chymase might convert angiotensin I to angiotensin II. Mast cells are present in human heart and in human coronary arteries raising the possibility that local activation of cardiac mast cells might contribute to certain cardiovascular diseases. Recent evidence also suggests that mast cells and basophils can play a role during viral and bacterial infections. It is now evident that in man these two cells not only participate in inflammation associated with allergic disease, but also in chronic and fibrotic disorders affecting several organs and in host defense against bacterial and viral infections.

iii. late phase reactions

REVIEW:
O'Byrne P
Asthma pathogenesis and allergen-induced late responses
J Allergy Clin Immunol 1998;102:S85-S90
Increases in airway eosinophils occur during the late asthmatic response, 7 hours after allergen inhalation, and these can persist for 3 days. Also, increases in airway metachromatic cells occur which are most marked after 7 hours. These increases in airway cells are associated with increases in bone marrow progenitors, which are caused by an increased responsiveness of the bone marrow to IL-5 after allergen because of an increased expression of the IL-5 receptor on the progenitors. These studies suggest that after allergen inhalation, signals are sent from the airways to the bone marrow, which increase production of progenitors and make more cells available to be recruited into the airways.

b. Type II – Antibody induced reactions Response

REVIEW:
Domen RE
An overview of immune hemolytic anemias
Cleve Clin J Med. 1998;65:89-99
Often patients with immune hemolytic anemias present with symptoms that are common in anemia of any cause. In the different types of immune hemolytic anemia, red blood cells are destroyed by processes mediated by antibodies. This article reviews the pathophysiology, diagnosis, and treatment of this group of diseases.

c. Type III – Immune-Complex mediated reactions

REVIEW:
Kohl J.. Gessner JE
On the role of complement and Fc gamma-receptors in the Arthus reaction.
Molecular Immunology. 1999;36:893-903
The contribution of either the complement system or the activation of Fc receptors for IgG (FcyRs) to the inflammatory response in immune complex (IC) disease is puzzling. A series of studies has been performed in mice with engineered deficiencies of either FcgammaRs, the complement

components C3, C4 or the C5a receptor. In addition, different C5-deficient mice strains have been evaluated. Mice with gene targeted disruption of the gamma-subunit, which mediates surface expression and signal transduction of the high affinity Fc receptor type I for IgG (FcgammaRI), the low affinity receptor Fc receptor type III for IgG (FcgammaRIII) and the high affinity receptor type I for IgE (IgepsilonRI), showed an impaired inflammatory response in the reverse passive Arthus reaction in skin, peritoneum and lung. These data suggest, that the activation of FgammaRs is the initial event triggering the inflammatory cascade in IC disease. On the other hand, C5aR deficient mice are either protected from tissue injury induced by ICs, as in the lung, or the degree of the inflammatory response is markedly attenuated, as in peritoneum and skin. A detailed analysis of data obtained with the different knock-out strains revealed that both the activation of the complement system as well as the activation of different effector cells via FcgammaRs contribute to the inflammatory sequelae leading to tissue destruction in IC disease. The relative contributions of FcgammaRI or FcgammaRIII and the main effector cells through which these receptors mediate their effector functions are tissue dependent. The activation of the C5a receptor pathway appears to be the prominent contribution of the complement system.

d. Type IV – Cell mediated /Delayed Hypersensitivity Response

REVIEW:

Biedermann T. Rocken M. Carballido JM

TH1 and TH2 lymphocyte development and regulation of TH cell-mediated immune responses of the skin

J Invest Derm 2004;9:5-14.

Since the first description of the subpopulations of TH1 and TH2 cells, insights into the development and control of these cells as two polarized and physiologically balanced subsets have been generated. In particular, implications of the TH1-TH2 concept for TH cell-mediated skin disorders have been discovered. This article will review the basic factors that control the development of TH1 and TH2 cells, such as the cytokines IL-12 and IL-4 and transcription factors, the possible role of costimulatory molecules, and specialized dendritic cell populations. These regulatory mechanisms will be discussed in the context of polarized TH1 or TH2 skin disorders such as psoriasis and atopic dermatitis. Also presented are the principles that govern how chemokines and chemokine receptors recruit TH1 and TH2 cells to inflammatory sites and how they amplify these polarized TH cell responses. All of these concepts, including a novel role for IL-4-inducing TH1 responses, can contribute to the design of better therapeutic strategies to modulate TH cell-mediated immune responses.

RESEARCH FRONTIER:

Watanabe H

Activation of the IL-1beta-processing inflammasome is involved in contact hypersensitivity.

J Invest Dermatol. 2007;127:1956-63. The inflammasome is a cytosolic protein complex regulating the activation of caspase-1, which cleaves the pro-inflammatory cytokines IL-1beta and IL-18 into their active form. The inflammasome is composed of a NACHT-, LRR- and pyrin (NALP) family member that acts as a sensor for danger signals and the adaptor protein apoptosis-associated speck-like protein containing a CARD domain (ASC), which allows the recruitment of caspase-1 in the complex. In the skin, exposure to contact sensitizers (CS) such as trinitro-chlorobenzene causes an immune response called contact hypersensitivity (CHS) or eczema. In this delayed-type hypersensitivity response, efficient priming of the adaptive immunity depends on

the concomitant activation of the innate immune system, including IL-1beta/IL-18 activation in the skin. To determine if the inflammasome contributes to CHS, we have analyzed its capacity to react to CS in vitro and in vivo. We show here that key components of the inflammasome are present in human keratinocytes and that CS like trinitro-chlorobenzene induce caspase-1/ASC dependent IL-1beta and IL-18 processing and secretion. We also show that ASC- and NALP3-deficient mice display an impaired response to CS. These findings suggest that CS act as danger signals that activate the inflammasome in the skin, and reveal a new role of NALP3 and ASC as regulators of innate immunity in CHS.

6. T cell mediated immunity

REVIEW:
Jiang H
Regulation of Immune Responses by T Cells
N Engl J Med 2006;354:1166-76
The T-cell branch of the immune system can respond to a virtually infinite variety of antigens, in part because it includes a very large repertoire of T-cell clones, each with a unique receptor for antigen. It is inevitable that this diverse repertoire contains T cells with receptors that can recognize the body's own antigens — self-reactive T cells — and instigate harmful autoimmunity. For this reason, a means of restraining such T cells is essential. The controls depend on two mechanisms that not only avert autoimmunity but also maintain protective immunity: shaping of the T-cell repertoire in the thymus and regulation of T cells in the periphery.

a. T cell activation – T cell receptor structure and function, epitope recognition and accessory molecules in signal transduction

REVIEW:
Rudolph MG
How TCRs bind MHCs, peptides, and coreceptors
Ann Rev Immunol 2006;24:419-66
Since the first crystal structure determinations of alphabeta T cell receptors (TCRs) bound to class I MHC-peptide (pMHC) antigens in 1996, a sizable database of 24 class I and class II TCR/pMHC complexes has been accumulated that now defines a substantial degree of structural variability in TCR/pMHC recognition. Recent determination of free and bound gammadelta TCR structures has enabled comparisons of the modes of antigen recognition by alphabeta and gammadelta T cells and antibodies. Crystal structures of TCR accessory (CD4, CD8) and coreceptor molecules (CD3epsilondelta, CD3epsilongamma) have further advanced our structural understanding of most of the components that constitute the TCR signaling complex. Despite all these efforts, the structural basis for MHC restriction and signaling remains elusive as no structural features that define a common binding mode or signaling mechanism have yet been gleaned from the current set of TCR/pMHC complexes. Notwithstanding, the impressive array of self, foreign (microbial), and autoimmune TCR complexes have uncovered the diverse ways in which antigens can be specifically recognized by TCRs.

REVIEW:
Kuhns MS
Deconstructing the form and function of the TCR/CD3 complex.
Immunity. 2006;24:133-9

When T cells encounter antigens via the T cell antigen receptor (TCR), information about the quantity and quality of antigen engagement is relayed to the intracellular signal transduction machinery. This process is poorly understood. The TCR itself lacks a significant intracellular domain. Instead, it is associated with CD3 molecules that contain intracellular signaling domains that couple the TCR/CD3 complex to the downstream signaling machinery. The earliest events in TCR signaling must involve the transfer of information from the antigen binding TCR subunit to the CD3 signaling subunits of the TCR/CD3 complex. Elucidating the structural organization of the TCR with the associated CD3 signaling molecules is necessary for understanding the mechanism by which TCR engagement is coupled to activation. Here, we review the current state of our understanding of the structure and organization of the TCR/CD3 complex.

REVIEW:
Choudhuri K.
Molecular mechanisms involved in T cell receptor triggering.
Semin Immunol. 2007 Aug;19:255-61
Despite intensive investigation we still do not understand how the T cell antigen receptor (TCR) tranduces signals across the plasma membrane, a process referred to as TCR triggering. Three basic mechanisms have been proposed, involving aggregation, conformational change, or segregation of the TCR upon binding pMHC ligand. Given the low density of pMHC ligand it remains doubtful that TCR aggregation initiates triggering, although it is likely to enhance subsequent signalling. Structural studies to date have not provided definitive evidence for or against a conformational change mechanism, but they have ruled out certain types of conformational change. Size-induced segregation of the bound TCR from inhibitory membrane tyrosine phosphatases seems to be required, but is probably not the only mechanism. Current evidence suggests that TCR triggering is initiated by a combination of segregation and conformational change, with subsequent aggregation contributing to amplification of the signal.

REVIEW:
Woodfolk JA
T-cell responses to allergens
J Allergy Clin Immunol 2007.119:280-294
This article highlights recent advances in the characterization of allergen-specific memory TH2 cells and discusses the heterogeneous nature of regulatory T cells and possible mechanisms of action. The relevance of T-cell epitope mapping studies to understanding the unique nature of T-cell responses to different allergens, as well as to peptide vaccine development, is reviewed.

b. Cytokines and co-stimulatory molecules in T cell activation

REVIEW:
Kallinich T
T-cell co-stimulatory molecules: their role in allergic immune reactions. -
Eur Respir J 2007; 29:1246-55
A key role in the fine tuning of any T-cell response is provided by the engagement of so- called co-stimulatory molecules that are required for the full activation of T-cells and the recognition of antigens via the antigen-specific T-cell receptor. Due to their pivotal impact on T-cell differentiation and control, co-stimulatory molecules are promising targets for therapeutic intervention in T-cell-regulated or -mediated immune disorders, including allergic diseases and

asthma. In this excellent review, an attempt is made to summarise the current knowledge on the basic concept of co-stimulation, the presently known co-stimulatory molecules and their various functions on T-cell activation or suppression.

REVIEW:
Ziegler S.
Thymic stromal lymphopoietin in normal and pathogenic T cell development and function.
Nature Immunol 2006;7:709-14
Thymic stromal lymphopoietin, a four helix-bundle cytokine, is expressed mainly by barrier epithelial cells and is a potent activator of several cell types, particularly myeloid dendritic cells. TSLP influences the outcome of interactions between dendritic cells and CD4+ thymocytes and T cells in many situations, such as the regulation of the positive selection of regulatory T cells, maintenance of peripheral CD4+ T cell homeostasis and induction of CD4+ T cell-mediated allergic inflammation.

REVIEW:
Gutcher I
APC-derived cytokines and T cell polarization in autoimmune inflammation
J Clin Invest 2007;117:1119-1127
T cell-mediated autoimmune diseases such as multiple sclerosis and rheumatoid arthritis are driven by autoaggressive Th cells. The pathogenicity of such Th cells has, in the past, been considered to be dictated by their cytokine polarization profile. The polarization of such effector T cells relies critically upon the actions of cytokines secreted by APCs. While Th1 polarization has long been associated with the pathogenesis of autoimmune diseases, recent data obtained in gene-targeted mice and the discovery of Th17 cell involvement in autoimmunity conflict with this hypothesis. In light of these recent developments, we discuss in this review the actions of APC-derived cytokines and their emerging roles in T cell polarization in the context of autoimmune inflammatory responses.

c. T cell mediated immune responses – participating cells. Properties and functions of antigen presenting cells.

REVIEW:
Vallejo AN.
Biology Of T lymphocytes
Rheum Dis Clin North Am 2004:30:135-157
This is a good overview of the subject. Molecular mechanisms are not reviewed in depth. The review covers antigen recognition, TCR structure and function and diversity, T cell development, subsets and senescence, innate immunity, activation and regulation, T cell dependent tolerance and auto immunity.

REVIEW:
Sundberg EJ
TCR recognition of peptide/MHC class II complexes and superantigens
Semin Immunol 2007;19:262-271
Major histocompatibility complex (MHC) class II molecules display peptides to the T cell receptor (TCR). The ability of the TCR to discriminate foreign from self-peptides presented by MHC

molecules is a requirement of an effective adaptive immune response. Dysregulation of this molecular recognition event often leads to a disease state. Recently, a number of structural studies have provided significant insight into several such dysregulated interactions between peptide/MHC complexes and TCR molecules. These include TCR recognition of self-peptides, which results in autoimmune reactions, and of mutant self-peptides, common in the immunosurveillance of tumors, as well as the engagement of TCRs by superantigens, a family of bacterial toxins responsible for toxic shock syndrome.

RESEARCH FRONTIER:
Wells JW
Regulation of allergic airway inflammation by class I-restricted allergen presentation and CD8 T-cell infiltration.
J Allergy Clin Immunol 2007; 119:226-34
This study explores the dynamics, nature, and immunoregulatory activities of the class I CD8 T-cell response to inhaled allergen using a murine model of respiratory allergen sensitization, adoptive transfer of transgenic T cells, and flow cytometric analysis of lung infiltrates. The data suggest that CD8 cells specific for inhaled allergens are generated in draining lymph nodes but suppress allergic airway inflammation through induction of IL-12 in the lung during interaction with respiratory dendritic cells. The clinical implications for allergen induced asthma include using novel peptide immunotherapeutics which target the class I-restricted CD8 T-cell response to allergen.

RESEARCH FRONTIER:
Schmidt-Weber CB
TH17 cells in the big picture of immunology
J Allergy Clin Immunol 2007; 120; 247-254
The pathogenesis of chronic inflammatory diseases is assumed to depend on activated T cells interacting with resident tissue cells or migratory inflammatory cells. The discovery of new T-cell subsets such as the IL-17–producing T_H17 and T-regulatory cells innovated our understanding of T-cell biology. Studies on new subsets confirm the important role of T cells in the instruction of tissue cells and also demonstrate the important role of feedback regulation for the polarization toward distinct T-cell subsets. The understanding of IL-17 and T_H17 differentiation pathways has also changed the perspective of immunologists regarding the basis of chronic tissue inflammation, particularly where T_H1 cells were considered as driving force of the pathology. This review summarizes the recent developments on T_H cell subsets and integrates these findings into existing concepts of immunopathologic mechanisms.

LANDMARK PUBLICATION:
Cher DJ, Mosmann TR.
Two types of murine helper T cell clone. II. Delayed-Type Hypersensitivity is Mediated by TH1 Clones.
J Immunology 1987;138:3688-94.
We have previously shown that at least two types of Lyt-1+, Lyt-2-, L3T4+ helper T cell clones can be distinguished in vitro by different patterns of lymphokine secretion and by different forms of B cell help. Evidence is presented here to show that one type of helper T cell clone (TH1) causes delayed-type hypersensitivity (DTH) when injected with the appropriate antigen into the

footpads of naive mice. The antigen-specific, major histocompatability complex (MHC)-restricted footpad swelling reaction peaked at approximately 24 hr. Footpad swelling was induced by all TH1 clones tested so far, including clones specific for soluble, particulate, or allogeneic antigens. In contrast, local transfer of TH2 cells and antigen did not produce a DTH reaction, even when supplemented with syngeneic spleen accessory cells. Similarly, local transfer of an alloreactive cytotoxic T lymphocyte clone into appropriate recipients did not produce DTH. The requirements for the DTH reaction induced by TH1 cells were investigated further by using TH1 clones with dual specificity for both foreign antigens and M1s antigens. Although these clones responded in vitro to either antigen + syngeneic presenting cells, or M1s disparate spleen cells, they responded in vivo only to antigen + MHC and did not cause footpad swelling in an M1s-disparate mouse in the absence of antigen. Moreover, in vitro preactivation of TH1 or TH2 cells with the lectin concanavalin A was insufficient to induce DTH reactions upon subsequent injection into footpads. From these results, we conclude that the lack of DTH given by TH2 clones in vivo could be due to the inability of the TH2 cells to produce the correct mediators of DTH, or to a lack of stimulation of TH2 clones in the footpad environment.

LANDMARK PUBLICATION:
Cherwinski HM, Schumacher JH, Brown KD, Mosmann TR.
Two types of murine helper T cell clone. III. Further Differences in Lymphokine Synthesis between Th1 and Th2 Clones Revealed by RNA Hybridization, Functionally Monospecific Bioassays, and Monoclonal Antibodies.
J Exp Med 1987;166:1229-44.
Lymphokine synthesis patterns of a panel of 19 T cell clones have been evaluated, using mRNA hybridization methods to examine 11 different mRNAs induced by Con A. The two types of CD4+ Th cell clone described previously were clearly distinguished by this procedure, and the differences between the two types have now been extended to six induced products. With minor exceptions, only Th1 clones synthesized mRNA for IL-2, IFN-gamma, and lymphotoxin, and only Th2 clones synthesized mRNA for IL-4, IL-5, and another induced gene, P600. Four more induced products were expressed preferentially but not uniquely by one or another type of clone: mRNAs for GMCSF, TNF, and another induced, secreted product (TY5) were produced in larger amounts by Th1 clones, whereas preproenkephalin was preferentially expressed by Th2 clones. IL-3 was produced in similar amounts by both types of clone. mAbs were used to establish three bioassays that were functionally monospecific for IL-2, IL-3, and IL-4, and a new anti-IFN gamma mAb, XMG1.2, was used to establish an ELISA for IFN-gamma. These four assays were used to show that secreted protein and mRNA levels correlated well for all cell lines. The implications of these findings for normal T cells are discussed.

LANDMARK PUBLICATION:
Fiorentino DF, Bond MW, Mosmann TR
Two types of murine helper T cell clone. IV. Th2 Clones Secrete a Factor that Inhibits Cytokine Production by Th1 Clones..
J Exp Med 1989;170:2081-95.
A cytokine synthesis inhibitory factor (CSIF) is secreted by Th2 clones in response to Con A or antigen stimulation, but is absent in supernatants from Con A-induced Th1 clones. CSIF can inhibit the production of IL-2, IL-3, lymphotoxin (LT)/TNF, IFNgamma, and granulocyte-macrophage CSF (GM-CSF) by Th1 cells responding to antigen and APC, but Th2 cytokine

synthesis is not significantly affected. Transforming growth factor beta (TGF-beta) also inhibits IFN-gamma production, although less effectively than CSIF, whereas IL-2 and IL-4 partially antagonize the activity of CSIF. CSIF inhibition of cytokine synthesis is not complete, since early cytokine synthesis (before 8 h) is not significantly affected, whereas later synthesis is strongly inhibited. In the presence of CSIF, IFN-gamma mRNA levels are reduced slightly at 8, and strongly at 12 h after stimulation. Inhibition of cytokine expression by CSIF is not due to a general reduction in Th1 cell viability, since actin mRNA levels were not reduced, and proliferation of antigen-stimulated cells in response to IL-2, was unaffected. Biochemical characterization, mAbs, and recombinant or purified cytokines showed that CSIF is distinct from IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IFN-gamma, GM-CSF, TGF-beta, TNF, LT, and P40. The potential role of CSIF in crossregulation of Th1 and Th2 responses is discussed.

RESEARCH FRONTIER:
Zou L, Barnett B, Safah H, et al.
Bone Marrow is a Reservoir for CD4+CD25+ Regulatory T cells that Traffic through CXCL12/CXCR4 signals.
Cancer Res 2004,64:8451-5.
CD4(+)CD25(+) regulatory T cells (Tregs) mediate peripheral T-cell homeostasis and contribute to self-tolerance. Their homeostatic and pathologic trafficking is poorly understood. Under homeostatic conditions, we show a relatively high prevalence of functional Tregs in human bone marrow. Bone marrow strongly expresses functional stromal-derived factor (CXCL12), the ligand for CXCR4. Human Tregs traffic to and are retained in bone marrow through CXCR4/CXCL12 signals as shown in chimeric nonobese diabetic/severe combined immunodeficient mice. Granulocyte colonystimulating factor (G-CSF) reduces human bone marrow CXCL12 expression invivo, associated with mobilization of marrow Tregs to peripheral blood in human volunteers. These findings show a mechanism for homeostatic Treg trafficking and indicate that bone marrow is a significant reservoir for Tregs. These data also suggest a novel mechanism explaining reduced acute graft-versus-host disease and improvement in autoimmune diseases following G-CSF treatment. Rasmitogen activated protein kinase activation. These pathways activate transcription factors, such as activator protein 1, nuclear factor of activated T cells, and Rel proteins, which ultimately lead to the expression of genes that control cellular proliferation, differentiation, anergy, or apoptosis. This review also describes how costimulatory receptors assist in signal transduction and assembly ofmacromolecular complexes at the TCR contact site with the antigen-presenting cell, also known as the immune synapse. These basic concepts of TCR signal transduction will be used in part 2 to explain how T-cell function can be altered by therapeutic targeting of TCR signaling components, as well as to explain modification of TCR signaling during T(H)1/T(H)2 differentiation, tolerance, and immune senescence.

d. T cell subsets

REVIEW:
Jiang H
An integrated view of suppressor T cell subsets in immunoregulation
J Clin Invest 2004;114:1198-208
The immune system evolved to protect organisms from a virtually infinite variety of disease-causing agents but to avoid harmful responses to self. Because immune protective mechanisms include the elaboration of potent inflammatory molecules, antibodies, and killer cell activation--

which together can not only destroy invading microorganisms, pathogenic autoreactive cells, and tumors, but also mortally injure normal cells--the immune system is inherently a "double-edged sword" and must be tightly regulated. Immune response regulation includes homeostatic mechanisms intrinsic to the activation and differentiation of antigen-triggered immunocompetent cells and extrinsic mechanisms mediated by suppressor cells. This review series will focus on recent advances indicating that distinct subsets of regulatory CD4+ and CD8+ T cells as well as NK T cells control the outgrowth of potentially pathogenic antigen-reactive T cells and will highlight the evidence that these suppressor T cells may play potentially important clinical roles in preventing and treating immune-mediated disease. Here we provide a historical overview of suppressor cells and the experimental basis for the existence of functionally and phenotypically distinct suppressor subsets. Finally, we will speculate on how the distinct suppressor cell subsets may function in concert to regulate immune responses.

REVIEW:
Stockinger B.
Differentiation and function of Th17 T cells.
Current Opinion in Immunology2007;19:281-6.
IL-17-producing T cells have recently been classified as a new effector T-cell subset, termed Th17, which is distinct from Th1, Th2 and Treg subsets. There has been much progress in the past year, leading to identification of the molecular mechanisms that drive differentiation of Th17 T cells. This has helped to clarify many aspects of their role in host defense as well as in autoimmunity. Nevertheless, many intriguing questions remain to be answered regarding the regulation of Th17-mediated responses as well as their interactions with the other T-cell subsets. Furthermore, the role of pathogens and pathogen-derived molecules in influencing effector T-cell polarization needs to be re-evaluated in the light of the differentiation conditions that favor Th17 T-cell responses.

REVIEW:
Schmidt-Weber CB.
TH17 cells in the big picture of immunology
J Allergy Clin Immunol 2007;120:247-254
The pathogenesis of chronic inflammatory diseases is assumed to depend on activated T cells interacting with resident tissue cells or migratory inflammatory cells. The discovery of new T-cell subsets such as the IL-17-producing T(H)17 and T-regulatory cells innovated our understanding of T-cell biology. Studies on new subsets confirm the important role of T cells in the instruction of tissue cells and also demonstrate the important role of feedback regulation for the polarization toward distinct T-cell subsets. The understanding of IL-17 and T(H)17 differentiation pathways has also changed the perspective of immunologists regarding the basis of chronic tissue inflammation, particularly where T(H)1 cells were considered as driving force of the pathology. This review summarizes the recent developments on T(H) cell subsets and integrates these findings into existing concepts of immunopathologic mechanisms

REVIEW:
Van Kaer. L
NKT cells: T lymphocytes with innate effector functions
Curr Opin Immunol 200719:354-64

Natural killer T (NKT) cells are innate-like T lymphocytes that recognize glycolipid antigens in the context of the MHC class I-related glycoprotein CD1d. Recent studies have identified multiple ways in which NKT cells can become activated during microbial infection. Mechanisms of CD1d-restricted antigen presentation are being unraveled, and a surprising connection has been made to proteins that control lipid metabolism and atherosclerosis. It appears that several microorganisms have developed strategies to interfere with the CD1d antigen-presentation pathway. New studies have also provided important insight into the mechanisms that control effector cell differentiation of NKT cells and have revealed specialized functions of distinct NKT cell subsets. Finally, there is continued enthusiasm for the development of NKT cell-based therapies of human diseases.

e. Regulatory T cells and Memory T Cells

REVIEW:
Goleva E.
Factors that regulate naturally occurring T regulatory cell-mediated suppression
J Allergy Clin Immunol 2005. 116: 1094-100
This review discusses the factors that regulate naturally occurring Treg (nTreg) cell-mediated suppression. The involvement of cytokines, costimulatory molecules, and ligands on antigen-presenting cells in the inhibition of nTreg cell-mediated suppression in vitro is summarized. Applications to disease states is discussed.

RESEARCH FRONTIER:
Watanabe N.
Hassall's Corpuscles instruct dendritic cells to induce CD4+CD25+ regulatory T cells in human thymus
Nature 2005;436:1181-85
Hassall's corpuscles-first described in the human thymus over 150 years ago-are groups of epithelial cells within the thymic medulla. The physical nature of these structures differs between mammalian species. Although Hassall's corpuscles have been proposed to act in both the removal of apoptotic thymocytes and the maturation of developing thymocytes within the thymus, the function of Hassall's corpuscles has remained an enigma. Here we report that human Hassall's corpuscles express thymic stromal lymphopoietin (TSLP). Human TSLP activates thymic CD11c-positive dendritic cells to express high levels of CD80 and CD86. These TSLP-conditioned dendritic cells ar able to induce the proliferation and differentiation of CD4(+)CD8(-)CD25(-) thymic T cells into CD4(+)CD25(+)FOXP3(+) (forkhead box P3) regulatory T cells. This induction depends on peptide-major histocompatibility complex class II interactions, and the presence of CD80 and CD86, as well as interleukin 2. Immunohistochemistry studies reveal that CD25(+)CTLA4(+) (cytotoxic T-lymphocyte-associated protein 4) regulatory T cells associate in the thymic medulla with activated or mature dendritic cells and TSLP-expressing Hassall's corpuscles. These findings suggest that Hassall's corpuscles have a critical role in dendritic-cell-mediated secondary positive selection of medium-to-high affinity self-reactive T cells, leading to the generation of CD4(+)CD25(+) regulatory T cells within the thymus.

REVIEW:
Akdis M, Blaser K, Akdis CA
T regulatory cells in allergy: Novel concepts in the pathogenesis, prevention, and treatment of allergic diseases.

J Allergy Clin Immunol 2005;116: 949-959
The identification of T regulatory (TReg) cells as key regulators of immunologic processes in peripheral tolerance to allergens has opened an important era in the prevention and treatment of allergic diseases. Both naturally occurring CD4+CD25+ TReg cells and inducible populations of allergen-specific IL-10–secreting TR1 cells inhibit allergenspecific effector cells in experimental models. Allergen-specific TReg cell responses contribute to the control of allergic inflammation in several ways. Skewing of allergenspecific effector T cells to a TReg phenotype appears to be a crucial event in the development of a healthy immune response to allergens and successful outcome in allergen-specific immunotherapy. The increased levels of IL-10 and TGF-β produced by TReg cells can potently suppress IgE production while simultaneously increasing the production of the noninflammatory antibody isotypes IgG4 and IgA, respectively. TReg cells directly or indirectly suppress effector cells of allergic inflammation, such as mast cells, basophils, and eosinophils, and contribute to remodeling in asthma and atopic dermatitis. In addition, mediators of allergic inflammation that trigger cyclic AMP– associated G protein–coupled receptors, such as histamine receptor 2, might play a role in peripheral tolerance mechanisms against allergens. Current strategies for drug development and allergen-specific immunotherapy exploit these observations with the potential to provide cure for allergic diseases.

REVIEW:
Bacchetta R
Role of regulatory T cells and FOXP3 in human diseases
J Allergy Clin Immunol 2007;120:227-235
Immune regulation and tolerance are specific functions of the immune system, meaning at prevention or limitation of effector immune responses against inner and external insults. Regulatory T (Treg) cells are crucial players in this immune balance network. Research over the last 10 years has significantly contributed to characterizing Treg cell features, their mechanisms of function, and their role in human pathologies. The discovery of FOXP3 as an essential transcription factor not only for differentiation and function of naturally occurring Treg cells but also for regulation of intracellular molecules related to effector T-cell responses has provided new insights into the pathogenesis of immune-mediated diseases. Interestingly, there is increasing evidence that the individual signature of genes relevant for immune regulation definitely influences the final outcome of an immune response.

REVIEW:
Foley SH
Images in allergy and immunology: Regulatory T cells in allergic disease
J Allergy Clin Immunol 2007;120:482-86
An excellent pictorial review some of the discoveries that suggest that regulatory T cells are playing a central role in the pathophysiology and treatment of allergic disorders such as allergen immunotherapy.

REVIEW:
Tan JT
T cell memory
Curr Top Microbiol Immunol 2006;311:85-115.
Typical immune responses lead to prominent clonal expansion of antigen-specific T and

B cells followed by differentiation into effector cells. Most effector cells die at the end of the immune response but some of these cells survive and form long-lived memory cells. The factors controlling the formation and survival of memory T cells are reviewed.
T cell memory induced by prior infection or vaccination provides enhanced protection against subsequent microbial infections. The processes involved in generating and maintaining T cell memory are becoming better understood due to recent technological advances in identifying memory T cells and monitoring their behavior and function in vivo. Memory T cells develop in response to a progressive set of cues-starting with signals from antigen-loaded, activated antigen-presenting cells (APCs) and inflammatory mediators induced by the innate immune response, to the poorly defined subsequent signals triggered as the immune response wanes toward homeostasis. The persistence of the resting memory T cells that eventually develop is regulated by cytokines. This chapter discusses recent findings on how memory T cells develop to confer long-term protective immunity.

REVIEW:
Woodfolk J
T-cell responses to allergens.
J Allergy Clin Immunol 2007;119:280-94
The allergic response in human beings is engineered by CD4(+) T lymphocytes, which secrete T(H)2 cytokines in response to activation by allergen-derived peptides. Although T(H)2 cells have been well characterized, defining the properties of allergen-specific T cells has proved challenging in human beings because of their low frequency within the T-cell repertoire. However, recent studies have provided insight into the molecular signature of long-lived human memory T(H)2 cells, which are allergen-specific. T-cell responses directed against allergens develop in early life and are heavily influenced by the type and dose of allergen, and possibly coexposure to microbial products. These responses are susceptible to suppression by regulatory T cells. This article highlights recent advances in the characterization of allergen-specific memory T(H)2 cells and discusses the heterogeneous nature of regulatory T cells and possible mechanisms of action. The relevance of T-cell epitope mapping studies to understanding the unique nature of T-cell responses to different allergens, as well as to peptide vaccine development, is reviewed. Experimental techniques and approaches for analyzing allergen-specific T cells and identifying novel T-cell epitopes are described that may lead to new T-cell-based therapies.

RESEARCH FRONTIER:
Wang YH
Maintenance and polarization of human TH2 central memory T cells by thymic stromal lymphopoietin-activated dendritic cells
Immunity. 2006;24:827-38
The identity of TH2 memory cells and the mechanism regulating their maintenance during allergic inflammation remain elusive. We report that circulated human CD4+ T cells expressing the prostaglandin D2 receptor (CRTH2) are TH2 central memory T cells, characterized by their phenotype, TH2 cytokine production, gene-expression profile, and the ability to respond to allergens. Only dendritic cells (DCs) activated by thymic stromal lymphopoietin (TSLP) can induce a robust expansion of CRTH2+CD4+ TH2 memory cells, while maintaining their central memory phenotype and TH2 commitments. CRTH2+CD4+ TH2 memory cells activated by TSLP-DCs undergo further TH2 polarization and express cystatin A, Charcot-Leydon crystal protein, and

prostaglandin D2 synthase, implying their broader roles in allergic inflammation. Infiltrated CRTH2+CD4+ TH2 effector memory T cells in skin lesion of atopic dermatitis were associated with activated DCs, suggesting that TSLP-DCs play important roles not only in TH2 priming, but also in the maintenance and further polarization of TH2 central memory cells in allergic diseases.

RESEARCH FRONTIER:
Allakhverdi Z
Expression of CD103 identifies human regulatory T-cell subsets.
J Allergy Clin Immunol 2006;118:1342-9
BACKGROUND: Analysis of naturally occurring T regulatory CD4+ (nTreg) cells in human diseases is hampered by the lack of specific surface marker. Indeed, the CD25 antigen, which is typically used to identify nTreg cells, is also expressed on activated effector T cells. OBJECTIVE: We sought to examine whether CD4+ T cells bearing CD103 are suppressor cells, regardless of CD25 coexpression. METHODS: We first compared freshly isolated tonsillar CD103+ CD25- cells with their CD103- CD25high counterparts for their capacity to suppress T-cell response and their expression of FoxP3 mRNA. Next CD103 was induced on neonatal or adult CD4+ T cells stimulated with allogeneic dendritic cells, and the CD103+ and CD103- fractions were compared as above. RESULTS: Tonsillar CD4+ CD103+ CD25- T cells displayed comparable suppressive activity and contained similar amounts of FoxP3 mRNA as their CD103- CD25high counterparts. In vitro-generated alloantigen-primed CD103+ cells coexpressed CD25, suppressed T-cell activation, and contained more FoxP3 mRNA than the CD103- CD25+ cells isolated from the same cultures. Finally, neonatal alloreactive cells contained more CD103+ Treg cells than their adult counterparts and, unlike the latter, became hyporesponsive to the priming alloantigens. CONCLUSIONS: The examination of CD103 and CD25 coexpression allows identification of 3 subsets of human CD4+ nTreg cells, and the detection of CD103 on CD4+ T cells identifies nTreg cells, regardless of CD25 coexpression. CLINICAL IMPLICATIONS: The greater induction of CD103+ suppressor cells by cord blood should be related to its successful clinical use as an alternative to adult bone marrow transplantation.

f. NK T cells

REVIEW:
Kronenberg M
Toward an understanding of NKT cell biology: progress and paradoxes
Ann Rev Immunol 2005;23:877-900.
Natural killer T (NKT) cells constitute a conserved T cell sublineage with unique properties, including reactivity for a synthetic glycolipid presented by CD1d, expression of an invariant T cell antigen receptor (TCR) alpha chain, and unusual requirements for thymic selection. They rapidly produce many cytokines after stimulation and thus influence diverse immune responses and pathogenic processes. Because of intensive research effort, we have learned much about factors promoting the development and survival of NKT cells, regulation of their cytokine production, and the means by which they influence dendritic cells and other cell types. Despite this progress, knowledge of the natural antigen(s) they recognize and their physiologic role remain incomplete. The activation of NKT cells paradoxically can lead either to suppression or stimulation of immune responses, and we cannot predict which will occur. Despite this uncertainty, many investigators are hopeful that immune therapies can be developed based on NKT cell stimulation.

REVIEW:
Van Kaer. L
NKT cells: T lymphocytes with innate effector functions
Curr Opin Immunol 200719:354-64
Natural killer T (NKT) cells are innate-like T lymphocytes that recognize glycolipid antigens in the context of the MHC class I-related glycoprotein CD1d. Recent studies have identified multiple ways in which NKT cells can become activated during microbial infection. Mechanisms of CD1d-restricted antigen presentation are being unraveled, and a surprising connection has been made to proteins that control lipid metabolism and atherosclerosis. It appears that several microorganisms have developed strategies to interfere with the CD1d antigen-presentation pathway. New studies have also provided important insight into the mechanisms that control effector cell differentiation of NKT cells and have revealed specialized functions of distinct NKT cell subsets. Finally, there is continued enthusiasm for the development of NKT cell-based therapies of human diseases.

RESEARCH FRONTIER:
Akbari O
CD4+ invariant T-cell-receptor+ natural killer T cells in bronchial asthma
N Engl J Med 2006;354:1117-29.
BACKGROUND: Bronchial asthma is associated with an inflammatory process that is characterized by the presence in the airways of large numbers of CD4+ T cells producing interleukin-4 and interleukin-13. However, the CD4 antigen is expressed not only by class II major histocompatibility complex (MHC)-restricted CD4+ T cells, but also by a newly identified subgroup of T cells, CD1d-restricted natural killer T cells. These cells express a conserved (invariant) T-cell receptor and have a potent immunoregulatory function. Because mouse models of allergic asthma indicate that natural killer T cells are required for the development of allergen-induced airway hyperreactivity, we hypothesized that natural killer T cells play an important role in human asthma. METHODS: We used CD1d-tetramers, antibodies specific for natural killer T cells, as well as reverse-transcriptase-polymerase-chain-reaction analysis of the invariant T-cell receptor of natural killer T cells to assess the frequency and distribution of natural killer T cells in the lungs and in the circulating blood of 14 patients with asthma. RESULTS: About 60 percent of the pulmonary CD4+CD3+ cells in patients with moderate-to-severe persistent asthma were not class II MHC-restricted CD4+ T cells but, rather, natural killer T cells. The natural killer T cells expressed an invariant T-cell receptor and produced type 2 helper cytokines. In contrast, the CD4+ T cells found in the lungs of patients with sarcoidosis were conventional CD4+CD3+ T cells, not natural killer T cells. CONCLUSIONS: Together with studies in mice indicating a requirement for natural killer T cells in the development of allergen-induced airway hyperreactivity, our results strongly suggest that CD4+ natural killer T cells play a prominent pathogenic role in human asthma.

7. B cell mediated immunity

REVIEW:
McHeyzer-Williams MG.
B cells as effectors.
Curr Opin Immunol. 2003 Jun;15(3):354-61.
B cells act as immune effectors, primarily through antigen-specific clonal expansion and plasma cell differentiation. B1 (CD5(+)) B cells and marginal zone B cells dominate Tcell independent

humoral responses under the molecular control of activated dendritic cells. Helper T cell-regulated B-cell responses draw on follicular B cells as precursors and rely on qualitatively different patterns of immune synapse formation to regulate Bcell fate. These activities culminate in the germinal center reaction, during which somatic hypermutation and antigendriven selection produce and preserve high-affinity plasma cells with extended longevity and memory B cells as the sensitized precursors for antigen recall.

a. B cell activation – cytokines and signal transduction

REVIEW:
Dal Porto JM
B cell antigen receptor signaling 101
Mol Immunol. 2004;41:599-613
All cells continually survey their environment and make decisions based on cues encountered. This requires specific receptors that detect such cues, then transduce signals that initiate the appropriate responses. B lymphocytes provide an archetypal model for such 'adaptive' cellular responses, where signals transmitted by the B cell Ag-receptor (BCR) influence not only cellular selection, maturation, and survival, but are imperative in generating the ultimate effector function of B cells, i.e. antibody production. While other extracellular stimuli and their cognate receptor signals can also influence B cell development, BCR-mediated signals and the way in which they are integrated and regulated are paramount in defining the cell's physiological fate.

REVIEW:
Gerondakis S.
Regulating B-cell activation and survival in response to TLR signals
Immunol Cell Biol. 2007:85:471-5
Following encounters with microbes, cellular activation programs that involve the control of proliferation and survival are initiated in follicular B cells either via the B-cell receptor in a specific antigen-defined manner, or through Toll-like receptors (TLRs) that recognize specific microbial products. This review summarizes and discusses recent findings that shed light on how the nuclear factor kappaB pathway controls and coordinates B-cell division and survival following TLR4 engagement.

REVIEW:
Kang, J
Cytokine functions in the formative stages of a lymphocyte's life.
Curr Opin Immunol 2004;16:180-90
Five core cytokines that control lymphocyte differentiation and maintenance have been identified and studied in depth. IL-7 sits at the apex of this cytokine hierarchy in terms of functional significance during lymphocyte development. The IL-7-dominant phase of lymphopoiesis is preceded by the actions of c-Kit ligand (also called stem cell factor; SCF) and fetal liver kinase 2 ligand (Flk-2L); the function of both of these cytokines is essential for the maintenance and development of the progenitor compartment of multiple lineages. IL-7 activity is complemented by two cytokines whose receptors share components of the IL-7 receptor: thymic stromal lymphopoietin (TSLP) and IL-15. The influences of these core cytokines on precursor lymphocyte subsets overlap during development and are often synergistic. Recent studies are beginning to uncover the molecular mechanisms of these interrelated core cytokine functions.

REVIEW:
Harnett MM, Katz E, Ford CA.
Differential signaling during B-cell maturation.
Immunol Lett. 2005; Apr 15;98:33-44
The molecular mechanism by which the antigen receptors (BCR) on B cells can elicit differential maturation state-specific responses is one of the central problems in B-cell differentiation yet to be resolved. Indeed, many of the early signalling events detected following BCR ligation, such as activation of protein tyrosine kinases (PTK), phospholipase C (PLC), phosphoinositide-3-kinase (PI 3K), protein kinase C (PKC) and the RasMAPK (mitogen activating protein kinase) signaling cascades are observed throughout B-cell maturation. However, it is becoming clear that the differential functional responses of these BCR-coupled signals observed during B-cell maturation are dependent on a number of parameters including signal strength and duration, subcellular localisation of the signal, maturation-restricted expression of downstream signaling effector elements/isoforms and modulation of signal by co-receptors. Thus, the combined signature of BCR signaling is likely to dictate the functional response and act as a developmental checkpoint for Bcell maturation.

REVIEW:
Gauld SB, Dal Porto JM, Cambier JC.
B cell antigen receptor signaling: roles in cell development and disease.
Science. 2002; May 31;296(5573):1641-2.
Signals propagated through the B cell antigen receptor (BCR) are vital for the development and survival of B lymphocytes in both the bone marrow and the periphery. These signals not only guide maturation and activation but also affect the removal of potentially self-reactive B lymphocytes. Interestingly, these signals are known to be either ligand-independent ("tonic" signals) or induced by ligand (antigen) binding to the BCR. We focus on the problems that occur in B cell development due to defects in signals emanating from the BCR. In addition, we present the B Cell Antigen Receptor Pathway, an STKE Connections Map that illustrates the events involved in B cell signaling

REVIEW:
Patke A
Survival signaling in resting B cells.
Curr Opin Immunol 2004; 16:251-5
The survival of mature resting B cells in the periphery depends on signaling from the Bcell receptor (BCR) and the B-cell activating factor of the TNF family receptor (BAFFR). Engagement of both receptors promotes NF-kappa B activity, which contributes to Bcell survival through different pathways. BCR signaling leads to activation of the inhibitor of NF-kappa B kinase (IKK) complex via Carma1, Bcl10 and MALT1, whereas BAFF-R engagement promotes processing of NF-kappa B2 protein p100, which is dependent on NF-kappa B-inducing kinase (NIK) and IKK alpha. Proximal signaling intermediates are potentially common to both pathways. This study suggests that BCR and BAFF-R survival signaling are mutually dependent and that BAFF-R signaling enhances the expression of survival genes through direct chromatin modifications in NFkappa B target gene promoters.

b. Epitope recognition and immunoglobulin production

REVIEW:
Carrasco YR
B cell recognition of membrane-bound antigen: an exquisite way of sensing ligands
Curr Opinion in Immunology 2006:18(3):286-91
B cell recognition of membrane-bound antigens leads to the formation of an immunological synapse and efficient B cell activation. Ongoing research has been directed towards identifying the parameters that regulate this process. Furthermore, considerable attention has also been focused on the cell types that mediate presentation of intact antigens to B cells, as well as on the mechanisms that underlie it. Whilst there are still many unanswered questions, recent developments in these areas begin to shed light on an emerging field.

REVIEW:
Niiro H and Clark EA.
Regulation of B-cell fate by Antigen-receptor signals.
Nature Rev Immunology. 2002; 2(12) 945-56.
Recent evidence indicates that B cells are instructed continuously by B cell receptor (BCR) signals to make crucial cell-fate decisions at several checkpoints during their development. Targeted disruption of BCR signaling components leads to distinct blocks in B-cell maturation, which indicates that key kinases and adaptors fine-tune BCR signaling to direct appropriate cell fates. Recent progress in unraveling the molecular mechanisms of the BCR signaling pathways has helped to clarify how BCR signals regulate proliferation, survival and apoptosis of developing B cells.

REVIEW:
McHeyzer-Williams LJ and McHeyzer-Williams MG.
Antigen-Specific Memory B Cell Development.
Annu Rev. Immunol. 2005; 23: 487-513.
Helper T (Th) cell–regulated B cell immunity progresses in an ordered cascade of cellular development that culminates in the production of antigen-specific memory B cells. The recognition
of peptide MHC class II complexes on activated antigen-presenting cells is critical for effective Th cell selection, clonal expansion, and effector Th cell function development (Phase I). Cognate effector Th cell–B cell interactions then promote the development of either short-lived plasma cells
(PCs) or germinal centers (GCs) (Phase II). These GCs expand, diversify, and select high-affinity variants of antigen-specific B cells for entry into the long-lived memory B cell compartment (Phase III). Upon antigen rechallenge, memory B cells rapidly expand and differentiate into PCs under the cognate control of memory Th cells (Phase IV). We review the cellular and molecular regulators of this dynamic process with emphasis on the multiple memory B cell fates that develop in vivo.

RESEARCH FRONTIER:
Nair DT
Epitope recognition by diverse antibodies suggests conformational convergence in an antibodyresponse.

J Immunol 2002; 168:2371-82
Crystal structures of distinct mAbs that recognize a common epitope of a peptide Ag have been determined and analyzed in the unbound and bound forms. These Abs display dissimilar binding site structures in the absence of the Ag. The dissimilarity is primarily expressed in the conformations of complementarity-determining region H3, which is responsible for defining the epitope specificity. Interestingly, however, the three Abs exhibit similar complementaritydetermining region conformations in the Ag binding site while recognizing the common epitope, indicating that different pathways of binding are used for Ag recognition. The epitope also exhibits conformational similarity when bound to each of these Abs, although the peptide Ag was otherwise flexible. The observed conformational convergence in the epitope and the Ag binding site was facilitated by the plasticity in the nature of interactions.

RESEARCH FRONTIER:
Zheng NY
Human immunoglobulin selection associated with class switch and possible tolerogenic origins for C delta class-switched B cells.
J Clin Invest 2004; 113:1188-201
Changes to the human antibody repertoire for a well-characterized autoreactivity from antibodies encoded by the V(H)4-34 gene and for other hallmarks of an autoreactive repertoire are apparent mainly for class-switched B cells and not for IgM germinal center, IgM memory, or IgM plasma cells. Other possible indicators of autoreactivity found selected with immunoglobulin class include J(H)6 gene segment usage, increased frequency of B cells with long third hypervariable regions, and distal J(kappa) gene segment bias. Of particular interest is the finding that B cells with these same characteristics are selected into the lineage of B cells that have undergone the unusual class switch from constant region C mu to C delta (C delta-CS). The C delta-CS population also displays
an increased frequency of charged amino acids localized to the complementarity-determining regions, further suggesting autoreactivity, and evidence is presented that these B cells had undergone extensive receptor editing. Thus, the C delta- CS lineage may be a "sink" for B cells harboring autoreactive specificities in normal humans. A model for a new tolerizing mechanism that could account for the C delta-CS lineage is presented.

c. Maturation of B lymphocytes

REVIEW:
Rothenberg EV.
Cell lineage regulators in B and T cell development.
Nat Immunol 2007;8:441-4.
This article provides a nice summary of the contents of a special issue on B and T cell development that highlights a pivotal set of regulatory molecules that have emerged as central controllers of cell identity in the immune system. Pax5 operates at all levels of B cell development, through its unique combination of positive and negative regulatory activities. In the process, it competes with two different antagonists, Notch and Blimp-1, which are each much more stage specific and context dependent than Pax5 in their modes of action.

REVIEW:
Nutt SL.

The transcriptional regulation of B cell lineage commitment.
Immunity 2007;26:715-25.
The expression of lineage-associated genes, as well as the survival and expansion of committed B cell progenitors, is controlled by multiple transcriptional regulators and growth-factor receptors. This review focuses on recent studies that have revealed that efficient B cell commitment requires the combined activity of multiple transcription factors in a complex gene regulatory network.

REVIEW:
Shapiro-Shelef M,
Regulation of Plasma-Cell Development.
Nat Rev Immunol. 2005: 5, 230-242.
Plasma cells are the terminally differentiated, non-dividing effector cells of the B-cell lineage. They are cellular factories devoted to the task of synthesizing and secreting thousands of molecules of clonospecific antibody each second. To respond to microbial pathogens with the necessary specificity and rapidity, B cells are exquisitely regulated with respect to both development in the bone marrow and activation in the periphery. This review focuses on the terminal differentiation of B cells into plasma cells, including the different subsets of B cells that become plasma cells, the mechanism of regulation of this transition, the transcription factors that control each developmental stage and the characteristics of long-lived plasma cells.

RESEARCH FRONTIER:
Tangye SG
Human IgM+CD27+ B cells: memory B cells or "memory" B cells?
J Immunol 2007;179:13-9.
Memory B cells are generated in germinal centers (GC) and contribute to serological immunity by rapidly differentiating into plasma cells. Human memory B cells can be identified by the expression of CD27. These cells exhibit more rapid responses than naïve (CD27-) B cells following stimulation in vitro, consistent with the heightened kinetics of secondary responses in vivo. CD27+ B cells express mutated immunoglobulin V region genes; however, a significant proportion continues to express IgM, suggesting the existence of IgM+ memory B cells. The observation that mutated IgM+CD27+ B cells are generated in humans who cannot form GC led to the conclusions that these cells are generated independently of GC and thus are not memory cells and that they mediate responses to T cell-independent antigen. Although some studies support the idea that IgM+CD27+ B cells participate in T cell-independent responses, many do not. This review provides alternate interpretations of the biology of IgM+CD27+ B cells and proposes that they indeed are memory cells.

RESEARCH FRONTIER:
Cobaleda C
Pax5: the guardian of B cell identity and function.
Nat Immunol 2007;8:463-70.
The transcription factor Pax5 is essential for commitment of lymphoid progenitors to the B lymphocyte lineage. Pax5 fulfills a dual role by repressing B lineage "inappropriate" genes and simultaneously activating B lineage-specific genes. This transcriptional reprogramming restricts the broad signaling capacity of uncommitted progenitors to the B cell pathway, regulates cell adhesion and migration, induces V(H)-DJ(H) recombination, facilitates (pre-)B cell receptor

signaling and promotes development to the mature B cell stage. Conditional Pax5 inactivation in early and late B lymphocytes revealed an essential role for Pax5 in controlling the identity and function of B cells throughout B lymphopoiesis. Pax5 has also been implicated in human B cell malignancies, where it is deregulated by chromosomal translocations in a subset of acute lymphoblastic leukemias and non-Hodgkin lymphomas.

d. Maturation of the antibody response

REVIEW:
De Noia JM
Molecular mechanisms of antibody somatic hypermutation
Annual Rev of Biochem 2007;76:1-22
Functional antibody genes are assembled by V-D-J joining and then diversified by somatic hypermutation. This hypermutation results from stepwise incorporation of single nucleotide substitutions into the V gene, underpinning much of antibody diversity and affinity maturation. Hypermutation is triggered by activation-induced deaminase (AID), an enzyme which catalyzes targeted deamination of deoxycytidine residues in DNA. The pathways used for processing the AID-generated U:G lesions determine the variety of base substitutions observed during somatic hypermutation. Thus, DNA replication across the uracil yields transition mutations at C:G pairs, whereas uracil excision by UNG uracil-DNA glycosylase creates abasic sites that can also yield transversions. Recognition of the U:G mismatch by MSH2/MSH6 triggers a mutagenic patch repair in which polymerase eta plays a major role and leads to mutations at A:T pairs. AID-triggered DNA deamination also underpins immunoglobulin variable (IgV) gene conversion, isotype class switching, and some oncogenic translocations in B cell tumors.

REVIEW:
de Villartay JP, Fischer A, Durandy A.
The mechanisms of immune diversification and their disorders.
Nat Rev Immunol 2003; 3:962--972.
This paper provides a good description of the causes of immunodeficiency with descriptions of generation of diversity and class switch recombination and somatic hypermutation.

REVIEW:
Geha RS, Jabara HH, Brodeur SR.
The regulation of immunoglobulin E class switch recombination.
Nat Rev Immunol. 2003; 3:721--732.
Immunoglobulin E (IgE) isotype antibodies are associated with atopic disease, namely allergic rhinitis, asthma and atopic dermatitis, but are also involved in host immune defense mechanisms against parasitic infection. The commitment of a B cell to isotype class switch to an IgE-producing cell is a tightly regulated process, and our understanding of the regulation of IgE-antibody production is central to the prevention and treatment of atopic disease. Both those that are presently in use and potential future therapies to prevent IgE-mediated disease take advantage of our existing knowledge of the specific mechanisms that are required for IgE class switching.

LANDMARK PUBLICATION:
Muramatsu M

Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential RNA editing enzyme
Cell 2000;102:541-4

LANDMARK PUBLICATION:
Burnet, F. M.
A modification of Jerne's theory of antibody production using the concept of clonal selection.
Australian Journal of Science. 1957: 20, 67-69.

e. Biologic process initiated by antibody: opsonization, complement fixation, antibody dependent cell mediated cytotoxicity

REVIEW:
Joshi T
Fc gamma receptor signaling in phagocytes
Intern J Hematol 2006; 84:210-6
Fcgamma receptors are among the best-studied phagocytic receptors. The key features of Fcgamma receptor-mediated phagocytosis include phagocytic cup formation by extensive actin cytoskeletal rearrangements, particle engulfment, and the release of proinflammatory mediators such as cytokines and reactive oxygen species. These events are elegantly regulated by the simultaneous engagement of activating and inhibitory Fcgamma receptors and by intracellular signaling molecules. Extensive studies in the past several years have defined the molecular mechanisms of the phagocytic process. The purpose of this review is to revisit some of the well-established signaling pathways as well as to summarize the new findings in this field.

REVIEW:
Takai T.
Fc receptors and their role in immune regulation and autoimmunity
J Clin Immunol. 2005;25:1-18
The activation threshold of cells in the immune system is often tuned by cell surface molecules. The Fc receptors expressed on various hematopoietic cells constitute critical elements for activating or downmodulating immune responses and combines humoral and cell-mediated immunity. Thus, Fc receptors are the intelligent sensors of the immune status in the individual. However, impaired regulation by Fc receptors will lead to unresponsiveness or hyperreactivity to foreign as well as self-antigens. Murine models for autoimmune disease indicate the indispensable roles of the inhibitory Fc receptor in the suppression of such disorders, whereas activating-type FcRs are crucial for the onset and exacerbation of the disease. The development of many autoimmune diseases in humans may be caused by impairment of the human Fc receptor regulatory system. This review is aimed at providing a current overview of the mechanism of Fc receptor-based immune regulation and the possible scenario of how autoimmune disease might result from their dysfunction.

REVIEW:
Barrington R
The role of complement in inflammation and adaptive immunity
Immunol Rev 2001; 180: 5-15
This article reviews two important aspects of the complement system, i) host protection and

inflammation, and ii) regulation of B lymphocytes of adaptive immunity. While these two roles appear distinct, they are linked. Nnatural antibody and classical pathway complement work together in host protection against bacterial infection on the one hand but, on the other, they co-operate to induce inflammation as observed in reperfusion injury.

REVIEW:
Casadevall A
Antibody-mediated regulation of cellular immunity and the inflammatory response.
Trends Immunol 2003; 24:474-8
For many pathogens the role of antibody-mediated immunity (AMI) is poorly understood, in part because of the limited tools available to establish antibody efficacy. AMI is classically associated with opsonization, toxin and viral neutralization, complement fixation and antibody-dependent cellular cytotoxicity. However, recent studies indicate new functions for AMI ranging from direct antimicrobial action to modulation of the inflammatory response. The efficacy of AMI against some pathogens is dependent on cell-mediated immunity. A new interpretation of the role of AMI is proposed whereby it is in proinflammatory the early stages of infection and anti-inflammatory at later stages of the host–microbe interaction and in the setting of established immunity and/or in an immune individual.

LANDMARK INVESTIGATION:
Graziano RF
Fc gamma RI and Fc gamma RII on monocytes and granulocytes are cytotoxic trigger molecules for tumor cells
J Immunol. 1987;139:3536-41
As part of an effort to define the cytotoxic trigger molecules on human myeloid cells, the ability of the different Fc receptors for IgG (Fc gamma R) to mediate killing of tumor cell lines by monocytes and granulocytes was examined. This was accomplished by studying cytolysis of hybridoma cell (HC) targets bearing surface antibody directed toward the different Fc gamma R. The HC line, HC IV.3A, which bears Ig directed to the low affinity Fc gamma R (Fc gamma RII) on monocytes and neutrophils was lysed by human monocytes. The extent of lysis of HC IV.3A was approximately equal to that of anti-Fc gamma RI (the high affinity Fc gamma R on human monocytes) bearing HC lines (HC 32.2A and HC 62A) and was not augmented by treatment of the monocytes with interferon-gamma (IFN-gamma). In contrast, neutrophils lysed HC IV.3A and HC 32.2A only after activation with IFN-gamma. Since Fc gamma RI is not detectable on untreated neutrophils and is induced by IFN-gamma on these cells, lysis of HC 32.2A by IFN-gamma-activated neutrophils correlated with receptor induction. On the other hand, Fc gamma RII was present at equal levels on untreated and IFN-gamma-treated neutrophils, but only IFN-gamma-treated neutrophils mediated cytotoxicity via Fc gamma RII. In this case, enhanced killing appeared to be due to events other than an increase in Fc gamma RII number. Neither untreated nor IFN-gamma-treated neutrophils mediated the lysis of the anti-Fc gamma RIII bearing HC 3G8A. Thus, binding to the tumor target via this Fc receptor does not lead to lysis and may initiate signals distinct from those triggered through Fc gamma RI or Fc gamma RII. Surprisingly, HC bearing high amounts of mouse IgG1 antibody of irrelevant specificity were also lysed by monocytes. This lysis was blocked by soluble IV.3 antibody and thus appeared to be due to binding of the Fc portion of the surface Ig to Fc gamma RII on monocytes. Furthermore, monocytes from donors with a form of Fc gamma RII incapable of binding aggregated mouse

IgG1 did not lyse these HC, but displayed normal lysis of HC IV.3, demonstrating that this structurally different Fc gamma RII remained a functional trigger molecule. Overall, these studies have demonstrated the specificity of Fc receptors in triggering monocyte- and granulocyte-mediated antibody-dependent tumor cell killing and have begun to dissect functional similarities and differences among the three defined Fc gamma R on human myeloid cells.

f. IgE mediated immediate and late phase reactions

REVIEW:
Hansen I
Mediators of inflammation in the early and the late phase of allergic rhinitis.
Curr Opin Allergy Clin Immunol 2004;4:159-63
Inflammatory mediators are released and cells are activated and recruited to the mucosa as a result of an IgE mediated immune response. In this review, early and late phase responses of the allergic type I reaction are described, including the different cell types and mediators involved. Special attention is paid to new inflammatory processes.

REVIEW:
Rosenwaser L
New insights into the pathophysiology of allergic rhinitis
Allergy Asthma Proc. 2007;28:10-5
The immune response to an allergen is dependent on an initial sensitization process, with future exposures triggering a two-part allergic response including an early and a late phase. The process by which an allergen is recognized as such, including which cell types and cytokines are involved in the sensitization process, has become clearer over the last several years. Similarly, the roles of the different preformed mediators responsible for many of the signs and symptoms of the early phase response have been elucidated. Recent work also has shed some light on the multitude of cells and mediators involved in the late-phase reactions, which can lead to priming and long-term inflammation. This article will discuss some of this recent work as well as review the basics behind all of the stages of the allergic response, especially as they apply to the nose and upper airway.

LANDMARK PUBLICATION:
Solley GO
The late phase of the immediate wheal and flare skin reaction. Its dependence upon IgE antibodies
J Clin Invest. 1976;58:408-20
IgE antibodies are usually thought to induce only immediate skin reactions. We have shown that the intradermal injection of a number of different allergens can produce a prolonged inflammatory reaction after the immediate wheal and flare in most sensitive subjects. This late inflammatory response occurs 6-12 h after challenge and is characterized by diffuse edema, erythema, pruritus, and heat. Both immediate and late responses can also be seen after passive sensitization of skin sites in nonatopic subjects. That IgE is involved in inducing the reaction was shown by the abolition of both immediate and late responses by passive transfer tests in the following experiments: (a) heating atopic serum at 56degreesC for 4 h, (b) removing IgE from the atopic serum by a solid phase anti-IgE immunoabsorbent, and (c) competitively inhibiting the binding of IgE antibodies to cells by an IgE myeloma protein. In addition, both responses were induced by

affinity chromatography-purified IgE antibody, followed by antigenic challenge. Very similar lesions could also be induced by intradermal injection of Compound 48/80, thus suggesting a central role in the reaction for the mast cell or basophil. Histologically, the late phase is characterized by edema and a mixed cellular infiltration, predominantly lymphocytic but also containing eosinophils, neutrophils and basophils. Direct immunofluorescent staining did not show deposition of immunoglobulins or complement components, except IgM in 2 of 15 and C3 in 1 of 15 patients. This finding indicates that the late phase does not depend on the deposition of immune complexes. The results of the study suggest that IgE-allergen interaction on the surfaces of mast cells or on infiltrating basophils causes both immediate and late cutaneous responses.

g. Immune complexes – immunologic properties and mechanisms of clearance

REVIEW:
Nydegger U
Immune complex pathophysiology
Ann NY Acad Sci 2007;1109:66-83

Antigen-antibody (Ab) interactions that lead to the formation of immune complexes (ICs) are subtle biochemical processes determining health or disease according to the outcome. Good laboratory practice (GLP)-acknowledged IC detection methods reveal that plasma levels of up to 15 microg/mL heat-aggregated immunoglobulin G (IgG) equivalents are normal, indicating the physiological role of ICs. Among the major variables that influence the equilibrium association constant Ka, are specificity and epitope density of the antigen, Ig class/subclass of the Ab, IC complement (C)-activating capacity, Fc receptor (FcR) interaction, and cytokine activation pattern. The Ka of antigen-Ab binding at approximately 20 degrees C ranges from low affinity (105) to high affinity (107-1011). Beneficial ICs serve to remove and/or neutralize infectious or toxic antigens, following an infectious attack in immune and vaccinated hosts. Circulating ICs are more prone for benefit than tissue-bound ICs, which reflect in situ formation and/or undesired deposition in tissues due to overflow from insufficient reticuloendothelial system (RES) removal. The classical textbook topic on ICs still holds true but is under revision because of the improved knowledge of effector systems, such as C, cytokine, and FcR apparatus. Therapeutic options to treat IC-associated diseases include intravenous immunoglobulins (IVIG) at their onset and monoclonal antibodies (mAb) directed at C activation products and/or cytokines.

REVIEW:
Jancar S
Immune complex-mediated tissue injury: a multistep paradigm.
Trends Immunol 2005;26:48-55.

Antigen-antibody complexes can damage tissues by triggering inflammation. Recent studies have enabled the description of a sequence of steps, which depend on the intra- or perivascular location of complex formation. Acute lethal toxicity and circulatory shock as a result of the acute release of inflammatory mediators can occur after intravascular complex formation. The lesions associated with perivascular complexes are characterized by plasma leakage and the recruitment of polymorphonuclear leukocytes. These lesions are modulated by mediators released from endothelial cells, namely nitric oxide, endothelins and lipid mediators, and provide an appropriate basis for the activation of both arms of hemostasis: coagulation and fibrinolysis. The balance between both activation systems can explain the late occurrence of both tissue fibrosis and organ remodeling.

8. Other immune and inflammatory mechanisms

a. Natural killer cells, their CD markers and functions

REVIEW:
Boyton RJ, Altmann DM.
Natural killer cells, killer immunoglobulin-like receptors and human leucocyte antigen class I in disease.
Clin Exp Immunol. 2007;149:1-8
Natural killer cells constitute a potent, rapid part of the innate immune response to infection or transformation, and also generate a link to priming of adaptive immunity. Their function can encompass direct cytotoxicity as well as the release of cytokines and chemokines. In humans, a major component of natural killer (NK) cell target recognition depends mainly on the surveillance of human leucocyte antigen (HLA) class I molecules by killer immunoglobulin-like receptors (KIR). Different KIR can transmit inhibitory or activatory signals to the cell, and effector function is considered to result from the balance of these contributing signals. The regulation of NK cell responses depends on a number of variables: KIR genotype, HLA genotype, heterozygosity versus homozygosity for these, whether there is cognate recognition between the HLA and KIR products carried by an individual, clonal variation between individual NK cells in KIR expression, and the specific modulation of HLA expression by infection, transformation or peptide binding. Different HLA/KIR genotypes can impart different thresholds of activation to the NK cell repertoire and such genotypic variation has been found to confer altered risk in a number of diseases including human immunodeficiency virus (HIV) susceptibility and progression, hepatitis C virus clearance, idiopathic bronchiectasis, autoimmunity and cancer.

REVIEW:
Radaev S
Structure and function of natural killer cell surface receptors
Annu Rev Biophys Biomol Struct. 2003;32:93-114
Since mid-1990, with cloning and identification of several families of natural killer (NK) receptors, research on NK cells began to receive appreciable attention. Determination of structures of NK cell surface receptors and their ligand complexes led to a fast growth in our understanding of the activation and ligand recognition by these receptors as well as their function in innate immunity. Functionally, NK cell surface receptors are divided into two groups, the inhibitory and the activating receptors. Structurally, they belong to either the immunoglobulin (Ig)-like receptor superfamily or the C-type lectin-like receptor (CTLR) superfamily. Their ligands are either members of class I major histocompatibility complexes (MHC) or homologs of class I MHC molecules. The inhibitory form of NK receptors provides the protective immunity through recognizing class I MHC molecules with self-peptides on healthy host cells. The activating, or the noninhibitory, NK receptors mediate the killing of tumor or virally infected cells through their specific ligand recognition. The structures of activating and inhibitory NK cell surface receptors and their complexes with the ligands determined to date, including killer immunoglobulin-like receptors (KIRs) and their complexes with HLA molecules, CD94, Ly49A, and its complex with H-2Dd, and NKG2D receptors and their complexes with class I MHC homologs, are reviewed here.

REVIEW:
Tupin E, Kinjo Y, Kronenberg M.
The unique role of natural killer T cells in the response to microorganisms.
Nat Rev Microbiol. 2007;5:405-17
Natural killer T (NKT) cells combine features of the innate and adaptive immune systems. Recently, it has become evident that these T cells have crucial roles in the response to infectious agents. The antigen receptor expressed by NKT cells directly recognizes unusual glycolipids that are part of the membrane of certain Gram-negative bacteria and spirochetes. Moreover, even in the absence of microbial glycolipid antigens, these T cells respond to innate cytokines produced by dendritic cells that have been activated by microbes. This indirect sensing of infection, by responding to cytokines from activated dendritic cells, allows NKT cells to react to a broad range of infectious agents.

b. Lymphokine activated killer cells and their effects

REVIEW:
June CH
Adoptive T cell therapy for cancer in the clinic
J Clinical Investm2007;117:1466-76
The transfusion of lymphocytes, referred to as adoptive T cell therapy, is being tested for the treatment of cancer and chronic infections. Adoptive T cell therapy has the potential to enhance antitumor immunity, augment vaccine efficacy, and limit graft-versus-host disease. This form of personalized medicine is now in various early- and late-stage clinical trials. These trials are currently testing strategies to infuse tumor-infiltrating lymphocytes, CTLs, Th cells, and Tregs. Improved molecular biology techniques have also increased enthusiasm and feasibility for testing genetically engineered T cells. The current status of the field and prospects for clinical translation are reviewed herein.

KEY INVESTIGATION:
Winter H
Tumor regression after adoptive transfer of effector T cells is independent of perforin or Fas ligand (APO-1L/CD95L).
J Immunol. 1999;163:4462-72
The adoptive transfer of tumor-specific effector T cells can result in complete regression and cure mice with systemic melanoma, but the mechanisms responsible for regression are not well characterized. Perforin- and Fas ligand (APO-1/CD95 ligand)-mediated cytotoxicity have been proposed as mechanisms for T cell-mediated tumor destruction. To determine the role of perforin and Fas ligand (FasL) in T cell-mediated tumor regression in a murine melanoma model, B16BL6-D5 (D5), we generated D5-specific effector T cells from tumor vaccine-draining lymph nodes of wild type (wt), perforin knock out (PKO), or FasL mutant (gld) mice and treated established D5 metastases in mice with the same genotype. Effector T cells from wt, PKO and gld mice induced complete regression of pulmonary metastases and significantly prolonged survival of the treated animals regardless of their genotype. Complete tumor regression induced by PKO effector T cells was also observed in a sarcoma model (MCA-310). Furthermore, adoptive transfer of PKO and wt effector T cells provided long-term immunity to D5. Therapeutic T cells from wt, PKO, or gld mice exhibit a tumor-specific type 1 cytokine profile; they secrete IFN-gamma, but not IL-4. In

these models, T cell-mediated tumor regression and long-term antitumor immunity are perforin and FasL independent.

LANDMARK PUBLICATION:
Grimm EA
Lymphokine-activated killer cell phenomenon. Lysis of natural killer-resistant fresh solid tumor cells by interleukin 2-activated autologous human peripheral blood lymphocytes.
J Exp Med. 1982;155:1823-41
Activation in lectin-free interleukin 2 (IL-2) containing supernatants of peripheral blood mononuclear leukocytes (PBL) from cancer patients or normal individuals resulted in expression of cytotoxicity toward 20 of 21 natural killer (NK)-resistant fresh solid tumor cells tested. Fresh solid tumor cells were resistant to NK-mediated lysis in 10 autologous patients' PBL-tumor interactions, and from 17 normal individuals tested against 13 allogeneic fresh tumors. Culture of PBL in IL-2 for 2-3 d was required for the lymphokine activated killers (LAK) to be expressed, and lytic activity toward a variety of NK-resistant fresh and cultured tumor targets developed in parallel. Autologous IL-2 was functional in LAK activation, as well as interferon-depleted IL-2 preparations. Irradiation of responder PBL before culture in IL-2 prevented LAK development. Precursors of LAK were present in PBL depleted of adherent cells and in NK-void thoracic duct lymphocytes, suggesting that the precursor is neither a monocyte nor an NK cell. LAK effectors expressed the serologically defined T cell markers of OKT.3, Leu-1, and 4F2, but did not express the monocyte/NK marker OKM-1. Lysis of autologous fresh solid tumors by LAK from cancer patients' PBL was demonstrated in 85% of the patient-fresh tumor combinations. Our data present evidence that the LAK system is a phenomenon distinct from either NK or CTL systems that probably accounts for a large number of reported nonclassical cytotoxicities. The biological role of LAK cells is not yet known, although it is suggested that these cells may be functional in immune surveillance against human solid tumors.

c. Basophil mediated inflammatory states

REVIEW:
Obata K, Mukai K, Tsujimura Y, Ishiwata K, Kawano Y, Minegishi Y, Wanatabe N, Karasuyama H.
Basophils are essential initiators of a novel type of chronic allergic inflammation.
Blood. 2007;110:913-20.
Basophils represent less than 1% of peripheral blood leukocytes and have often been considered as minor and possibly redundant circulating mast cells. The recent finding that basophils readily generate large quantities of T helper 2 (Th2) cytokines such as IL-4 provided new insights into the possible role of basophils in allergic disorders and immunity to pathogens. However, in-depth studies on basophils, particularly their functions in vivo, have been hampered by the lack of appropriate animal models, such as mutant animals deficient only in basophils. Here, we established a mAb that reacted with mouse basophils and depleted them when administered in vivo. The mAb treatment of mice did not show any significant effect on classical allergic reactions such as passive cutaneous anaphylaxis and contact hypersensitivity. In contrast, it completely abolished the development of IgE-mediated chronic allergic dermatitis that is characterized by massive eosinophil infiltration, even though basophils accounted for only approximately 2% of the infiltrates. The treatment during the progression of the dermatitis resulted in drastic reduction in numbers of infiltrating eosinophils and neutrophils, concomitantly with elimination of basophils

from the skin lesions. Thus, basophils play a pivotal role in the development of IgE-mediated chronic allergic inflammation, as an initiator rather than as an effector.

REVIEW:
Gibbs BF
Human basophils as effectors and immunomodulators of allergic inflammation and innate immunity
Clin Exp Med 2005;5:43-9
Basophils have often stood in the shadow of their tissue-fixed mast cell counterparts which share some, common features, such as high-affinity IgE receptor expression and the ability to release histamine. That rodent mast cells produce a variety of pro-allergic and inflammatory cytokines has further added to the deception that basophils only play a minor role in allergic inflammation. Surprisingly, in humans, basophils, but not mast cells, appear to be the prime early producers of the Th2-type cytokines IL-4 and IL-13, which perform several crucial functions in initiating and maintaining allergic responses. This putative immunomodulatory role of basophils is supported further by their ability to express CD40 ligand, which, together with IL-4 and IL-13, serve as inductors of B-cell proliferation and class switching to IgE and IgG4. Moreover, human basophils are the main cellular source for rapid IL-4 generation, a mandatory requirement for the development of Th2 responses. Recent specific staining techniques have localised basophils in various tissues affected by allergic diseases and it appears likely, but remains to be proven, that the interaction of basophils, T cells and B cells at these sites propagate pro-allergic immune responses. Additionally, basophil activation is not restricted to antigen-specific IgE crosslinking but can be caused in non-sensitised individuals by parasitic antigens, plant lectins and viral superantigens binding to non-specific IgEs. Finally, the presence of novel IgE-independent receptor targets that cause trafficking and Th2 cytokine release from basophils further underlines their potential role in innate as well as adaptive immunity.

RESEARCH FRONTIER:
De Swerdt A
Detection of basophil activated IgG autoantibodies in chronic idiopathic urticaria by induction of CD 63.
J Allergy Clin Immunol 2005 : 662-7.
Approximately 40% to 50% of patients with chronic idiopathic urticaria (CIU) have functional IgG autoantibodies against FcepsilonRIalpha or IgE, which induce histamine release from basophils and cutaneous mast cells. A positive autologous serum skin test response is believed to reflect the presence of these autoantibodies. OBJECTIVE: We sought to further define the functional properties of and develop a sensitive functional assay for detection of autoantibodies in patients with CIU. METHODS: Sera from patients with CIU (n=61) and sera from healthy control subjects (n=23) were incubated with donor basophils. Activation of basophils was determined on the basis of CD 63 surface expression, as analyzed on a FACScan flow cytometer. RESULTS: A positive basophil activation test result was found in 51% of patients with CIU, and basophil-activating properties were present in the IgG fractions of sera. When both the in vitro test and the autologous serum skin test were considered, basophil/mast cell-activating autoantibodies were present in 62% of the patients. Patients with a positive basophil activation test result had a significantly higher prevalence of other autoantibodies, had more severe urticaria, and were more likely to have angioedema.

d. Kinin mediated inflammation

REVIEW:

Kaplan A

Pathways for bradykinin formation and inflammatory disease

J Allergy Clin Immunol 2002;109:195-209

Bradykinin is formed by the interaction of factor XII, prekallikrein, and high-molecular-weight kininogen on negatively charged inorganic surfaces (silicates, urate, and pyrophosphate) or macromolecular organic surfaces (heparin, other mucopolysaccharides, and sulfatides) or on assembly along the surface of cells. Catalysis along the cell surface requires zinc-dependent binding of factor XII and high-molecular-weight kininogen to proteins, such as the receptor for the globular heads of the C1q subcomponent of complement, cytokeratin 1, and urokinase plasminogen activator receptor. These 3 proteins complex together within the cell membrane, and initiation depends on autoactivation of factor XII on binding to gC1qR (the receptor for the globular heads of the C1q subcomponent of complement). There is also a factor XII-independent bypass mechanism requiring a cell-derived cofactor or protease that activates prekallikrein. Bradykinin is degraded by carboxypeptidase N and angiotensin-converting enzyme. Angioedema that is bradykinin dependent results from hereditary or acquired C1 inhibitor deficiencies or use of angiotensin-converting enzyme inhibitors to treat hypertension, heart failure, diabetes, or scleroderma. The role for bradykinin in allergic rhinitis, asthma, and anaphylaxis is to contribute to tissue hyperresponsiveness, local inflammation, and hypotension. Activation of the plasma cascade occurs as a result of heparin release and endothelial-cell activation and as a secondary event caused by other pathways of inflammation.

RESEARCH FRONTIER:

Bork K

Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant)

J Allergy Clin Immunol 2007;119:1497-1503

Background -In hereditary angioedema, bradykinin is assumed to be the most important mediator of edema formation.

Objective- To assess whether the selective bradykinin receptor-2 antagonist Icatibant is effective in acute edema attacks of hereditary angioedema.

Methods- In this uncontrolled pilot study, 15 patients with 20 attacks were treated with Icatibant. The attacks were analyzed by using a standardized and validated visual analog scale measurement and compared with historical data of untreated attacks. Plasma bradykinin concentration was measured before and 4 hours after intravenous Icatibant treatment.

Results- Symptom intensity decreased within 4 hours after administration of Icatibant; the median time to onset of symptom relief was 1.50, 1.42, and 1.13 hours in the intravenous groups and 0.58 and 0.45 hours in the subcutaneous groups, respectively. The median difference in the 10-cm visual analog scale 4 hours after start of treatment was 4.11 cm (95% CI, 1.72-6.07). Compared with untreated attacks, Icatibant treatment reduced the mean (SD) time to onset of symptom relief by 97% from 42 ± 14 to 1.16 ± 0.95 hours (all groups combined). Median bradykinin concentration was 7-fold above the norm during acute attacks at 48.5 pmol/L and decreased to 18.0 pmol/L 4 hours after Icatibant infusion or injection.

Conclusion -Icatibant was effective in treating acute attacks of hereditary angioedema.

Clinical implications -This is the first report demonstrating the clinical usefulness of antagonizing bradykinin binding to bradykinin receptor-2 in hereditary angioedema.

RESEARCH FRONTIER:
Bertram CM, Baltic S, Misso NL, Bhoola KD, Foster PS, et al
Expression of kinin B1 and B2 receptors in immature, monocyte-derived dendritic cells and bradykinin-mediated increase in intracellular CA2+ and cell migration.
J Leukoc Biol. 2007;81:1445-54.
The kinins, bradykinin (BK) and Lys-des[Arg(9)]-BK, are important inflammatory mediators that act via two specific G protein-coupled kinins, B(1) and B(2) receptors (B(2)R). Kinins influence the activity of immune cells by stimulating the synthesis of cytokines, eicosanoids, and chemotactic factors. Whether human dendritic cells (DC) express kinin receptors and whether kinins influence DC function are unknown. Fluorescence immunocytochemistry and RT-PCR were used to demonstrate that immature human monocyte-derived DC (hMo-DC) constitutively expressed kinins B(1)R and B(2)R. Kinin receptor expression was induced on the 3rd and 4th days of culture during differentiation of hMo-DC from monocytes and was not dependent on the presence of IL-4 or GM-CSF. Although monocytes also expressed B(2)R mRNA, the protein was not detected. The kinin agonists BK and Lys-des[Arg(9)]-BK up-regulated the expression of their respective receptors. BK, acting via the B(2)R, increased intracellular Ca(2+), as visualized by confocal microscopy using the fluorescent Ca(2+) dye, Fluor-4 AM. Evaluation of migration in Trans-well chambers demonstrated significant enhancement by BK of migration of immature hMo-DC, which was B(2)R-dependent. However, kinins did not induce maturation of hMo-DC. The novel finding that kinin receptors are constitutively expressed in immature hMo-DC suggests that these receptors may be expressed in the absence of proinflammatory stimuli. BK, which increases the migration of immature hMo-DC in vitro, may play an important role in the migration of immature DC in noninflammatory conditions and may also be involved in the recruitment of immature DC to sites of inflammation.

e. Arachidonic Acid Metabolites and Inflammation

REVIEW:
Boyce JA.
Mast cells and eicosanoid mediators: a system of reciprocal paracrine and autocrine regulation.
Immunol Rev. 2007;217:168-85.
When activated by specific antigen, complement, or other transmembrane stimuli, mast cells (MCs) generate three eicosanoids: prostaglandin (PG)D(2), leukotriene (LT)B(4), and LTC(4), the parent molecule of the cysteinyl leukotrienes (cysLTs). These diverse lipid mediators, which are generated from a single cell membrane-associated precursor, arachidonic acid, can initiate, amplify, or dampen inflammatory responses and influence the magnitude, duration, and nature of subsequent immune responses. PGD(2) and cysLTs, which were originally recognized for their bronchoconstricting and vasoactive properties, also serve diverse and pivotal functions in effector cell trafficking, antigen presentation, leukocyte activation, matrix deposition, and fibrosis. LTB(4) is a powerful chemoattractant for neutrophils and certain lymphocyte subsets. Thus, MCs can contribute to each of these processes through eicosanoid generation. Additionally, MCs express G-protein-coupled receptors specific for cysLTs, LTB(4), and another eicosanoid, PGE(2). Each of these receptors can regulate MC functions in vivo by autocrine and paracrine mechanisms. This

review focuses on the biologic functions for MC-associated eicosanoids, the regulation of their production, and the mechanisms by which eicosanoids may regulate MC function in host defense and disease.

REVIEW:
Peters-Golden M
Leukotrienes.
N Engl J Med. 2007;357:1841-54
Leukotrienes ("leuko," from white blood cells; and "trienes," three conjugated double bonds) comprise a family of products of the 5-lipoxygenase pathway of arachidonic acid metabolism. The cysteinyl leukotrienes C4, D4, and E4 account for the biologic activity that was previously termed "slow-reacting substance of anaphylaxis," and the efficacy of antagonists to type 1 cysteinyl leukotriene receptor (CysLT1) in asthma validates the importance of cysteinyl leukotrienes and CysLT1 in this disease.1 This article reviews both established understanding and recent advances in our knowledge about leukotrienes.

REVIEW:
Moore ML.
Update on the role of prostaglandins in allergic lung inflammation: separating friends from foes, harder than you might think.
J Allerg Clin Immunol 2006;117:1036-9
Prostaglandins (PGs), small lipid molecules derived from arachidonic acid by COX enzymes, are critical mediators of allergic inflammation. Our understanding of the role of PGs in allergic lung inflammation has been hampered by the very short biologic half-life of these mediators, which has made mechanistic studies difficult in human subjects. However, advances in molecular biology and pharmacology have given investigators the opportunity to examine the role of specific prostanoids in the development of allergic inflammation in animal models. Studies investigating specific PG receptors are also elucidating the mechanisms by which PGs regulate the pulmonary allergic phenotype. This review summarizes the current literature on the role of PGs and PG receptors in allergic lung inflammation.

RESEARCH FRONTIER:
Jiang Y.
Interleukin 4-dependent mast cell proliferation requires autocrine/intracrine cysteinyl leukotriene-induced signaling.
J Immunol. 2006;177:2755-9
Reactive mastocytosis (RM) in epithelial surfaces is a consistent Th2-associated feature of allergic disease. RM fails to develop in mice lacking leukotriene (LT) C4 synthase (LTC4S), which is required for cysteinyl leukotriene (cys-LT) production. We now report that IL-4, which induces LTC4S expression by mast cells (MCs), requires cys-LTs, the cys-LT type 1 receptor (CysLT1), and Gi proteins to promote MC proliferation. LTD4 (10-1000 nM) enhanced proliferation of human MCs in a CysLT1-dependent, pertussis toxin-sensitive manner. LTD4-induced phosphorylation of ERK required transactivation of c-kit. IL-4-driven comitogenesis was likewise sensitive to pertussis toxin or a CysLT1-selective antagonist and was attenuated by treatment with leukotriene synthesis inhibitors. Mouse MCs lacking LTC4S or CysLT1 showed substantially

diminished IL-4-induced comitogenesis. Thus, IL-4 induces proliferation in part by inducing LTC4S and cys-LT generation, which causes CysLT1 to transactivate c-kit in RM.

f. Cytokines/Chemokines and their receptors

REVIEW:
Chemokines and their receptors in allergic disease.
Pease JE
J Allergy Clin Immunol. 2006;118:305-18
Mechanisms of chemoattraction underlie the spatial organization of the cells of the immune system under basal conditions and the localization of these cells to sites of inflammation. The chemokines, a family of around 50 small proteins, play a major role in these processes. Leukocytes are equipped with cell-surface sensors for chemokines. There are 19 such receptors that are differentially expressed on leukocytes: the repertoire of receptor expression depending on the type of leukocyte and its stage in maturation. From observations in animal models, clinical studies, in vitro cell biology, and molecular analysis, a working hypothesis has been established to explain the cellular interactions underlying allergic responses and the chemokines-chemokine receptors involved. Chemokines signal through G protein-coupled receptors that are used typically for sensory functions (eg, detection of olfactory signals in the nose). This type of receptor can be blocked selectively by small-molecule antagonists. This provides the opportunity for the development of therapeutic compounds designed to suppress the recruitment of particular leukocyte types in allergic reactions.

REVIEW:
Charo IF
The Many Roles of Chemokines and Chemokine Receptors in Inflammation
N Engl J Med 2006; 354:610-621
Chemokines (chemotactic cytokines) are small heparin-binding proteins that direct the movement of circulating leukocytes to sites of inflammation or injury. During the eight years since chemokines and chemokine receptors were last reviewed in the *Journal*,[1] a vast expansion in the understanding of chemokine biology has occurred. Originally studied because of their role in inflammation, chemokines and their receptors are now known to play a crucial part in directing the movement of mononuclear cells throughout the body, engendering the adaptive immune response and contributing to the pathogenesis of a variety of diseases. Chemokine receptors are some of the most tractable drug targets in the huge battery of molecules that regulate inflammation and immunity. For this reason, clinical trials involving chemokine-receptor antagonists for the treatment of inflammatory conditions have recently begun. In this review, we survey the properties of chemokines and their receptors and highlight the roles of these chemoattractants in selected clinical disorders.

REVIEW:
Allen SJ
Chemokines: receptor structure, interactions, and antagonism.
Annu Rev Immunol. 2007;25:787-820.
Chemokines are critical mediators of cell migration during routine immune surveillance, inflammation, and development. Chemokines bind to G protein-coupled receptors and cause conformational changes that trigger intracellular signaling pathways involved in cell movement

and activation. Although chemokines evolved to benefit the host, inappropriate regulation or utilization of these proteins can contribute to or cause many diseases. Specific chemokine receptors provide the portals for HIV to get into cells, and others contribute to inflammatory diseases and cancer. Thus, there is significant interest in developing receptor antagonists. To this end, the structures of ligands coupled with mutagenesis studies have revealed mechanisms for antagonism based on modified proteins. Although little direct structural information is available on the receptors, binding of small molecules to mutant receptors has allowed the identification of key residues involved in the receptor-binding pockets. In this review, we discuss the current knowledge of chemokine:receptor structure and function, and its contribution to drug discovery.

REVIEW:
Ziegler S.
Thymic stromal lymphopoietin in normal and pathogenic T cell development and function.
Nature Immunol 2006;7:709-14
Thymic stromal lymphopoietin, a four helix-bundle cytokine, is expressed mainly by barrier epithelial cells and is a potent activator of several cell types, particularly myeloid dendritic cells. TSLP influences the outcome of interactions between dendritic cells and CD4+ thymocytes and T cells in many situations, such as the regulation of the positive selection of regulatory T cells, maintenance of peripheral CD4+ T cell homeostasis and induction of CD4+ T cell-mediated allergic inflammation.

REVIEW:
Steinke JW
Miniprimer: Cytokines and Chemokines
J Allergy Clin Immunol 2006;117:S441-5
Cytokines and chemokines are secreted proteins with growth, differentiation, and activation functions that regulate the nature of immune responses. Cytokines are involved in nearly every facet of immunity and inflammation, from induction of the innate immune response to the generation of cytotoxic T cells and the development of antibodies by the humoral immune system. The combination of cytokines that are produced in response to an immune insult determines which arm of the immune system will be activated. For this update, recent advances in our understanding of cytokines will be discussed, which includes the IL-10, IL-17, and IL-27 families.

REVIEW:
Chung EK.
Antenatal risk factors, cytokines and the development of atopic disease in early childhood.
Arch Dis Child Fetal Neonatal Ed 2007;92:F68-73
Atopic diseases are complex entities influenced by an array of risk factors, including genetic predisposition, environmental allergens, antenatal exposures, infections and psychosocial factors. One proposed mechanism by which these risk factors contribute to the development of atopic disease is through changes in the production of T helper cell type 1 (Th1) and T helper cell type 2 (Th2) cytokines. The objectives of this review are to discuss antenatal exposures that are associated with paediatric atopic diseases, to discuss the influence of the intrauterine environment on neonatal immune responses, to provide an overview of the Th1 and Th2 pathways and how they relate to atopic disease, and to summarise our current understanding of the association between cytokine responses in cord blood and the development of atopic disease in early childhood.

g. Growth factors

REVIEW:
Möhle R
Hematopoietic growth factors for hematopoietic stem cell mobilization and expansion.
Semin Hematol. 2007;44:193-202.
During inflammation and cytopenia, increased levels of hematopoietic growth factors (HPGFs) induce mobilization and proliferation of hematopoietic stem cells and hematopoietic progenitor cells (HPCs), resulting in spatial and quantitative in vivo expansion of the hematopoietic tissue. Exogenous administration of recombinant HPGFs, particularly granulocyte colony-stimulating factor (G-CSF), is routine for mobilization of stem cells, followed by collection and transplantation of autologous or allogeneic stem cells. In this review, we summarize experience using different HPGFs and HPGF combinations for stem cell mobilization, such as G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), stem cell factor (SCF), and others. Preclinical and clinical studies of so-called early- and late-acting HPGFs for ex vivo expansion of HPCs are discussed, also with respect to the unresolved question whether expansion of repopulating stem cells can be achieved in vitro.

REVIEW:
Kaushansky K.
Lineage-specific hematopoietic growth factors.
N Engl J Med. 2006;354:2034-45.
Hematopoiesis is the process that generates blood cells of all lineages. Calculations based on the blood volume and the level and half-life of each type of blood cell in the circulation indicate that each day an adult produces approximately 200 billion erythrocytes, 100 billion leukocytes, and 100 billion platelets. Moreover, these rates can increase by a factor or 10 or more when the demand for blood cells increases. This article covers the basic mechanisms of growth factor regulation of lineage specific development of leukocytes and erythrocytes.

9. Receptor Ligand interactions in immune functioning—signal transduction resulting from receptor ligand interaction - genetic polymorphisms

REVIEW:
Liu YJ
Thymic stromal lymphopoietin and OX40 ligand pathway in the initiation of dendritic cell-mediated allergic inflammation. J
Allergy Clin Immunol. 2007;120:238-44
It was demonstrated 5 years ago that thymic stromal lymphopoietin (TSLP), a IL-7-like cytokine produced by epithelial cells, could strongly activate human myeloid dendritic cells to induce an inflammatory T(H)2 response characterized by high TNF-alpha and little IL-10 production, distinct from the regulatory T(H)2 responses characterized by low TNF-alpha and high IL-10 production. TSLP was found highly expressed by keratinocytes of skin lesions of atopic dermatitis and associated with dendritic cell activation in situ. This suggests for the first time that TSLP represents a master switch of allergic inflammation at the epithelial cell and dendritic cell interface. During the last several years, the evidence for the association of TSLP with human asthma was revealed. The direct link between TSLP expression with the pathogenesis of atopic dermatitis and asthma in vivo was demonstrated. In addition, OX40 ligand was found to be the

TSLP-induced molecule on dendritic cells that triggers inflammatory T(H)2 differentiation in the absence of IL-12. TSLP was also demonstrated to direct the innate phase of allergic immune responses through activating mast cells. Therefore, TSLP and OX40 ligand may represent important targets for intervention of the initiation of allergic inflammatory responses.

REVIEW:
Kambayashi T
Proximal signaling events in Fc epsilon RI-mediated mast cell activation
J Allergy Clin Immunol. 2007;119:544-52
Mast cells are central mediators of allergic diseases. Their involvement in allergic reactions is largely dependent on activation through the specific receptor for IgE (Fc epsilon RI). Cross-linking of Fc epsilon RI on mast cells initiates a cascade of signaling events that eventually results in degranulation, cytokine/chemokine production, and leukotriene release, contributing to allergic symptomology. Because of the importance of IgE in allergy, much focus has been placed on deciphering the signaling events that take place downstream of Fc epsilon RI. Studies have identified spleen tyrosine kinase as a key proximal regulator of Fc epsilon RI-mediated signaling. In this review, we discuss the multiple pathways that diverge from spleen tyrosine kinase with emphasis on the role of adapter molecules to orchestrate these signaling events. Understanding the molecular mechanisms underlying mast cell activation ideally will provide insights into the development of novel therapeutics to control allergic disease

REVIEW:
Trinchieri G
Cooperation of Toll-like receptor signals in innate immune defence
Nature Rev Immunol. 2007;7:179-90
The mechanisms by which the recognition of Toll-like receptor (TLR) ligands leads to host immunity remain poorly defined. It is now thought that to induce an effective immune response, microorganisms must stimulate complex sets of pattern-recognition receptors, both within and outside of the TLR family. The combined activation of these different receptors can result in complementary, synergistic or antagonistic effects that modulate innate and adaptive immunity. Therefore, a complete understanding of the role of TLRs in host resistance to infection requires 'decoding' of these multiple receptor interactions. This review highlights recent advances in the newly emerging field of TLR cooperation and discusses their implications for the development of adjuvants and immunotherapies.

REVIEW:
Schwartz DA
Polymorphisms of the Toll-like receptors and human disease
Clin Infect Dis. 2005;41:S403-7
The Toll-like receptor (TLR) family regulates both innate and adaptive immune responses. Given its broad effect on immunity, the function of TLRs in various human diseases has been investigated largely by comparing the incidence of disease among persons with different polymorphisms in the genes that participate in TLR signaling. These studies demonstrate that TLR function affects several diseases, including sepsis, immunodeficiencies, atherosclerosis, and asthma. These findings have resulted in new opportunities to study the pathogenesis of disease,

identify subpopulations at greater risk of disease, and, potentially, identify novel therapeutic approaches

REVIEW:
O'Sullivan LA
Cytokine receptor signaling through the Jak-Stat-Socs pathway in disease.
Molec Immunol 2007;44:2497-506
The complexity of multicellular organisms is dependent on systems enabling cells to respond to specific stimuli. Cytokines and their receptors are one such system, whose perturbation can lead to a variety of disease states. This review represents an overview of our current understanding of the cytokine receptors, Janus kinases (Jaks), Signal transducers and activators of transcription (Stats) and Suppressors of cytokine signaling (Socs), focussing on their contribution to diseases of an immune or hematologic nature.

REVIEW:
Cunningham-Rundles C
Molecular defects in T- and B-cell primary immunodeficiency diseases.
Nat Rev. Immunol. 2005;5:880-92
More than 120 inherited primary immunodeficiency diseases have been discovered in the past five decades, and the precise genetic defect in many of these diseases has now been identified. Increasing understanding of these molecular defects has considerably influenced both basic and translational research, and this has extended to many branches of medicine. Recent advances in both diagnosis and therapeutic modalities have allowed these defects to be identified earlier and to be more precisely defined, and they have also resulted in more promising long-term outcomes. The prospect of gene therapy continues to be included in the armamentarium of treatment considerations, because these conditions could be among the first to benefit from gene-therapy trials in humans.

REVIEW:
Kelly M
Modulating leukocyte recruitment in inflammation.
J Allergy Clin Immunol. 2007;120:3-10
Much information has been obtained regarding how white cells are recruited in the microcirculation to sites of inflammation. In this review we summarize the leukocyte recruitment cascade, highlighting the molecular mechanisms that underlie each of the major steps. Major emphasis is placed on the selectins and integrins and their role in rolling and adhesion. Intraluminal crawling and emigration are also briefly discussed. In addition, we summarize some of the data that implicate these molecules in eosinophil recruitment in animal models of asthma and in lymphocyte recruitment in skin contact sensitivity. There is a growing body of evidence to suggest that leukocyte recruitment could be used as an effective means for future therapeutics, and some of these issues are also raised.

REVIEW:
Greenwald RJ, Freeman GJ, Sharpe AH.
The B7 family revisited.

Annu Rev Immunol 2005;23:515-48.
The discovery of new functions for the original B7 family members, together with the identification of additional B7 and CD28 family members, have revealed new ways in which the B7:CD28 family regulates T cell activation and tolerance. B7-1/B7-2:CD28 interactions not only promote initial T cell activation but also regulate self-tolerance by supporting CD4+CD25+ T regulatory cell homeostasis. CTLA-4 can exert its inhibitory effects in both B7-1/B7-2 dependent and independent fashions. B7-1 and B7-2 can signal bidirectionally by engaging CD28 and CTLA-4 on T cells and by delivering signals into B7-expressing cells. The five new B7 family members, ICOS ligand, PD-L1 (B7-H1), PD-L2 (B7-DC), B7-H3, and B7-H4 (B7x/B7-S1) are expressed on professional antigen-presenting cells as well as on cells within nonlymphoid organs, providing new means for regulating T cell activation and tolerance in peripheral tissues. The new CD28 families members, ICOS, PD-1, and BTLA, are inducibly expressed on T cells, and they have important roles in regulating previously activated T cells. PD-1 and BTLA also are expressed on B cells and may have broader immunoregulatory functions. The ICOS:ICOSL pathway appears to be particularly important for stimulating effector T cell responses and T cell-dependent B cell responses, but it also has an important role in regulating T cell tolerance. In addition, the PD-1:PD-L1/PD-L2 pathway plays a critical role in regulating T cell activation and tolerance. In this review, we revisit the roles of the B7:CD28 family members in regulating immune responses, and we discuss their therapeutic potential.

CLINICAL RESEARCH FRONTIER:
Suntharalingam G
Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412
N Engl J Med 2006; 355:1018-1028
Six healthy young male volunteers at a contract research organization were enrolled in the first phase 1 clinical trial of TGN1412, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells. Within 90 minutes after receiving a single intravenous dose of the drug, all six volunteers had a systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension. Within 12 to 16 hours after infusion, they became critically ill, with pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation. Severe and unexpected depletion of lymphocytes and monocytes occurred within 24 hours after infusion. All six patients were transferred to the care of the authors at an intensive care unit at a public hospital, where they received intensive cardiopulmonary support (including dialysis), high-dose methylprednisolone, and an anti–interleukin-2 receptor antagonist antibody. Prolonged cardiovascular shock and acute respiratory distress syndrome developed in two patients, who required intensive organ support for 8 and 16 days. Despite evidence of the multiple cytokine-release syndrome, all six patients survived. Documentation of the clinical course occurring over the 30 days after infusion offers insight into the systemic inflammatory response syndrome in the absence of contaminating pathogens, endotoxin, or underlying disease.

ASSOCIATED COMMENTARY:
Sharpe AH
T-Cell Costimulation — Biology, Therapeutic Potential, and Challenges
N Engl J Med 2006;355:973-75

The immune system has the remarkable ability to defend against diverse microbial pathogens and yet not to respond to self. T cells are key mediators of the immune response, and their activation is tightly regulated to prevent autoreactivity. The processes of T-cell activation and self-tolerance are therefore potential targets for manipulation by drugs — hence, the recent phase 1 trial of a "superagonistic" monoclonal anti-CD28 antibody that was conducted in Britain on behalf of the German firm TeGenero, with the unexpected and devastating results described by Suntharalingam et al. in this issue of the *Journal*

RESEARCH FRONTIER:
Kessell J
Ligation of intercellular adhesion molecule 3 induces apoptosis of human blood eosinophils and neutrophils
J Allergy Clin Immunol 2006;118: 831-836
BACKGROUND: Intercellular adhesion molecule 3 (ICAM-3) is highly expressed on human granulocytes, including eosinophils and neutrophils, but the functions of ICAM-3 in these cells are not well understood. OBJECTIVE: Our studies test the hypothesis that ICAM-3 regulates granulocyte apoptosis. METHODS: Intercellular adhesion molecule 3 was activated by a mAb that recognizes an ICAM-3 epitope that binds its ligand, CD11a/CD18. In some experiments with eosinophils, recombinant human IL-5 or GM-CSF was added to mimic in vivo antiapoptotic conditions. Staining with annexin V–fluorescein isothiocyanate and propidium iodide identified apoptotic cells. RESULTS: Binding of ICAM-3 increased apoptosis of both eosinophils (18 and 48 hours) and neutrophils (18 hours). At 18 hours, eosinophil apoptosis increased from 31.4% ± 3.5 SE (IgG control) to 45.2% ± 3.8 SE (anti–ICAM-3), and neutrophil apoptosis increased from 48% ± 4.1 SE (IgG control) to 55.3% ± 4.5 SE (anti–ICAM-3). At 48 hours, eosinophil apoptosis increased 2-fold under baseline conditions and also in the presence of recombinant human IL-5 or GM-CSF. In both eosinophils and neutrophils, incubation with a blocking antibody against CD18 integrins blunted ICAM-3–induced apoptosis. In eosinophils, blocking peptides for caspases 8 and 9, proteases critical to apoptosis, also decreased ICAM-3–induced apoptosis to control levels. CONCLUSION: Through its effect on eosinophil and neutrophil apoptosis, ICAM-3 may be an important anti-inflammatory molecule that can oppose the proinflammatory effects of IL-5 and GM-CSF. CLINICAL IMPLCATIONS: These findings provide a mechanism for apoptotic clearance of eosinophils and neutrophils involved in allergic inflammation that, unlike necrosis, does not cause nonspecific tissue injury.

10. Immunologic Memory

REVIEW:
Anderson SM
Intrinsic properties of human and murine memory B cells.
Immunol Rev 2006;211:280-94
The central question of how the immune system responds in a qualitatively and quantitatively better way upon re-exposure to a pathogen is largely unanswered. Both the increased frequency of antigen-specific memory cells and the intrinsic properties that memory cells acquire after antigen experience could contribute to the faster and more robust responses seen after repeated exposure to antigen. In the case of the memory B-cell response, it has been difficult to discern the individual contributions of these two effects. However, because of recent advances in identifying memory B cells, there is an increasing understanding of the intrinsic properties of these cells. The current

insights into the unique properties of memory B cells and the progress that has been made in understanding how these affect secondary responses in both the human and the mouse systems are discussed. In addition, we compare the various advantages and disadvantages inherent in each of these systems, in terms of studying the intrinsic properties of memory B cells, and introduce the details of the system that we have developed using conventional heavy chain transgenic (Tgic) mice, which addresses some of the drawbacks of traditional memory models.

REVIEW:
Tangye SG
Human IgM+CD27+ B cells: memory B cells or "memory" B cells?.
J Immunol 2007;179:13-9
Memory B cells are generated in germinal centers (GC) and contribute to serological immunity by rapidly differentiating into plasma cells. Human memory B cells can be identified by the expression of CD27. These cells exhibit more rapid responses than naive (CD27-) B cells following stimulation in vitro, consistent with the heightened kinetics of secondary responses in vivo. CD27+ B cells express mutated Ig V region genes; however a significant proportion continue to express IgM, suggesting the existence of IgM+ memory B cells. The observation that mutated IgM+CD27+ B cells are generated in humans who cannot form GC led to the conclusions that these cells are generated independently of GC and thus are not memory cells and that they mediate responses to T cell-independent Ag. Although some studies support the idea that IgM+CD27+ B cells participate in T cell-independent responses, many others do not. In this review we will provide alternate interpretations of the biology of IgM+CD27+ B cells and propose that they are indeed memory cells.

KEY CLINICAL RESEARCH
Amanna IJ.
Duration of humoral immunity to common viral and vaccine antigens.
N Engl J Med 2007;357:1903-15
BACKGROUND: Maintenance of long-term antibody responses is critical for protective immunity against many pathogens. However, the duration of humoral immunity and the role played by memory B cells remain poorly defined. METHODS: We performed a longitudinal analysis of antibody titers specific for viral antigens (vaccinia, measles, mumps, rubella, varicella-zoster virus, and Epstein-Barr virus) and nonreplicating antigens (tetanus and diphtheria) in 45 subjects for a period of up to 26 years. In addition, we measured antigen-specific memory B cells by means of limiting-dilution analysis, and we compared memory B-cell frequencies to their corresponding serum antibody levels. RESULTS: Antiviral antibody responses were remarkably stable, with half-lives ranging from an estimated 50 years for varicella-zoster virus to more than 200 years for other viruses such as measles and mumps. Antibody responses against tetanus and diphtheria antigens waned more quickly, with estimated half-lives of 11 years and 19 years, respectively. B-cell memory was long-lived, but there was no significant correlation between peripheral memory B-cell numbers and antibody levels for five of the eight antigens tested. CONCLUSIONS: These studies provide quantitative analysis of serologic memory for multiple antigens in subjects followed longitudinally over the course of more than one decade. In cases in which multiple exposures or repeated vaccinations were common, memory B-cell numbers did not correlate with antibody titers. This finding suggests that peripheral memory B cells and antibody-secreting

plasma cells may represent independently regulated cell populations and may play different roles in the maintenance of protective immunity

REVIEW:
Prlic M
Requirements for CD8 T-cell priming, memory generation and maintenance
Curr Opin Immunol 2007;19:315-9.
Immunological memory is characterized by the ability to provide protection from secondary exposure to pathogens. CD8(+) memory T cells provide protection from cell-associated antigens owing to their elevated frequency, rapid response and localization to sites of infection. Events occurring during primary exposure to antigen can impact not only the magnitude and quality of the initial cytotoxic T lymphocyte response but also the efficacy and longevity of the ensuing CD8(+) memory pool. Recent advances shed light on the relative roles of TCR signals and environmental cues in guiding the development of CD8(+) effector T cells into CD8(+) memory T cells and supporting CD8(+) memory T-cell maintenance.

REVIEW:
Fazilleau N
Local development of effector and memory T helper cells.
Curr Opin Immunol 2007;19:259-67
Clonal evolution underpins all facets of adaptive immunity. In particular, antigen-specific helper T (Th) cell development is central to high-affinity B cell immunity and protective vaccination. Dendritic cell maturation and TCR affinity-based selection mechanisms control the recruitment and effective propagation of preferred antigen-specific Th cell cohorts in local lymphoid tissue. Importantly, follicular B helper T (T(FH)) cells emerge as the specialized local effector Th cells that orchestrate the stepwise development of B cell immunity in these local environments. Recent studies also introduce the role of persistent antigen in the development of effector Th cells with evidence for long-term antigen depots that might contribute to local antigen-specific Th cell memory.

REVIEW:
Ndejembi MP.
Reshaping the past: Strategies for modulating T-cell memory immune responses
Clin Immunol 2007; 122:1-12
Memory T cells are generated following an initial encounter with antigen, persist over the lifetime of an individual, and mediate rapid and robust functional responses upon antigenic recall. While immune memory is generally associated with protective immune response to pathogens, memory T cells can be generated to diverse types of antigens including autoantigens and alloantigens through homologous or crossreactive priming and comprise the majority of circulating T cells during adulthood. Memory T cells can therefore play critical roles in propagating and perpetuating autoimmune disease and in mediating allograft rejection, although the precise pathways for regulation of memory immune responses remain largely undefined. Moreover, evaluating and designing strategies to modulate memory T-cell responses are challenging given the remarkable heterogeneity of memory T cells, with different subsets predominating in lymphoid versus non-lymphoid tissue sites. In this review, we discuss what is presently known regarding the effect of

current immunomodulation strategies on the memory T-cell compartment and potential strategies for controlling immunological recall.

REVIEW:
Williams MA
Effector and Memory CTL Differentiation
Ann Rev Immunol 2007;25:171-192
Technological advances in recent years have allowed for an ever-expanding ability to analyze and quantify in vivo immune responses. MHC tetramers, intracellular cytokine staining, an increasing repertoire of transgenic and "knockout" mice, and the detailed characterization of a variety of infectious models have all facilitated more precise and definitive analyses of the generation and function of cytotoxic T lymphocytes (CTL). Understanding the mechanisms behind the differentiation of effector and memory CTL is of increasing importance to develop vaccination strategies against a variety of established and emerging infectious diseases. This review focuses on recent advances in our understanding of how effector and memory CTL differentiate and survive in vivo in response to viral or bacterial infection

REVIEW:
Woodfolk J
T-cell responses to allergens.
J Allergy Clin Immunol 2007;119:280-94
The allergic response in human beings is engineered by CD4(+) T lymphocytes, which secrete T(H)2 cytokines in response to activation by allergen-derived peptides. Although T(H)2 cells have been well characterized, defining the properties of allergen-specific T cells has proved challenging in human beings because of their low frequency within the T-cell repertoire. However, recent studies have provided insight into the molecular signature of long-lived human memory T(H)2 cells, which are allergen-specific. T-cell responses directed against allergens develop in early life and are heavily influenced by the type and dose of allergen, and possibly coexposure to microbial products. These responses are susceptible to suppression by regulatory T cells. This article highlights recent advances in the characterization of allergen-specific memory T(H)2 cells and discusses the heterogeneous nature of regulatory T cells and possible mechanisms of action. The relevance of T-cell epitope mapping studies to understanding the unique nature of T-cell responses to different allergens, as well as to peptide vaccine development, is reviewed. Experimental techniques and approaches for analyzing allergen-specific T cells and identifying novel T-cell epitopes are described that may lead to new T-cell-based therapies.

RESEARCH FRONTIER:
Bosco A
Identification of novel Th2-associated genes in T memory responses to allergens.
J Immunol 2006; 176:4766-77
Atopic diseases are associated with hyperexpression of Th2 cytokines by allergen-specific T memory cells. However, clinical trials with recently developed Th2 inhibitors in atopics have proven disappointing, suggesting underlying complexities in atopy pathogenesis which are not satisfactorily explained via the classical Th1/Th2 paradigm. One likely possibility is that additional Th2-associated genes which are central to disease pathogenesis remain unidentified. The aim of the present study was to identify such novel Th2-associated genes in recall responses to the

inhalant allergen house dust mite. In contrast to earlier human microarray studies in atopy which focused on mitogen-activated T cell lines and clones, we concentrated on PBMC-derived primary T cells stimulated under more physiological conditions of low dose allergen exposure. We screened initially for allergen-induced gene activation by microarray, and validated novel genes in independent panels of subjects by quantitative RT-PCR. Kinetic analysis of allergen responses in PBMC revealed an early wave of novel atopy-associated genes involved in signaling which were coexpressed with IL-4 and IL-4R, followed by a later wave of genes encoding the classical Th2 effector cytokines. We further demonstrate that these novel activation-associated Th2 genes up-regulate in response to another atopy-associated physiological stimulus bacterial superantigen, but remain quiescent in nonphysiological responses in primary T cells or cell lines driven by potent mitogens, which may account for their failure to be detected in earlier microarray studies.

C. Mucosal Immunity

REVIEW:
Tosi, MF
Innate immune responses to infection.
J Allergy Clin Immunol 2005; 116(2): 241-9; quiz 250
This articles reviews the protective mechanisms that do not depend on specific antigenic recognition (adaptive immunity) and allow the host to survive infectious challenges. Antimicrobial peptides are released at epithelial surfaces and disrupt the membranes of many microbial pathogens. Toll-like receptors on epithelial cells and leukocytes recognize a range of microbial molecular patterns and generate intracellular signals for activation of a range of host responses. Cytokines released from leukocytes and other cells exhibit a vast array of regulatory functions in both adaptive and innate immunity. Chemokines released from infected tissues recruit diverse populations of leukocytes that express distinct chemokine receptors. Natural killer cells recognize and bind virus-infected host cells and tumor cells and induce their apoptosis. Complement, through the alternative and mannose-binding lectin pathways, mediates antibody-independent opsonization, phagocyte recruitment, and microbial lysis. Phagocytes migrate from the microcirculation into infected tissue and ingest and kill invading microbes. These innate immune mechanisms and their interactions in defense against infection provide the host with the time needed to mobilize the more slowly developing mechanisms of adaptive immunity, which might protect against subsequent challenges.

REVIEW:
Wershil BK
Gastrointestinal mucosal immunity.
J Allergy Clin Immunol - 01-FEB-2008; 121(2 Suppl): S380-3; quiz S415
Mucosal surfaces constitute a large host-environmental interface that must be protected from pathogenic organisms. The mucosal immune system has evolved as a distinct immune organ functioning independently from its systemic counterpart. This article describes the unique cellular components and functional aspects of the gut mucosal immune system that allow it to mount protective responses to invading microorganisms while maintaining a state of nonresponsiveness to commensal bacteria and food antigens.

REVIEW:
Hull MW

Indigenous microflora and innate immunity of the head and neck.
Infect Dis Clin North Am JUN-2007; 21(2): 265-82
The normal flora of the head and neck exists in a delicate balance within tightly regulated ecologic niches, counterbalanced by a highly efficient innate immune system of the host. Invasion by the normal oral flora is rare when mucosal defenses remain intact. The article reviews the balance between the indigenous microflora and the innate mucosal defense mechanisms.

RESEARCH FRONTIER:
Bochud PY
Innate immunogenetics: a tool for exploring new frontiers of host defence.
Lancet Infect Dis 2007; 7(8): 531-42
This article is a concise and informative overview of elements of the innate immune system and their respective genes. Included are Toll-like receptors (TLRs), nucleotide-binding oligomerisation domain-like receptors (NLRs), and related signal-transducing molecules. Recent immunogenetic studies have associated polymorphisms of the genes encoding TLRs, NLRs, and key signal-transducing molecules, such as interleukin-1 receptor-associated kinase 4 (IRAK4), with increased susceptibility to, or outcome of, infectious diseases. With the availability of high-throughput genotyping techniques, it is becoming increasingly evident that analyses of genetic polymorphisms of innate immune genes will further improve our knowledge of the host antimicrobial defence response and help in identifying individuals who are at increased risk of life-threatening infections. This is likely to open new perspectives for the development of diagnostic, predictive, and preventive management strategies to combat infectious diseases.

REVIEW:
Menendez A
Defensins in the immunology of bacterial infections.
Curr Opin Immunol 2007; 19(4): 385-91
Defensins are a component of the host response against bacterial infections. Multiple studies suggest a linked upregulation of beta-defensins and pro-inflammatory cytokines expression in various tissues, as well as the possibility of mutual induction. Recent data demonstrate the importance of nucleotide-binding oligomerization proteins for the expression of defensins, and associate low levels of alpha-defensins expression by intestinal Paneth cells with susceptibility to Crohn's disease of the ileum. A novel anti-toxin activity has been identified for several alpha- and theta-defensins, expanding the repertoire of the antimicrobial functions of defensins. It has been shown that bacterial proteins can inactivate the action of defensins and that pathogen type III secretion systems (T3SS) manipulate defensins expression via T3SS-mediated inhibition of the NF-kappaB pathway.

REVIEW:
Alma J. Nauta, Anja Roos, Mohamed R. Daha.
A Regulatory Role for Complement in Innate Immunity and Autoimmunity
Int Arch Allergy Immunol 2004;134:310-323 (DOI: 10.1159/000079261).
The complement system comprises a strong defense against various pathogens and is a major component of our innate immune system. While earlier studies have established a crucial role of complement in recognition, opsonization and enhanced phagocytosis of microorganisms by professional phagocytes such as polymorphonuclear leukocytes and macrophages, recent studies

delineate an additional role of complement in initiation and maintenance of the acquired immune response. In addition, it seems that opsonization of apoptotic cells by complement may lead to polarization of the response of professional antigen-presenting cells to a more inflammatory or tolerogenic response. The present review summarizes these different contributions of complement to the shaping of the immune balance.

REVIEW:
Schleimer RP
Epithelium: at the interface of the innate and adaptive immune response
J Allergy Clin Immunol 2007. 120:1279-1284
This article reviews the role of epithelia cells as both mediators and regulators of innate immune responses and adaptive responses as well as the transition from innate to adaptive immunity. Molecular and cellular mechanisms by which epithelial cells shape the responses of dendritic cells, T cells and B cells is discussed.

REVIEW:
MacDonald TT, Gordon JN
Bacterial regulation of intestinal immune responses
Gastroenterol Clin North Am 2005; 34:401-412
The mucosal immune system of healthy individuals is a host response to the commensal bacterial flora. The presence of the flora must alter epithelial and immune function in the gut, and immune responses to nominal antigens occur in an environment where products of the flora are controlling dendritic cell function. This review describes the cross-talk between the commensal flora and the mucosal immune system giving insight into why tolerance develops and why inappropriate responses to the flora may lead to pathology.

1. Adaptive Immunity

a. Responses to bacteria viruses and parasites

REVIEW:
Palmer EG.
Immune response to commensal and environmental microbes.
Nature Immunology 2007;8:1173-1178.
The mammalian immune system discriminates among microbes, inactivating pathogens while tolerating colonization by commensal organisms. Calibrating immune responses to microbes on this basis, however, is complex, as microbial virulence is often context dependent, being influenced by the host's immune status and the microbial milieu. Many microbial pathogens infecting immunocompromised hosts, for example, are innocuous in immune-competent individuals, and other microbes cause disease only when the commensal flora is compromised by antibiotic therapy. Recent studies have begun to reveal how the immune system tips the balance in favor of some microbes, allowing commensals to persist on mucosal surfaces while eliminating disease-causing pathogens.

REVIEW:
Acheson DW, Luccioli S.
Microbial-gut interactions in health and disease. Mucosal immune responses.

Best Pract Res Clin Gastroenterol. 2004;18:387-404.
The host gastrointestinal tract is exposed to countless numbers of foreign antigens and has embedded a unique and complex network of immunological and non-immunological mechanisms, often termed the gastrointestinal 'mucosal barrier', to protect the host from potentially harmful pathogens while at the same time 'tolerating' other resident microbes to allow absorption and utilization of nutrients. Of the many important roles of this barrier, it is the distinct responsibility of the mucosal immune system to sample and discriminate between harmful and beneficial antigens and to prevent entry of food-borne pathogens through the gastrointestinal (GI) tract. This system comprises an immunological network termed the gut-associated lymphoid tissue (GALT) that consists of unique arrangements of B cells, T cells and phagocytes which sample luminal antigens through specialized epithelia termed the follicle associated epithelia (FAE) and orchestrate co-ordinated molecular responses between immune cells and other components of the mucosal barrier. Certain pathogens have developed ways to bypass and/or withstand defence by the mucosal immune system to establish disease in the host. Some 'opportunistic' pathogens (such as Clostridium difficile) take advantage of host or other factors (diet, stress, antibiotic use) which may alter or weaken the response of the immune system. Other pathogens have developed mechanisms for invading gastrointestinal epithelium and evading phagocytosis/destruction by immune system defences. Once cellular invasion occurs, host responses are activated to limit local mucosal damage and repel the foreign influence. Some pathogens (Shigella spp, parasites and viruses) primarily establish localized disease while others (Salmonella, Yersinia, Listeria) use the lymphatic system to enter organs or the bloodstream and cause more systemic illness. In some cases, pathogens (Helicobacter pylori and Salmonella typhi) colonize the GI tract or associated lymphoid structures for extended periods of time and these persistent pathogens may also be potential triggers for other chronic or inflammatory diseases, including inflammatory bowel disease and malignancies. The ability of certain pathogens to avoid or withstand the host's immune assault and/or utilize these host responses to their own advantage (i.e. enhance further colonization) will dictate the pathogen's success in promoting illness and furthering its own survival.

b. Mucosal Immunoglobulins

REVIEW:
Brandtzaeg P.
Induction of secretory immunity and memory at mucosal surfaces
Vaccine 2007;25:5467-5484.
Mucosal epithelia comprise an extensive vulnerable barrier which is reinforced by numerous innate defence mechanisms cooperating intimately with adaptive immunity. Local generation of secretory IgA (SIgA) constitutes the largest humoral immune system of the body. Secretory antibodies function both by performing antigen exclusion at mucosal surfaces and by virus and endotoxin neutralization within epithelial cells without causing tissue damage. SIgA is thus persistently containing commensal bacteria outside the epithelial barrier but can also target invasion of pathogens and penetration of harmful antigens. Resistance to toxin-producing bacteria such as Vibrio cholerae and enterotoxigenic Escherichia coli appears to depend largely on SIgA, and so does herd protection against horizontal faecal–oral spread of enteric pathogens under naïve or immunized conditions—with a substantial innate impact both on cross-reactivity and memory. Like natural infections, live mucosal vaccines or adequate combinations of non-replicating vaccines and mucosal adjuvants, give rise not only to SIgA antibodies but also to longstanding

serum IgG and IgA responses. However, there is considerably disparity with regard to migration of memory/effector cells from mucosal inductive sites to secretory effector sites and systemic immune organs. Also, although immunological memory is generated after mucosal priming, this may be masked by a self-limiting response protecting the inductive lymphoid tissue in the gut. The intranasal route of vaccine application targeting nasopharynx-associated lymphoid tissue may be more advantageous for certain infections, but only if successful stimulation is achieved without the use of toxic adjuvants that might reach the central nervous system. The degree of protection obtained after mucosal vaccination ranges from reduction of symptoms to complete inhibition of re-infection. In this scenario, it is often difficult to determine the relative importance of SIgA versus serum antibodies, but infection models in knockout mice strongly support the notion that SIgA exerts a decisive role in protection and cross-protection against a variety of infectious agents. Nevertheless, relatively few mucosal vaccines have been approved for human use, and more basic work is needed in vaccine and adjuvant design, including particulate or live-vectored combinations.

REVIEW:
Woof JM, Mestecky J.
Mucosal immunoglobulins.
Immunological Reviews 2005;206:64-82.
Due to their vast surface area, the mucosal surfaces of the body represent a major site of potential attack by invading pathogens. The secretions that bathe mucosal surfaces contain significant levels of immunoglobulins (Igs), which play key roles in immune defense of these surfaces. IgA is the predominant antibody class in many external secretions and has many functional attributes, both direct and indirect, that serve to prevent infective agents such as bacteria and viruses from breaching the mucosal barrier. This review details current understanding of the structural and functional characteristics of IgA, including interaction with specific receptors (such as FcαRI, Fcα/μR, and CD71) and presents examples of the means by which certain pathogens circumvent the protective properties of this important Ig.

i. Secretory IgA

REVIEW:
Suzuki K, Ha S, Tsuji M, Fagarasan S.
Intestinal IgA synthesis: A primitive form of adaptive immunity that regulates microbial communities in the gut.
Seminars in Immunology 2007;19:127-135
Our intestine is colonized by an impressive community of bacteria that has profound effects on the immune functions. The relationship between gut microbiota and the immune system is one of reciprocity: bacteria have important contribution in nutrient processing and education of the immune system and conversely, the immune system, particularly gut-associated lymphoid tissues (GALT) plays a key role in shaping the repertoire of gut microbiota. In this review we discuss new insights into the role of IgA in the maintenance of immune homeostasis and the reciprocal interactions between gut B cells and intestinal bacteria.

REVIEW:
Pilette C. Ouadrhiri Y. Godding V. et al.
Lung mucosal immunity : immunoglobulin-A revisited

Eur Respir J 2001;18:571-88.
Mucosal defence mechanisms are critical in preventing colonization of the respiratory tract by pathogens and penetration of antigens through the epithelial barrier. Recent research has now illustrated the active contribution of the respiratory epithelium to the exclusion of microbes and particles, but also to the control of the inflammatory and immune responses in the airways and in the alveoli. Epithelial cells also mediate the active transport of polymeric immunoglobulin-A from the lamina propria to the airway lumen through the polymeric immunoglobulin receptor. The role of IgA in the defence of mucosal surfaces has now expanded from a limited role of scavenger of exogenous material to a broader protective function with potential applications in immunotherapy. In addition, the recent identification of receptors for IgA on the surface of blood leukocytes and alveolar macrophages provides an additional mechanism of interaction between the cellular and humoral immune systems at the level of the respiratory tract.

ii. Ig Transport

RESEARCH FRONTIER:
Hongxing L. Nowak-Wegrzyn A. Charlop-Powers Z. et al.
Transcytosis of IgE-antigen complexes by CD23a in human intestinal epithelial cells and its role in food allergy
Gastroenterology 2006;131:47-58
BACKGROUND & AIMS: Secreted immunoglobulins play an integral role in host defense at mucosal surfaces, and recent evidence shows that IgG can participate in antigen sampling from the intestinal lumen. We examined whether IgE also could facilitate transepithelial antigen sampling. METHODS: Stool samples from food-allergic patients undergoing oral food challenge were analyzed for CD23 and food-specific IgE. CD23 isoform expression on primary human intestinal epithelial cells (IEC) was analyzed by polymerase chain reaction. The role of CD23 isoforms in transcytosis of antigen and IgE–antigen complexes was assessed using polarized human T84 cells retrovirally transfected with CD23a or CD23b. RESULTS: CD23 was expressed constitutively on IECs, and food-allergic patients had increased levels of soluble CD23 and food-specific IgE in the stool after challenge. CD23a, but not CD23b, was expressed by primary human IECs. We show in transcytosis assays that CD23a, but not CD23b, acts as a bidirectional transporter of IgE. In addition, specific IgE facilitated the uptake of antigen from the apical surface of an epithelial monolayer by diverting antigen from delivery to lysosomes. Finally, delivery of antigen–IgE complexes across the epithelial barrier could induce the degranulation of rat basophil leukemia cells transfected with the human high-affinity IgE receptor. CONCLUSIONS: These studies show that CD23a is expressed normally on human IECs, and in the presence of IgE can function as an antigen-sampling mechanism capable of activating subepithelial mast cells. IgE may serve as a secretory immunoglobulin that in concert with CD23 participates in food-induced pathophysiology of the gastrointestinal tract.

REVIEW:
Rojas R. Apodaca G.
Immunoglobulin transport across polarized epithelial cells
Nature Reviews Molecular Cell Biology 2202;3:944-55
IgA, IgG and IgM are transported across epithelial cells in a receptor-mediated process known as transcytosis. In addition to neutralizing pathogens in the lumen of the gastrointestinal, respiratory and urogenital tracts, these antibody–receptor complexes are now known to mediate intracellular

neutralization of pathogens and might also be important in immune activation and tolerance. Recent studies on the intracellular transport pathways of antibody–receptor complexes and antibody-stimulated receptor-mediated transcytosis are providing new insight into the nature and regulation of endocytic pathways.

iii. Fcy function

REVIEW:

Yoshida M. Masuda A. Kuo-Kanna Kobayashi T. et al.

IgG transport across mucosal barriers by neonatal Fc receptor for IgG and mucosal immunity

Springer Semin Immun 2006;28:397-403

Mucosal secretions of the human gastrointestinal, respiratory, and genital tracts contain significant quantities of IgG. The neonatal Fc receptor for IgG (FcRn) plays a major role in regulating host IgG levels and transporting IgG and associated antigens across polarized epithelial barriers. The FcRn can then recycle the IgG/antigen complex back across the intestinal barrier into the lamina propria for processing by dendritic cells and presentation to $CD4^+$ T cells in regional organized lymphoid structures. FcRn, through its ability to secrete and absorb IgG, thus integrates luminal antigen encounters with systemic immune compartments and, as such, provides essential host defense and immunoregulatory functions at the mucosal surfaces.

iv. Mucosal associated lymphoid tissue (MALT)

REVIEW:

Garside P. Millington O. Smith KM

The anatomy of mucosal immune responses.

Ann N Y Acad Sci 2004;1029:9-15

It remains unclear how and where unresponsiveness to fed antigens is induced. This "oral tolerance" is probably necessary to prevent the array of immune effector mechanisms required to counteract pathogens of the mucosae from being misdirected against food antigens or commensal flora. It will obviously be important to dissect where, when, and how such immunological homeostasis is maintained in the gut, but it will also be necessary to determine whether similar inductive and effector mechanisms are required for the therapeutic applications of oral tolerance systemically. This may be influenced by anatomical and microenvironmental effects on the phenotype and/or activation state of the antigen-presenting cell (APC), which presents orally delivered antigen. Fed antigen passes from the intestinal lumen either via the villus epithelium and M cells in the Peyer's patches (PP) or the mucosal lamina propria to the organized lymphoid tissues of the PP and mesenteric lymph nodes (MLN). In addition, there is evidence that mucosally administered antigen also gains access directly to peripheral lymphoid organs. Each of these sites contains distinctive populations of APCs and has unique local microenvironments that may influence the immune response in different ways. We propose that feeding antigen in high doses may induce clonal anergy, deletion, or altered differentiation because it gains direct access to resting APCs in the T cell areas of both the gut-associated lymphoid tissues (GALT) and peripheral lymphoid organs, with presentation occurring in the absence of productive costimulation. By contrast, low doses of tolerizing antigen may be taken up and presented preferentially by APCs in the GALT, where the local environment may favor the induction of regulatory T cells. This is consistent with our own and others findings, using adoptive transfer of TcR tg T cells. These studies have shown that antigen-specific CD4(+) T cells are activated

simultaneously in all peripheral and gut-associated lymphoid organs after feeding high doses of proteins, but that this may be more restricted to local tissues when lower doses are used. Another level of anatomical control is imposed within lymphoid organs, where migration of T cells through distinct anatomical compartments can affect their differentiation. We find that, in contrast to orally primed T cells, orally tolerized T cells are unable to migrate into B cell follicles during their initial exposure to antigen. This affects their differentiation as upon subsequent challenge with antigen in adjuvant, tolerized T cells can be found in follicles but are unable to provide the B cell help that primed T cells can deliver. We hypothesize that the initial defective migration of tolerized T cells prevents them from receiving signals from antigen-specific B cells in follicles and results in abortive differentiation. Thus, both gross and fine anatomical location of fed antigen presentation may be important in mucosal immunoregulation.

REVIEW:
Kunisawa J. Fukuyama S. Kiyono H.
Mucosa-associated lymphoid tissues in the aerodigestive tract: Their shared and divergent traits and their importance to the orchestration of the mucosal immune system.
Current Molecular Medicine 2005;5:557-572
As inductive tissues for the initiation of antigen-specific T and B cell responses, the various mucosa-associated lymphoid tissues (MALT) of the aerodigestive tract, which include gut-associated lymphoid tissue (GALT), nasopharynx-associated lymphoid tissue (NALT) and bronchus-associated lymphoid tissue (BALT), share many histological and immunological characteristics. However, recent advances in our molecular and cellular understanding of immunological development have revealed that the various types of MALT also exhibit different molecular and cellular interactions for their organogenesis. In this review, we delineate the distinctive features of GALT, NALT and BALT and seek to show the role played by those features in the regulation of mucosal tissue organogenesis, the mucosal immune system, and mucosal homeostasis, all in an attempt to provide insights which might lead to a prospective mucosal vaccine.

REVIEW:
Knop E. Knop N.
The role of eye-associated lymphoid tissue in corneal immune protection.
J. Anat. 2005;206:271-285
Because the cornea is optimized for refraction, it relies on supporting tissues for moistening and nutrition and in particular for immune protection. Its main support tissue is the conjunctiva, in addition to the lacrimal gland, the latter which provides soluble mediators via the tear film. The cornea and conjunctiva constitute a moist mucosal surface and there is increasing evidence that apart from innate defence mechanisms, also lymphoid cells contribute to the normal homeostasis of the corneal surface. A *Medline*-based literature search was performed in order to review the existing literature on the existence, composition and functions of mucosa-associated lymphoid tissue (MALT) at the ocular surface for corneal protection. The existence of lymphoid cells at the ocular surface and appendage has been known for many years, but for a long time they were believed erroneously to be inflammatory cells. More recent research has shown that in addition to the known presence of lymphoid cells in the lacrimal gland, they also form MALT in the conjunctiva as conjunctiva-associated lymphoid tissue (CALT) and in the lacrimal drainage system as lacrimal drainage-associated lymphoid tissue (LDALT). Together this constitutes an eye-

associated lymphoid tissue (EALT), which is a new component of the mucosal immune system of the body. When the topographical distribution of CALT is projected onto the ocular surface, it overlies the cornea during eye closure and is hence in a suitable position to assist the corneal immune protection during blinking and overnight. It can detect corneal antigens and prime respective effector cells, or distribute protective factors as secretory IgA.

2. Passive immunization

REVIEW:
Hanson L.
Feeding and infant development. Breast-feeding and immune function
Proceedings of the Nutrition Society 2007;66:384-396

The newborn receives, via the placenta, maternal IgG antibodies against the microbes present in its surroundings, but such antibodies have a pro-inflammatory action, initiating the complement system and phagocytes. Although the host defence mechanisms of the neonate that involve inflammatory reactivity are somewhat inefficient, this defence system can still have catabolic effects. Breast-feeding compensates for this relative inefficiency of host defence in the neonate by providing considerable amounts of secretory IgA antibodies directed particularly against the microbial flora of the mother and her environment. These antibodies bind the microbes that are appearing on the infant's mucosal membranes, preventing activation of the pro-inflammatory defence. The major milk protein lactoferrin can destroy microbes and reduce inflammatory responses. The non-absorbed milk oligosaccharides block attachment of microbes to the infant's mucosae, preventing infections. The milk may contain anti-secretory factor, which is anti-inflammatory, preventing mastitis in mothers and diarrhoea in infants. Numerous additional factors in the milk are of unknown function, although IL-7 is linked to the larger size of the thymus and the enhanced development of intestinal Tγδ lymphocytes in breast-fed compared with non-breast-fed infants. Several additional components in the milk may help to explain why breast-feeding can reduce infant mortality, protecting against neonatal septicaemia and meningitis. It is therefore important to start breast-feeding immediately. Protection is also apparent against diarrhoea, respiratory infections and otitis media. There may be protection against urinary tract infections and necrotizing enterocolitis, and possibly also against allergy and certain other immunological diseases, and tumours. In conclusion, breast-feeding provides a very broad multifactorial anti-inflammatory defence for the infant.

REVIEW:
Englund JA.
The influence of maternal immunization on infant immune responses
J. Comp. Path. 2007;137:S16-S19

The vaccination of human mothers during pregnancy leads to transplacental transfer of antibody which can provide protection to the neonate during early life. This active transfer is a receptor-mediated event with preferential transport of antibody of the IgG1 and IgG3 subclasses via the FcR_n receptor. The efficiency of trans-placental transfer is dependent on a range of factors including: placental integrity, the total IgG concentration in maternal blood, the type of vaccine, the timing of vaccine administration during gestation, the gestational age of the fetus at birth and the IgG subclass involved. The kinetics of maternal and infant serological responses has been extensively studied using Haemophilus influenzae b (Hib) vaccination as a model.

D. Transplantation Immunology

REVIEW:
Hale DA
Basic Transplantation Immunology.
Surg Clin North Am - 01-OCT-2006; 86(5): 1103-25, v
"…this article seeks to provide nontransplant surgeons with an appreciation of the general organization and function of the human immune system. Some specific immunologic consequences of allotransplantation, the practical implications of this knowledge, and the theoretic basis of modern immunosuppression are addressed subsequently."

REVIEW:
Vincenti F
Costimulation blockade in autoimmunity and transplantation.
J Allergy Clin Immunol - 01-FEB-2008; 121(2): 299-306
A very quick read with pertinent information to current understanding of costumlatory signaling in transplantation immunology and autoimmunity. A very helpful glossary of terms, wonderful diagrams and discussion on current therapeutic approaches.

1. Allograft rejection

REVIEW:
Burton JR Jr
Diagnosis and Management of Allograft Failure.
Clin Liver Dis - 01-MAY-2006; 10(2): 407-35, x
In addition to detailed discussion on hepatic transplantation immunology, this article reviews allograft rejection from the cellular level up. Diagnosis, management and ethical considerations for retransplantation are reviewed.

2. Graft versus host reactions (GVRH)

REVIEW:
Kaplan B
Overcoming Barriers to Long-Term Graft Survival.
Am J Kidney Dis - 01-APR-2006; 47(4 Suppl 2): S52-64.
A review of the trends in long-term graft survival. Review of markers as predictors for failure and strategies for prevention.

3. Maintenance of tolerance

REVIEW:
Torgerson TR
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked: Forkhead box protein 3 mutations and lack of regulatory T cells.
J Allergy Clin Immunol - 01-OCT-2007; 120(4): 744-50.
This review focuses on the spectrum of clinical symptoms and laboratory findings in patients with IPEX and IPEX-like syndromes and describe the role of FOXP3 in the generation of regulatory t cells. An excellent review of our current understanding of tolerance and dysregulation.

E. Tumor Immunology

REVIEW:

Derhovanessian E, Solana R, Labri A, Pawelec G

Immunity, ageing, and cancer

Immunity & Ageing 2008; 5: 11

Compromised immunity contributes to the decreased ability of the elderly to control infectious disease and to their generally poor response to vaccination. It is controversial as to how far this phenomenon contributes to the well-known age-associated increase in the occurrence of many cancers in the elderly. However, should the immune system be important in controlling cancer, for which there is a great deal of evidence, it is logical to propose that dysfunctional immunity in the elderly would contribute to compromised immunosurveillance and increased cancer occurrence. The chronological age at which immunosenescence becomes clinically important is known to be influenced by many factors, including the pathogen load to which individuals are exposed throughout life. It is proposed here that the cancer antigen load may have a similar effect on "immune exhaustion" and that pathogen load and tumor load may act additively to accelerate immunosenescence. Understanding how and why immune responsiveness changes in humans as they age is essential for developing strategies to prevent or restore dysregulated immunity and assure healthy longevity, clearly possible only if cancer is avoided. Here, we provide an overview of the impact of age on human immune competence, emphasizing T-cell-dependent adaptive immunity, which is the most sensitive to ageing. This knowledge will pave the way for rational interventions to maintain or restore appropriate immune function not only in the elderly but also in the cancer patient.

REVIEW:

Mumm JB, Oft M

Cytokine-based transformation of immune surveillance into tumor-promoting inflammation

Oncogene-2008; 27: 5913-5919.

During the last decade, it has become clear that the mammalian immune system is able to recognize and partially suppress nascent tumors. Human T cells specific to oncogenes and onco-fetal antigens are present in human cancer patients and their tumors. At the same time, molecular links between tumor-associated inflammation and tumor progression have been uncovered, providing an explanation for the long recognized epidemiological link between inflammation and cancer. The synopsis of these findings suggests a new interpretation of tumor immunity. It appears that antigen recognition or antigen-specific T-cell expansion at large is not as profoundly impaired in tumor patients as the correct polarization, the survival and the effector function of tumor-infiltrating T cells. This review will focus on pro-inflammatory cytokines likely to contribute to the deregulation of tumor-specific immunity and its consequences.

REVIEW:

Waldhauer I, Steinle A

NK cells and cancer immunosurveillance

Oncogene 2008; 27: 5932-5943

Natural killer (NK) cells are lymphocytes of the innate immune system that monitor cell surfaces of autologous cells for an aberrant expression of MHC class I molecules and cell stress markers. Since their first description more than 30 years ago, NK cells have been implicated in the immune defence against tumours. Here, we review the broadly accumulating evidence for a crucial

contribution of NK cells to the immunosurveillance of tumours and the molecular mechanisms that allow NK cells to distinguish malignant from healthy cells. Particular emphasis is placed on the activating NK receptor NKG2D, which recognizes a variety of MHC class I-related molecules believed to act as 'immuno-alerters' on malignant cells, and on tumour-mediated counterstrategies promoting escape from NKG2D-mediated recognition.

RESEARCH FRONTIER:
Montes CL, Capoval AI, Nelson J, Orhue V, Zhang X, Schulze DH, Strome SE, Gastman BR.
Tumor-Induced Senescent T Cells with Suppressor Function: A Potential Form of tumor Immune Evasion.
Cancer Res 2008; 68: 870-879
Senescent and suppressor T cells are reported to be increased in select patients with cancer and are poor prognostic indicators. Based on the association of these T cells and poor outcomes, we hypothesized that tumors induce senescence in T cells, which negatively effects antitumor immunity. In this report, we show that human T cells from healthy donors incubated with tumor for only 6 h at a low tumor to T-cell ratio undergo a senescence-like phenotype, characterized by the loss of CD27 and CD28 expression and telomere shortening. Tumor-induced senescence of T cells is induced by soluble factors and triggers increases in expression of senescence-associated molecules such as p53, p21, and p16. Importantly, these T cells are not only phenotypically altered, but also functionally altered as they can suppress the proliferation of responder T cells. This suppression requires cell-to-cell contact and is mediated by senescent $CD4^+$ and $CD8^+$ subpopulations, which are distinct from classically described natural T regulatory cells. Our observations support the novel concept that tumor can induce senescent T cells with suppressor function and may effect both the diagnosis and treatment of cancer.

REVIEW:
Aggarwal BB, Shishodia S, Sandur SK, Pandey M, Sethi G.
Inflammation and Cancer: how hot is the link?
Biochem Pharmacol 2006; 72: 1605-1621
Although inflammation has long been known as a localized protective reaction of tissue to irritation, injury, or infection, characterized by pain, redness, swelling, and sometimes loss of function, there has been a new realization about its role in a wide variety of diseases, including cancer. While acute inflammation is a part of the defense response, chronic inflammation can lead to cancer, diabetes, cardiovascular, pulmonary, and neurological diseases. Several pro-inflammatory gene products have been identified that mediate a critical role in suppression of apoptosis, proliferation, angiogenesis, invasion, and metastasis. Among these gene products are TNF and members of its superfamily, IL-1α, IL-1β, IL-6, IL-8, IL-18, chemokines, MMP-9, VEGF, COX-2, and 5-LOX. The expression of all these genes are mainly regulated by the transcription factor NF-κB, which is constitutively active in most tumors and is induced by carcinogens (such as cigarette smoke), tumor promoters, carcinogenic viral proteins (HIV-tat, HIV-nef, HIV-vpr, KHSV, EBV-LMP1, HTLV1-tax, HPV, HCV, and HBV), chemotherapeutic agents, and γ-irradiation. These observations imply that anti-inflammatory agents that suppress NF-κB or NF-κB-regulated products should have a potential in both the prevention and treatment of cancer. The current review describes in detail the critical link between inflammation and cancer.

RESEARCH FRONTIER:
Mathew R, Karantza-Wadsworth V, White E
Role of autophagy in cancer
Nature Reviews 2007; 7: 961-967
Autophagy is a cellular degradation pathway for the clearance of damaged or superfluous proteins and organelles. The recycling of these intracellular constituents also serves as an alternative energy source during periods of metabolic stress to maintain homeostasis and viability. In tumour cells with defects in apoptosis, autophagy allows prolonged survival. Paradoxically, autophagy defects are associated with increased tumorigenesis, but the mechanism behind this has not been determined. Recent evidence suggests that autophagy provides a protective function to limit tumour necrosis and inflammation, and to mitigate genome damage in tumour cells in response to metabolic stress.

1. Tumor specific and tumor associated antigens

REVIEW:
Simpson AJG, Caballero OL, Jungbluth A, Chen YT, Old LJ
Cancer/Testis Antigens, Gametogenesis and Cancer
Nature Reviews 2005; 5: 615-625
Cancer/testis (CT) antigens, of which more than 40 have now been identified, are encoded by genes that are normally expressed only in the human germ line, but are also expressed in various tumour types, including melanoma, and carcinomas of the bladder, lung and liver. These immunogenic proteins are being vigorously pursued as targets for therapeutic cancer vaccines. CT antigens are also being evaluated for their role in oncogenesis — recapitulation of portions of the germline gene-expression programme might contribute characteristic features to the neoplastic phenotype, including immortality, invasiveness, immune evasion, hypomethylation and metastatic capacity.

REVIEW:
Schietinger A, Philip M, Schreiber H
Specificity in cancer immunotherapy
Semin Immunol 2008; 20: 276-85
From the earliest days in the field of tumor immunology three questions have been asked: do cancer cells express tumor-specific antigens, does the immune system recognize these antigens and if so, what is their biochemical nature? We now know that truly tumor-specific antigens exist, that they are caused by somatic mutations, and that these antigens can induce both humoral and cell-mediated immune responses. Because tumor-specific antigens are exclusively expressed by the cancer cell and are often crucial for tumorigenicity, they are ideal targets for anti-cancer immunotherapy. Nevertheless, the antigens that are targeted today by anti-tumor immunotherapy are not tumor-specific antigens, but antigens that are normal molecules also expressed by normal tissues (so-called “tumor-associated” antigens). If tumor-specific antigens exist and are ideal targets for immunotherapy, why are they not being targeted?
In this review, we summarize current knowledge of tumor-specific antigens: their identification, immunological relevance and clinical use. We discuss novel tumor-specific epitopes and propose new approaches that could improve the success of cancer immunotherapy, especially for the treatment of solid tumors.

WEBSITE LINK:
Antigen-encoding genes and epitopes.
http://www.cancerimmunity.org
Cancer Immunity. A journal of the Academy of Cancer Immunology.
This link will get you to detailed lists of antigen-encoding genes and epitopes. The site contains topics of general interest to cancer immunologists.

2. Oncogenes, translocations & tumor suppressor genes.

REVIEW:
Gasparini P, Sozzi G, Pierotti MA
The role of Chromosomal Alterations in Human Cancer Development
J Cell Biochem 2007; 102: 320-331
Cancer cells become unstable and compromised because several cancer-predisposing mutations affect genes that are responsible for maintaining the genomic instability. Several factors influence the formation of chromosomal rearrangements and consequently of fusion genes and their role in tumorigenesis. Studies over the past decades have revealed that recurring chromosome rearrangements leading to fusion genes have a biological and clinical impact not only on leukemias and lymphomas, but also on certain epithelial tumors. With the implementation of new and powerful cytogenetic and molecular techniques the identification of fusion genes in solid tumors is being facilitated. Overall, the study of chromosomal translocations have revealed several recurring themes, and reached important insights into the process of malignant transformation. However, the mechanisms behind these translocations remain unclear. A more thorough understanding of the mechanisms that cause translocations will be aided by continuing characterization of translocation breakpoints and by developing in vitro and in vivo model systems that can generate chromosome translocation.

REVIEW:
Grisendi S, Pandolfi PP
Two Decades of Cancer Genetics: From Specificity to Pleiotropic Networks
Cold Spring Symposia on quantitative Biology 2005; Symposium 70: 83-91
Modeling cancer in mice has reached an even greater relevance in the field of hematological malignancies, due to the already advanced characterization of the molecular basis of many hematological disorders. These mouse models have often allowed us to achieve insight into the pathogenesis of the human disease as well as to test novel therapeutic modalities in preclinical studies. However, one of the most rewarding cultural shifts triggered by these modeling efforts stems from what was originally perceived as background noise or modeling inaccuracy. Manipulation of the involved genes often triggered cancer susceptibility in cell types other than the hematopoietic lineages. This prompted us to challenge a fundamental misconception in cancer genetics that the approximately 200 genes directly involved in chromosomal translocations associated with hematopoietic malignancies are specifically and functionally restricted to leukemia/lymphoma pathogenesis only. The genetics underlying the pathogenesis of leukemia and lymphoma have historically been regarded as distinct from those underlying the pathogenesis of solid tumors because hematopoietic malignancies are often associated with characteristic chromosomal translocations that are leukemia- or lymphoma-specific. In this paper, we discuss how leukemia/lymphoma genes indeed participate in fundamental proto-oncogenic and growth-suppressive networks and may play a wider role in cancer pathogenesis. We focus on paradigmatic

examples such as c-myc and PML, as well as on more recent findings from our laboratory concerning the role of NPM in tumorigenesis.

REVIEW:
Fukasawa K
Oncogenes and tumour suppressors take on centrosomes
Nature Reviews Cancer 2007; 7: 911-924
Chromosome instability, which is equated to mitotic defects and consequential chromosome segregation errors, provides a formidable basis for the acquisition of further malignant phenotypes during tumour progression. Centrosomes have a crucial role in the formation of bipolar mitotic spindles, which are essential for accurate chromosome segregation. Mutations of certain oncogenic and tumour-suppressor proteins directly induce chromosome instability by disrupting the normal function and numeral integrity of centrosomes. How these proteins control centrosome duplication and function, and how their mutational activation and/or inactivation results in numeral and functional centrosome abnormalities, is discussed in this review.

REVIEW:
Iacobuzio-Donahue C
Epigenetic changes in cancer
Annu Rev Pathol Mech Dis 2009; 4: 229-249
Cancer is as much an epigenetic disease as it is a genetic disease, and epigenetic alterations in cancer often serve as potent surrogates for genetic mutations. Normal epigenetic modifications of DNA encompass three types of changes: chromatin modifications, DNA methylation, and genomic imprinting, each of which is altered in cancer cells. This review addresses the various epigenetic modifications that are pervasive among human tumors and traces the history of cancer epigenetics from the first observations of altered global methylation content to the recently proposed epigenetic progenitor model, which provides a common unifying mechanism for cancer development.

WEBSITE LINK:
Tumor suppressor genes
http://web.indstate.edu/theme/mwking/tumor-suppressors.html
This link will get you directly to text that summarizes the commonly known onogene suppressors. There is also a very handy table of the tumor suppressor genes, the associations with familial cancer syndrome, function, chromosomal location and tumor type observed.

F. Immunoregulatory Mechanisms

1. Tolerance

REVIEW:
Mitchell Kronenberg and Alexander Rudensky
Regulation of immunity by self-reactive T cells
Nature 2005;435:598-604
A basic principle of immunology is that lymphocytes respond to foreign antigens but tolerate self tissues. For developing T cells, the ability to distinguish self from non-self is acquired in the thymus, where the majority of self-reactive cells are eliminated. Recently, however, it has become

apparent that some self-reactive T cells avoid being destroyed and instead differentiate into specialized regulatory cells. This appears to be beneficial. Subpopulations of self-reactive T cells have a strong influence on self tolerance and may represent targets for therapeutic intervention to control a variety of autoimmune diseases, tumour growth and infection

REVIEW:
Goodnow C, Sprent J, Fazekas de St Groth B and Vinuesa CG
Cellular and genetic mechanisms of self tolerance and autoimmunity
Nature 2005;435:590-597
The mammalian immune system has an extraordinary potential for making receptors that sense and neutralize any chemical entity entering the body. Inevitably, some of these receptors recognize components of our own body, and so cellular mechanisms have evolved to control the activity of these 'forbidden' receptors and achieve immunological self tolerance. Many of the genes and proteins involved are conserved between humans and other mammals. This provides the bridge between clinical studies and mechanisms defined in experimental animals to understand how sets of gene products coordinate self-tolerance mechanisms and how defects in these controls lead to autoimmune disease.

LANDMARK ARTICLE:
Aluvihare VR, Kallikourdis M, Betz AG
Regulatory T cells mediate maternal tolerance to the fetus
Nat Immunol. 2004 Mar;5(3):266-71.
Pregnancy constitutes a major challenge to the maternal immune system, as it has to tolerate the persistence of paternal alloantigen. Although localized mechanisms contribute to fetal evasion from immune attack, maternal alloreactive lymphocytes persist. We demonstrate here an alloantigenin dependent, systemic expansion of the maternal CD25+ T cell pool during pregnancy and show that this population contains dominant regulatory T cell activity. In addition to their function in suppressing autoimmune responses, maternal regulatory T cells suppressed an aggressive allogeneic response directed against the fetus. Their absence led to a failure of gestation due to immunological rejection of the fetus.

RESEARCH FRONTIER:
Hori S, Nomura T , Sakaguchi S.
Control of Regulatory T Cell Development by the Transcription Factor Foxp3
Science 2003:99;1057– 1061
Regulatory T cells engage in the maintenance of immunological self-tolerance by actively suppressing self-reactive lymphocytes. Little is known, however, about the molecular mechanism of their development. Here we show that *Foxp3*, which encodes a transcription factor that is genetically defective in an autoimmune and inflammatory syndrome in humans and mice, is specifically expressed in naturally arising CD4+ regulatory T cells. Furthermore, retroviral gene transfer of *Foxp3* converts naïve T cells toward a regulatory T cell phenotype similar to that of naturally occurring CD4+ regulatory T cells. Thus, *Foxp3* is a key regulatory gene for the development of regulatory T cells.

CUTTING EDGE:
Hernandez MG, Shen L, Rock KL.

J Immunol. 2008 Apr 1;180(7):4382-90.
CD40 on APCs is needed for optimal programming, maintenance, and recall of CD8+ T cell memory even in the absence of CD4+ T cell help.
CD40 stimulation is one of the many signals that can activate APCs and we have recently shown it to have a unique function in generating maximum primary CD8(+) T cell responses. However, whether CD40 signaling plays a role in memory CD8(+) T cell responses is still not completely understood. In this study, we show that in the absence of CD40 on all APCs or specifically on dendritic cells, memory CD8(+) T cells are generated but at significantly reduced levels. This reduction is due to a contribution of CD40 at several different steps in the generation of CD8(+) memory. In the initial T cell response, CD40 contributes to maximizing not only the number of effector cells that are generated but also the programming of ones that will differentiate into memory. Subsequently, CD40 is needed to maintain maximal numbers of the committed memory cells in a manner that is independent of the immunizing Ag. Finally, when memory CD8(+) T cells are reactivated there is a variable requirement for CD40 depending on whether CD40 or CD4(+) Th cells were present during the primary response. Therefore, CD40 signaling on APCs plays an important role in all phases of a memory CD8(+) T cell response.

CUTTING EDGE:
Goriely S, Goldman M.
Interleukin-12 family members and the balance between rejection and tolerance.
Curr Opin Organ Transplant. 2008 Feb;13(1):4-9
Allograft rejection involves multiple effector mechanisms. Interleukin(IL)-12 family members play a critical role in influencing helper T-cell differentiation and inflammatory processes, and their respective role in orchestrating inflammation of autoimmune or infectious origin starts to be unravelled. We highlight recent findings on the function of the different IL-12 family members: IL-12p70, IL-23, IL-27 and IL-35 and discuss their possible involvement in influencing the balance between graft rejection and tolerance. RECENT FINDINGS: The capacity of dendritic cells to produce IL-12 and IL-23 strongly influences the outcome of CD4 T-cell responses. While the IL-12/interferon-gamma axis has classically been involved in autoimmune pathologies and acute graft rejection, it is now clear that it also displays immunoregulatory properties. In contrast, IL-23 promotes the function of proinflammatory IL-17-producing cells in both mice and humans. Both IL-27 and IL-35 have recently emerged as important regulators of adaptive immune responses. SUMMARY: The contribution of the IL-12/interferon-gamma pathway to acute graft rejection may be more complicated than initially thought. As our understanding of the IL-12 family is rapidly growing and changing, the respective role of its members in orchestrating innate and adaptive immune responses toward alloantigens should be addressed.

2. Idiotypic networks

REVIEW:
Cohen IR , Quintana FJ, Mimran A
Tregs in T cell vaccination: exploring the regulation of regulation
J Clin. Invest. 2004;114:1227-1232
T cell vaccination (TCV) activates Tregs of 2 kinds: anti-idiotypic (anti-id) and anti-ergotypic (antierg). These regulators furnish a useful view of the physiology of T cell regulation of the immune response. Anti-id Tregs recognize specific effector clones by their unique TCR CDR3 peptides; anti-id networks of CD4+ and CD8+ Tregs have been described in detail. Here we shall

focus on anti-erg T regulators. Anti-erg T cells, unlike anti-id T cells, do not recognize the clonal identity of effector T cells; rather, anti-erg T cells recognize the state of activation of target effector T cells, irrespective of their TCR specificity. We consider several features of anti-erg T cells: their ontogeny, subset markers, and target ergotope molecules; mechanisms by which they regulate other T cells; mechanisms by which they get regulated; and therapeutic prospects for antierg upregulation and downregulation.

CUTTING EDGE:
Pendergraft WF 3rd, Preston GA, Shah RR, Tropsha A, Carter CW Jr, Jennette JC, Falk RJ
Autoimmunity is triggered by cPR-3(105-201), a protein complementary to human autoantigen proteinase-3.
Nat Med. 2004 Jan;10(1):72-9. Epub 2003 Dec 7.
Nat Med. 2004 Jan;10(1):17-18
It remains unclear how and why autoimmunity occurs. Here we show evidence for a previously unrecognized and possibly general mechanism of autoimmunity. This new finding was discovered serendipitously using material from patients with inflammatory vascular disease caused by antineutrophil cytoplasmic autoantibodies (ANCA) with specificity for proteinase-3 (PR-3). Such patients harbor not only antibodies to the autoantigen (PR-3), but also antibodies to a peptide translated from the antisense DNA strand of PR-3 (complementary PR-3, cPR-3) or to a mimic of this peptide. Immunization of mice with the middle region of cPR-3 resulted in production of antibodies not only to cPR-3, but also to the immunogen's sense peptide counterpart, PR-3. Both human and mouse antibodies to PR-3 and cPR-3 bound to each other, indicating idiotypic relationships. These findings indicate that autoimmunity can be initiated through an immune response against a peptide that is antisense or complementary to the autoantigen, which then induces anti-idiotypic antibodies (autoantibodies) that cross-react with the autoantigen.

3. Apoptosis

REVIEW:
Zhang N. Hartig H. Dzhagalov et al.
The role of apoptosis in the development and function of T lymphocytes.
Cell Research. 2005;15:749-69.
Apoptosis plays an essential role in T cell biology. Thymocytes expressing nonfunctional or autoreactive TCRs are eliminated by apoptosis during development. Apoptosis also leads to the deletion of expanded effector T cells during immune responses. The dysregulation of apoptosis in the immune system results in autoimmunity, tumorogenesis and immunodeficiency. Two major pathways lead to apoptosis: the intrinsic cell death pathway controlled by Bcl-2 family members and the extrinsic cell death pathway controlled by death receptor signaling. These two pathways work together to regulate T lymphocyte development and function.

LANDMARK ARTICLE:
Li Yu, Ajjai Alva, Helen Su, Parmesh Dutt et al.Regulation of an ATG7-beclin 1 Program of Autophagic Cell Death by Caspase-8
Science June 2004;304: 1500 – 1502
Caspases play a central role in apoptosis, a well-studied pathway of programmed cell death. Other programs of death potentially involving necrosis and autophagy may exist, but their relation to

apoptosis and mechanisms of regulation remains unclear. We define a new molecular pathway in which activation of the receptor-interacting protein (a serine-threonine kinase) and Jun aminoterminal kinase induced cell death with the morphology of autophagy. Autophagic death required the genes *ATG7* and *beclin 1* and was induced by caspase-8 inhibition. Clinical therapies involving caspase inhibitors may arrest apoptosis but also have the unanticipated effect of promoting autophagic cell death.

CUTTING EDGE:
Yamaoka T, Yan F, Cao H, Hobbs SS, Dise RS, Tong W, Polk DB.
Transactivation of EGF receptor and ErbB2 protects intestinal epithelial cells from TNF-induced apoptosis
Proc Natl Acad Sci U S A. 2008 Aug 19;105(33):11772-7. Epub 2008 Aug 13.
TNF is a pleiotropic cytokine that activates both anti- and proapoptotic signaling pathways, with cell fate determined by the balance between these two pathways. Activation of ErbB family members, including EGF receptor (EGFR/ErbB1), promotes cell survival and regulates several signals that overlap with those stimulated by TNF. This study was undertaken to determine the effects of TNF on EGFR and ErbB2 activation and intestinal epithelial cell survival. Mice, young adult mouse colon epithelial cells, and EGFR knockout mouse colon epithelial cells were treated with TNF. Activation of EGFR, ErbB2, Akt, Src, and apoptosis were determined in vivo and in vitro. TNF stimulated EGFR phosphorylation in young adult mouse colon epithelial cells, and loss of EGFR expression or inhibition of kinase activity increased TNF-induced apoptosis, which was prevented in WT but not by kinase-inactive EGFR expression. Similarly, TNF injection stimulated apoptosis in EGFR-kinase-defective mice (EGFR(wa2)) compared with WT mice. TNF also activated ErbB2, and loss of ErbB2 expression increased TNF-induced apoptosis. Furthermore, Src-kinase activity and the expression of both EGFR and ErbB2 were required for TNF-induced cell survival. Akt was shown to be a downstream target of TNF-activated EGFR and ErbB2. These findings demonstrate that EGFR and ErbB2 are critical mediators of TNF-regulated antiapoptotic signals in intestinal epithelial cells. Given evidence for TNF signaling in the development of colitis-associated carcinoma, this observation has significant implications for understanding the role of EGFR in maintaining intestinal epithelial cell homeostasis during cytokine-mediated inflammatory responses.

4. Anergy

LANDMARK ARTICLE
Boussiotis VA, Freeman GJ , Berezovskaya A, et al.
Maintenance of Human T Cell Anergy: Blocking of IL-2 Gene Transcription by Activated Rap1
Science 1997;278:124-8}
In the absence of costimulation, T cells activated through their antigen receptor become unresponsive (anergic) and do not transcribe the gene encoding interleukin-2 (IL-2) when restimulated with antigen. Anergic alloantigen-specific human T cells contained phosphorylated Cbl that coimmunoprecipitated with Fyn. The adapter protein CrkL was associated with both phosphorylated Cbl and the guanidine nucleotide-releasing factor C3G, which catalyzes guanosine triphosphate (GTP) exchange on Rap1. Active Rap1 (GTP-bound form) was present in anergic cells. Forced expression of low amounts ofRap1-GTP in Jurkat T cells recapitulated the anergic defect and blocked T cell antigen receptor (TCR)-and CD28-mediated IL-2 gene transcription.

Therefore, Rap1 functions as a negative regulator of TCRmediated IL-2 gene transcription and may be responsible for the specific defect in IL-2 production in T cell anergy.

REVIEW ARTICLE:
Kemper C, Chan AC, Green JM, et al.
Activation of human CD4+ cells with CD3 and CD46 induces a T-regulatory cell 1 phenotype
Nature 2003;421:388-392
The immune system must distinguish not only between self and non-self, but also between innocuous and pathological foreign antigens to prevent unnecessary or self-destructive immune responses. Unresponsiveness to harmless antigens is established through central and peripheral processes1. Whereas clonal deletion and anergy are mechanisms of peripheral tolerance2, 3, active suppression by T-regulatory 1 (Tr1) cells has emerged as an essential factor in the control of autoreactive cells 4. Tr1 cells are CD4+ T lymphocytes that are defined by their production of interleukin 10 (IL-10)5 and suppression of T-helper cells6; however, the physiological conditions underlying Tr1 differentiation are unknown. Here we show that co-engagement of CD3 and the complement regulator CD46 in the presence of IL-2 induces a Tr1-specific cytokine phenotype in human CD4+ T cells. These CD3/CD46-stimulated IL-10-producing CD4+ cells proliferate strongly, suppress activation of bystander T cells and acquire a memory phenotype. Our findings identify an endogenous receptor mediated event that drives Tr1 differentiation and suggest that the complement system has a previously unappreciated role in T-cell-mediated immunity and tolerance.

CUTTING EDGE:
Lineberry NB, Su LL, Lin JT, Coffey GP, Seroogy CM, Fathman CG
Cutting edge: The transmembrane E3 ligase GRAIL ubiquitinates the costimulatory molecule CD40 ligand during the induction of T cell anergy
J Immunol. 2008 Aug 1;181(3):1622-6.
Activation of naive T lymphocytes is regulated through a series of discrete checkpoints that maintain unresponsiveness to self. During this multistep process, costimulatory interactions act as inducible signals that allow APCs to selectively mobilize T cells against foreign Ags. In this study, we provide evidence that the anergy-associated E3 ubiquitin ligase GRAIL (gene related to anergy in lymphocytes) regulates expression of the costimulatory molecule CD40L on CD4 T cells. Using its luminal protease-associated domain, GRAIL binds to the luminal/extracellular portion of CD40L and facilitates transfer of ubiquitin molecules from the intracellular GRAIL RING (really interesting new gene) finger to the small cytosolic portion of CD40L. Down-regulation of CD40L occurred following ectopic expression of GRAIL in naive T cells from CD40(-/-) mice, and expression of GRAIL in bone marrow chimeric mice was associated with diminished lymphoid follicle formation. These data provide a model for intrinsic T cell regulation of costimulatory molecules and a molecular framework for the initiation of clonal T cell anergy.

G. Laboratory Measurements

1. Methodology and interpretation: measurements of immunoglobulin levels, immunoglobulin classes and subclasses

REVIEW ARTICLE:
Agarwal S, Cunningham-Rundles C.

Assessment and clinical interpretation of reduced IgG values
Ann Allergy Asthma Immunol. 2007;99:281-3.
Patients are often referred to immunologists for the evaluation of reduced serum IgG levels. Because antibody deficiencies are the most common of the primary immune defects, examination of humoral immunity in these patients is valuable.This article is the first in a series dealing with the diagnosis of immunodeficiency disorders, with focus on the interpretation of reduced IgG values. The information presented should be interpreted in the clinical context of each patient along with other evaluation measures, such as IgM and IgA levels and functional humoral immunity, discussed in subsequent articles.

REVIEW ARTICLE:
Paris K, Sorenson R.
Assessment and clinical interpretation of polysaccharide antibody responses
Ann Allergy Asthma Immunol. 2007;99:462-464.
This second article in the miniseries Practical Aspects of Ambulatory Diagnosis and Management of Immunodeficiency Disorders1 extends the discussion on evaluation of individuals with suspected humoral immunodeficiency2 by reviewing the logistics and interpretation of the patient's ability to produce antibodies to polysaccharide antigens, specifically pneumococcal surface polysaccharides. The response to these polysaccharides is important in the evaluation of patients with documented immune abnormalities and those individuals who have normal total immunoglobulin levels. Although profound immune deficiencies, such as X-linked agammaglobulinemia and severe combined immunodeficiency, are always associated with a defect in specific antibody production, some immune disorders may have variable responses, whereas others with persistent IgG or IgG subclass deficiencies may have normal or clearly abnormal antipolysaccharide antibodies. Measurement of the response to pneumococcal polysaccharides is preferred because of the availability of a pure polysaccharide vaccine for antigen challenge and standardized techniques to measure specific antibody responses.

REVIEW ARTICLE:
Ochs, H
Patients with abnormal IgM levels: assessment, clinical interpretation, and treatment.
Ann Allergy Asthma Immunol. 2008 May;100:509-11
This review of the role of IgM in cognate immunity is part of a series on ambulatory diagnoses and management of primary immune deficiency diseases edited by Chitra Dinakar, University of Missouri. IgM is phylogenetically the earliest antibody class identified and the first immunoglobulin isotype to appear in the circulation after exposure to a newantigen. IgM plays an important role in the ontogeny of B cells and in early cognate immune responses. (truncated)

REVIEW ARTICLE:
Pien GC, Orange JS.
Evaluation and clinical interpretation of hypergammaglobulinemia E: differentiating atopy from immunodeficiency
Ann Allergy Asthma Immunol. 2008 May;100:392-395
Total serum IgE levels are elevated in a broad array of clinical settings, including infectious, oncologic, inflammatory, allergic, and primary immunodeficiency disorders. It isneither a sensitive nor a specific diagnostic marker for any given disease. This article discusses the laboratory

quantitation and clinical interpretation of total IgE levels, with emphasis on differentiating atopy from underlying primary immunodeficiency as the cause of hypergammaglobulinemia E states.

REVIEW CHAPTER:
Homburger HA, Singh RJ
"Assessment of proteins of the immune system"
Clinical Immunology: Principles and Practice, Third Edition 2008 Elsevier Publishing.
Rich RR, Fleisher TA, Shearer WT et al editors pp.1419-1434
This chapter in the Third Edition (2008) of the Rich Clinical Immunology textbook describes the instrumentation, technology and interpretation methods for assessment of serum proteins including electrophoresis, precipitation, agglutination and immunometric techniques including the detection and measurement of immunoglobulins and specific antibodies. A discussion of emerging technologies including proteomics, microarray and multiplex testing is also included.

GUIDELINE / PRACTICE PARAMETER:
Bonilla FA, Bernstein IL, Khan DA et al.
Practice parameter for diagnosis and management of primary immunodeficiency
Ann Allergy Asthma Immunol 2005;94:S1-S63

a. serologic testing

i. ELISA, immunoblot

REVIEW CHAPTER:
Homburger HA, Singh RJ
"Assessment of proteins of the immune system"
Clinical Immunology: Principles and Practice, Third Edition 2008 Elsevier Publishing.
Rich RR, Fleisher TA, Shearer WT et al editors pp.1419-1434
This chapter in the recent version of the Rich Clinical Immunology textbook describes the instrumentation, technology and interpretation methods for assessment of serum proteins including electrophoresis, precipitation, agglutination and immunometric techniques including the detection and measurement of immunoglobulins and specific antibodies. A discussion of emerging technologies including proteomics, microarray and multiplex testing is also included.

ii. autoimmune serology

REVIEW ARTICLE:
Stinton LM and Fritzler MJ.
A clinical approach to autoantibody testing in systemic rheumatic disorders.
Autoimmun Rev. 2007; 7:77-84.
Musculoskeletal disorders constitute one of the most common clinical presentations to clinical care givers. Within this category of illnesses, systemic autoimmune rheumatic diseases (SARD) such as systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome and rheumatoid arthritis are included in the differential diagnosis. A hallmark of SARD is the production of autoantibodies, which are routinely requested as a guide to diagnosis and clinical decision making. The field of serological tests, including the detection of autoantibodies, is complex and often leads to confusion and misunderstanding. When used appropriately, autoantibodies can be a valuable adjunct to the

diagnosis, and occasionally therapy and prognosis, of SARD. The role of autoantibody testing and a 'practical' approach to using these tests is the focus of this paper.

iii. in vitro testing techniques for specific IgE

REVIEW ARTICLE:

Hamilton RG, Atkinson NF Jr.

In vitro assays for the diagnosis of IgE-mediated disorders.

J Allergy Clin Immunol. 2004;114:213-25

Advances in technology have provided new laboratory tools for the quantitation of allergen-specific IgE antibodies in serum and on the surface of basophils. This review examines the evolution from qualitative IgE antibody assays of the late 1960s to the present-day, third-generation, automated and quantitative allergen-specific IgE assays. The latest technology trend is toward microarrays in which crude or purified native and recombinant allergens can be spotted in microdot arrays on silica chips to permit extensive panels of specific IgE measurements to be performed with small quantities of serum. Although these technologies hold promise, their diagnostic performance requires further assessment once their technical details have been optimized. Potential abuses of this newer IgE antibody technology include the use of allergosorbent specificities (eg, especially food and drugs) that lack validation, application of IgE antibody measurements in the diagnosis of non-IgE-dependent disorders (eg, aspirin sensitivity), and modification of IgE antibody assays to measure food-specific IgG antibody for which there is no clinical indication. Basophil mediator release assays have evolved to include flow cytometric methods that can quantitatively detect the presence of cell surface-bound allergen-specific IgE antibodies. Assays for histamine and leukotriene C 4 released after in vitro basophil activation are now more accurate and standardized. Current analytic methods for IgE antibodies provide more quantitative and reproducible measurements of IgE than ever before, although still with less sensitivity that traditional skin testing. The current challenge is to translate the quantitative IgE antibody results into a more accurate diagnosis of allergic disease.

RESEARCH FRONTIER:

King EM, Vailes LD, Tsay A, Satinover SM, Chapman MD

Simultaneous detection of total and allergen-specific IgE by using purified allergens in a fluorescent multiplex array

J Allergy Clin Immunol. 2007;120:1126-31

BACKGROUND: Testing serum samples for total and allergen-specific IgE requires separate testing for each antibody and allergen specificity. OBJECTIVE: To apply fluorescent suspension array technology to allow simultaneous detection of total and allergen-specific IgE in serum in a single quantitative test. METHODS: A 7-plex suspension array for the simultaneous detection of total IgE and IgE specific to Der p 1, Der p 2, Fel d 1, Can f 1, Bet v 1, and Phl p 5 was developed, using mAb or purified allergens covalently coupled to fluorescent microspheres. The multiplex array was validated by comparing total and allergen-specific IgE levels in serum from patients with allergy with results obtained by enzyme immunoassays. RESULTS: There was a highly significant correlation between total IgE levels measured by multiplex array and fluorescent enzyme immunoassay ($r = 0.97$; $P < .001$; $n = 63$). Total and allergen-specific IgE levels also correlated with enzyme-linked and fluorescent enzyme immunoassay results ($r = 0.44$-0.94; $n = 95$ or 106). The multiplex array was reproducible ($r = 0.86$-0.99; mean coefficient of variance percentage, 12% to 25%). The sample volume required for a 7-plex assay was <20 microL per

sample, compared with >400 microL in current immunoassays. CONCLUSION: The multiplex array is a high-throughput system that allows simultaneous quantification of allergen-specific and total IgE. CLINICAL IMPLICATIONS: Our results suggest that fluorescent multiplex technology will facilitate large-scale epidemiologic studies of allergic sensitization. The reduced serum volume is an advantage for pediatric studies.

GUIDELINE PRACTICE PARAMETER:
Bernstein IL , Li JT, Bernstein DI, et al.
Allergy Diagnostic Testing: An Updated Practice Parameter
Ann Allergy Asthma Immunol 2008;100:S1-S148

iv. RAST Inhibition techniques

LANDMARK ARTICLE:
Gleich GJ, Leiferman KM, Jones RT, et al.
Analysis of the potency of extracts of June grass pollen by their inhibitor capacities in the radioallergosorbent test
J Allergy Clin Immunol. 1976;58:31-8.
The potencies of 11 commercial extracts of June grass pollen were analyzed by skin test end pointtitrations and compared to potencies as determined in vitro (1) by the radioallergosorbent test (RAST),(2) by Group I antigen content, and (3) by protein nitrogen units (PNU). RAST potencies were determined by the capacity of the extract to inhibit the binding of IgE antibody to solid-phase allergen, and they were expressed as the quantity of extract required for 50% inhibition of binding. Potencies determined by skin testing in 8 patients were significantly related among the various patients in 19 of 27 comparisons and showed differences of up to 95,000-fold in the strengths of the extracts. Estimation of potencies by RAST inhibition showed approximately a 100-fold difference among the extracts and in 5 of 8 cases these were significantly related to potencies measured by skin tests. Similarly, PNU determinations and Group I determinations were also significantly related to potencies by skin test titration in 5 of 8 and in 4 of 8 comparisons, respectively. Comparison of the geometric mean skin test potencies with RAST, PNU, and Group I potencies revealed that all were significantly related to skin test potencies although the correlation of RAST and skin potency was the highest. The results indicate that measurement of potency by RAST inhibition compares favorably with other in vitro measurements of potency. These results are compared with those of a prior study with extracts of short ragweed, and the reasons for the differences between the results in the two studies are discussed.

v. serologic testing for infectious disease

REVIEW ARTICLE:
Fierz W.
Basic problems of serological laboratory diagnosis.
Methods Mol Med. 2004;94:393-425
Serological laboratory diagnosis of infectious diseases is inflicted with several kinds of basic problems. One difficulty relates to the fact that the serological diagnosis of infectious diseases is double indirect: The first indirect aim in diagnosing an infectious disease is to identify the microbial agent that caused the disease. The second indirect aim is to identify this infectious agent by measuring the patient's immune response to the potential agent. Thus, the serological test is neither measuring directly disease nor the cause of the disease, but the patient's immune system.

The latter poses another type of problem, because each person's immune system is unique. The immune response to an infectious agent is usually of polyclonal nature, and the exact physicochemical properties of antibodies are unique for each clone of antibody. The clonal makeup and composition and, therefore, the way an individual's immune system sees an infectious agent, depends not only on the genetic background of the person but also on the individual experience from former encounters with various infectious agents. In consequence, the reaction of a patient's serum in an analytical system is not precisely predictable. Also, the antigenic makeup of an infectious agent is not always foreseeable. Antigenic variations leading to different serotypes is a quite common phenomenon. Altogether, these biological problems lead to complexities in selecting the appropriate tests and strategies for testing, in interpreting the results, and in standardizing serological test systems. For that reason, a close collaboration of the laboratory with the clinic is mandatory to avoid erroneous conclusions from serological test results, which might lead to wrong decisions in patient care.

vi. flow cytometry -cell surface marker and intracellular techniques

REVIEW ARTICLE:
Hernandez-Trujillo VP,Fleisher TA
Interpretation of flow cytometry in primary immunodeficiency disorders
Ann Allergy Asthma Immunol 2008;100:612-615
The laboratory evaluation of primary immunodeficiency disorders (PIDDs) has evolved with the development of new technologies, including flow cytometry, to characterize circulating lymphocytes. This article is part of a series on the ambulatory diagnosis of immunodeficiency disorders, and the focus of this discussion is on the application of flow cytometry in the diagnosis and/or evaluation of different groups of PIDDs, classified using the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification system.

REVIEW CHAPTER:
Fleisher TA, Bosco deOliveira J
"Flow Cytometry"
Clinical Immunology: Principles and Practice, Third Edition 2008 Elsevier Publishing.
Rich RR, Fleisher TA, Shearer WT et al editors pp1435-1446.
This chapter in the Third Edition (2008) of the Rich Clinical Immunology textbook describes the instrumentation, technology and interpretation techniques for flow cytometry. A discussion of typical applications and limitations of the technology including cell surface and intracellular detection is included as well.

b. Cellular functional responses

i. Chemotaxis and adhesion

REVIEW CHAPTER:
Kuhns DB.
Assessment of neutrophil function: neutrophil adherence and neutrophil chemotaxis.
In Rich R et al. Clinical Immunology: Principles and Practice Mosby, New York, Third Edition, 2008; 1463-1465.

REVIEW:
Garrood T , Lee L, Pitzalis T.
Molecular mechanisms of cell recruitment to inflammatory sites: general and tissuespecific pathway.
Rheumatology 2006 Mar;45(3):250-60.
The observation that circulating leucocytes adhere to and migrate across the vascular endothelium was first made 70 yr ago; this was noted to occur without breach of the endothelial barrier, suggesting the presence of complex regulatory mechanisms. More recently, in a series of classic experiments, Gowans and Knight observed that lymphocytes isolated from the rat thoracic duct homed rapidly back to lymph nodes and secondary lymphoid organs upon reinjection: furthermore, it was noted that this occurred across the distinctly shaped endothelial cells of the postcapillary venules. Since then we have learnt much about the molecular basis of leucocyte extravasation and the regulatory mechanisms involved. In this review we will describe molecular interactions involved in the stages of leucocyte recruitment and extravasation into the tissues. We will also describe the specific molecular interactions that allow the selective recruitment of tissue-specific leucocytes to inflammatory sites. Finally, we will emphasize the central role that adhesion molecules have in the development of the inflammatory response by drawing from examples of human disease, and describe recent progress in the therapeutic targeting of these molecules with particular reference to inflammatory arthritis.

REVIEW:
Stein JV, Nombela-Arrieta C.
Chemokine control of lymphocyte trafficking: a general overview.
Immunology 2005 Sep;116:1-12.
Chemokines are a large family of small, generally secreted polypeptides which guide lymphocyte movement throughout the body by controlling integrin avidity and inducing migration. Here, we look at recent, exciting findings on chemokine function throughout lymphocyte development and co-ordinated T and B cell migration during immune responses. Finally, we will review data on the regional control of immunity by tissue-specific chemokine receptors on effector/memory lymphocytes.

ii. mitogen or antigen induced proliferation and activation

REVIEW CHAPTER:
Laboratory techniques commonly used in immunology:
Methods for Studying T lymphocyte responses, Methods for studying B lymphocyte responses.
In Abbas et al. Cellular and Molecular Immunology, Saunders, Sixth Edition, 2007; 535-537.

iii. phagocytosis and intracellular killing

REVIEW CHAPTER:
Kuhns DB.
Assessment of neutrophil function.
In Rich R et al. Clinical Immunology: Principles and Practice Mosby, New York, Third Edition, 2008; 1447-1460.

REVIEW CHAPTER:
Lowell C.
Clinical Laboratory Methods for the Detection of Cellular Immunity.
In Medical Immunology. Parslow et al (eds.) 10th Edition. McGraw-Hill, New York, 2001; 245-247.

iv. cellular cytotoxicity

REVIEW CHAPTER:
O'Gorman, MRG.
Clinical Evaluation of Myeloid and Monocytic Cell functions.
In Manual of Molecular and Clinical Laboratory Immunology. Detrick et al (eds). 7th Edition, ASM press, Washington,DC, 2006, 272-280.

REVIEW CHAPTER TOPIC:
Bleesing JJ and Risma KA.
Assessment of cytolytic function.
In Rich R et al. Clinical Immunology: Principles and Practice, Mosby, New York, Third Edition, 2008; 1451-1453.

c. measurement of immune complexes, cryoprecipitable proteins, total serum complement activity, complement components and C1 Inhibitor assays.

REVIEW CHAPTER:
Laboratory techniques commonly used in immunology: Measurement of antigen-antibody interactions.
In Abbas et al. Cellular and Molecular Immunology, Saunders, Sixth Edition, 2007; 531-532.

REVIEW ARTICLE:
Kallemuchikkal U, Gorevic PD.
Evaluation of cryoglobulins.
Arch Pathol Lab Med. 1999;123:119-25
Cryoglobulins are immunoglobulins that precipitate as serum is cooled below core body temperatures. A cryoglobulin screen is the observation of a serum specimen collected and separated while warm for cryoprecipitation over a period of up to 7 days. Values of the screening may be reported as a cryocrit, which is the volume percent of the precipitate compared with the total volume of serum. Further proof that the precipitate is indeed a cryoglobulin can be obtained by demonstrating resolubilization with warming and immunochemical analysis by immunofixation. Detailed characterization of cryoglobulins may also require rigorous washing of the precipitate, quantitation of total protein and immunoglobulins, and evaluation of serum for monoclonal gammopathy, rheumatoid factor activity, evidence of complement activation, and presence of hepatitis C virus seroreactivity or hepatitis C virus RNA. The single most important variable confounding standardization of cryoglobulin testing is the frequently improper separation of warm serum from other blood elements prior to screening and characterization.

REVIEW ARTICLE:
Wen L, Atkinson JP, Giclas PC. Clinical and laboratory evaluation of complement deficiency. JACI 2004; 113: 585-593.

REVIEW CHAPTER:
Giclas, PC.
Hereditary and Acquired Complement Deficiencies.
In Manual of Molecular and Clinical Laboratory Immunology. Detrick et al (eds). 7th Edition, ASM press, Washington,DC, 2006, 914-922.

d. histocompatibility typing

REVIEW:
Susskind B.
The HLA System.
In: Rudmann SV. Textbook of Blood Banking and Transfusion Medicine. 2nd Ed. Elsevier, 2005.

REVIEW:
Gerlach JA.
Human lymphocyte antigen molecular typing.
Arch Pathol Lab Med. 2002; 126: 281-4 .
The human lymphocyte antigen (HLA) typing community was one of the early groups to adoptmolecular testing. This action was borne out of the need to identify the many alleles of the highly polymorphic HLA system. Early paradigms used restriction fragment length polymorphism regimes, but the polymerase chain reaction method of amplification quickly replaced that lessthandiscriminating choice. Methods currently in use for HLA typing, with commercial kits available, are sequence-specific oligonucleotide probe (both dot blot and the reverse blot dot), sequence-specific primer amplification, restriction fragment length polymorphism of amplified products, double-stranded sequence conformation polymorphism (with and without reference strand), sequence-based typing, and microarray technologies. More than 1250 alleles are recognized by the World Health Organization and meet their criteria for assignment. These alleles can be identified by molecular methods and represent alleles present at class I and class II loci of the HLA complex. On occasion, ambiguous results still persist, even with the best molecular typing methods. Therefore, it is clear to the HLA typing community that a combination of the above methods may be needed to allow true discrimination of the possible alleles an individual carries in their genetic makeup. It is also clear that a typing laboratory may need to resort to nonmolecular serology to understand the significance and impact of the type generated by the HLA molecular typing laboratory.

e. genetic techniques including TRECs, PCR and use of probes.

NOTE:
Genetic techniques are powerful tools that allow the identification of stages of cellular development, gene expression, cell function, and signaling pathways. Protocols for many of these assays can be found in textbooks as well as in the Current Protocol series including Current Protocols in Immunology and Current Protocols in Molecular Biology. These are available electronically in many academic libraries. The polymerase chain reaction (PCR) is an especially powerful tool that allows the amplification of small amounts of DNA, both qualitatively and quantitatively, as well as small amounts of RNA after reverse transcription into DNA. The

following are two review articles that discuss the use of real-time PCR for quantitative measurement of DNA/RNA:

REVIEW QUANTITATIVE PCR:
Belmont J.
Molecular methods.
In Rich, et al. Clinical Immunology Principles and Practice. 3rd Ed. Elsevier, 2008.
VanGuilder HD, Vrana KE, Freeman WM.
Twenty-five years of quantitative PCR for gene expression analysis.
Biotechniques 44(5):619-626, 2008.

Ginzinger, DG.
Gene quantification using real-time quantitative PCR: an emerging technology hits the Mainstream Exp. Hematol. 30: 503-512 (2002)
The recent flood of reports using real-time Q-PCR testifies to the transformation of this technology from an experimental tool into the scientific mainstream. Many of the applications of real-time QPCR include measuring mRNA expression levels, DNA copy number, transgene copy number and expression analysis, allelic discrimination, and measuring viral titers. The range of applications of real-time Q-PCR is immense and has been fueled in part by the proliferation of lower-cost instrumentation and reagents. Successful application of real-time Q-PCR is not trivial. However, this review will help guide the reader through the variables that can limit the usefulness of this technology. Careful consideration of the assay design, template preparation, and analytical methods are essential for accurate gene quantification.

REVIEW:
Giulietti, A, Overbergh, L, Valckx, D, Decallonne, B, Bouillon, R, Mathieu, C.
An overview of real-time quantitative PCR: applications to quantify cytokine gene expression. Methods 25: 386–401 (2001).
The analysis of cytokine profiles helps to clarify functional properties of immune cells, both for research and for clinical diagnosis. The real-time reverse transcription polymerase chain reaction (RT-PCR) is becoming widely used to quantify cytokines from cells, body fluids, tissues, or tissue biopsies. Being a very powerful and sensitive method it can be used to quantify mRNA expression levels of cytokines, which are often very low in the tissues under investigation. The method allows for the direct detection of PCR product during the exponential phase of the reaction, combining amplification and detection in one single step. In this review we discuss the principle of real-time RT-PCR, the different methodologies and chemistries available, the assets, and some of the pitfalls. With the TaqMan chemistry and the 7700 Sequence Detection System (Applied Biosystems), validation for a large panel of murine and human cytokines and other factors playing a role in the immune system is discussed in detail. In summary, the real-time RT-PCR technique is very accurate and sensitive, allows a high throughput, and can be performed on very small samples; therefore it is the method of choice for quantification of cytokine profiles in immune cells or inflamed tissues.

NOTE:
An example of the use of quantitative PCR is the measurement of T cell receptor excision circles

(TREC) as a marker of T cells that have recently emigrated from the thymus. T cells are longlived and therefore, it is difficult to distinguish between recent emigrants from the thymus and long-lived naïve T cells. During differentiation in the thymus, immature T cells randomly rearrange the variable regions of the T cell receptor chains. During this process, the intervening DNA between two approximated gene segments is excised as a circle and remains in the cell for a long time but does not replicate with cell division. Quantitative measurement of these circles using PCR can identify recent emigrants from the thymus. This was nicely demonstrated in HIV patients, who lost their peripheral CD4 T cells but were generating new T cells in their thymus that survived in the periphery after HIV therapy. Several factors affect the expression of TRECs in T cells that are discussed in the paper below:

REVIEW TREC:
Hazenberg MD, Verschuren MCM, Hamann D, et al
T cell receptor excision circles as markers for recent thymic emigrants: basic aspects, technical approach, and guidelines for interpretation. J Mol Med 79:631–640 (2001).
T cell differentiation in the thymus is characterized by a hierarchical order of rearrangement steps in the T cell receptor (TCR) genes, resulting in the joining of V, D, and J gene segments. During each of the rearrangement steps, DNA fragments between rearranging V, D, and J gene segments are deleted as circular excision products, the so-called TRECs (T cell receptor excision circles). TRECs are assumed to have a high over-time stability, but they can not multiply and consequently are diluted during T cell proliferation. It was recently suggested that quantitative detection of TRECs would allow for direct measurement of thymic output. The deltaRec-psiJalpha TREC appears to be the best marker, because the majority of thymocyte expansion occurs before this TREC is formed. However, apart from thymic output several other factors determine the TREC content of a T cell population, such as cell division and cell death. Likewise, the number of TRECs depends not only on thymic output, but also on the longevity of naive T cells. This warrants caution with regard to the interpretation of TREC data as measured in healthy and diseased individuals. deltaRec-psiJalpha TREC detection is a new and elegant tool for identification of recent thymic emigrants in the periphery, but further research is required for making quantitative estimations of thymic output with the use of TREC analysis.

LANDMARK ARTICLE TREC:
Livak, F. & Schatz, D.
T-cell receptor α locus V(D)J recombination by-products are abundant in thymocytes and mature T cells. Mol. Cell. Biol: 1996;16:609-618.
In addition to the assembled coding regions of immunoglobulin and T-cell receptor (TCR) genes, the V(D)J recombination reaction can in principle generate three types of by-products in normal developing lymphocytes: broken DNA molecules that terminate in a recombination signal sequence or a coding region (termed signal or coding end molecules, respectively) and DNA molecules containing fused recombination signal sequences (termed reciprocal products). Using a quantitative Southern blot analysis of the murine TCR alpha locus, we demonstrate that substantial amounts of signal end molecules and reciprocal products, but not coding end molecules, exist in thymocytes, while peripheral T cells contain substantial amounts of reciprocal products. At the 5' end of the J alpha locus, 20% of thymus DNA exists as signal end molecules. An additional 30 to 40% of the TCR alpha/delta locus exists as remarkably stable reciprocal products throughout Tcell development, with the consequence that the TCR C delta region is substantially retained in alpha

beta committed T cells. The disappearance of the broken DNA molecules occurs in the same developmental transition as termination of expression of the recombination activating genes, RAG-1 and RAG-2. These findings raise important questions concerning the mechanism of V(D)J recombination and the maintenance of genome integrity during lymphoid development.

LANDMARK ARTICLE – TREC:
Douek DC, McFarland RD, Keiser PH, et al.
Changes in thymic function with age and during the treatment of HIV infection.
Nature 1998;396:690–695.
The thymus represents the major site of the production and generation of T cells expressing alphabeta-type T-cell antigen receptors. Age-related involution may affect the ability of the thymus to reconstitute T cells expressing CD4 cell-surface antigens that are lost during HIV infection; this effect has been seen after chemotherapy and bone-marrow transplantation. Adult HIV-infected patients treated with highly active antiretroviral therapy (HAART) show a progressive increase in their number of naive CD4-positive T cells. These cells could arise through expansion of existing naive T cells in the periphery or through thymic production of new naive T cells. Here we quantify thymic output by measuring the excisional DNA products of TCR-gene rearrangement. We find that, although thymic function declines with age, substantial output is maintained into late adulthood. HIV infection leads to a decrease in thymic function that can be measured in the peripheral blood and lymphoid tissues. In adults treated with HAART, there is a rapid and sustained increase in thymic output in most subjects. These results indicate that the adult thymus can contribute to immune reconstitution following HAART.

MICROARRAY REVIEW:
Methods Mol Biol 404:409-430, 2007
Microarrays and related technologies have allowed investigators to ask biological questions in far greater detail than has previously been possible. Microarrays had a troubled beginning, but most of these problems resulted from the growing pains of this technology, which, like many new things, was initially more promise than delivery. Nevertheless, over the past few years, investigators have learned how to achieve optimal performance of technology, and now exciting discoveries are made using microarray-based research. Many of the advances have come from the realization that microarrays are not a magic tool but rather are like any other measurement device. Unless microarray experimentation is coupled with good experimental practices, it will not yield valid results or, worse yet, may lead to misleading results. In this chapter, we highlight some of the important steps that should be taken to successfully conduct a microarray study. These steps include a clearly stated biological question, experimental design, careful experimental conduct, complete statistical analysis, validation/verification of results, and dissemination of the data.

f. hybridoma and monoclonal antibody technology

NOTE:
Antibodies are important for immunity by their ability to recognize pathogens, neutralize their toxins, opsonize their uptake by phagocytic cells or kill them directly in conjunction with complement proteins. Antibodies are also used for laboratory investigation to specifically identify proteins in a multitude of situations and using a variety of techniques. The ability to generate a monoclonal antibody with a single specificity from a single B cell has revolutionized the use of antibodies in clinical and laboratory studies. B cells are fused with a myeloma cell to generate a

hybridoma that produces the same antibody as the B cell used in the fusion. The hybridoma is long-lived and provides a virtually unlimited amount of antibody as described below:

REVIEW Hybridoma technology:
Lonberg N
Human antibodies from transgenic mice.
Nat Biotech 2005;23:1117-1125.
Laboratory mice provide a ready source of diverse, high-affinity and high-specificity monoclonal antibodies (mAbs). However, development of rodent antibodies as therapeutic agents has been impaired by the inherent immunogenicity of these molecules.One technology that has been explored to generate low immunogenicity mAbs for *in vivo* therapy involves the use of transgenic mice expressing repertoires of human antibody gene sequences. This technology has now been exploited by over a dozen different pharmaceutical and biotechnology companies toward developing new therapeutic mAbs, and currently at least 33 different drugs in clinical testing—including several in pivotal trials—contain variable regions encoded by human sequences from transgenic mice. The emerging data from these trials provide an early glimpse of the safety and efficacy issues for these molecules. Nevertheless, actual product approval, the biggest challenge so far, is required to fully validate this technology as a drug discovery tool. In the future, it may be possible to extend this technology beyond rodents and use transgenic farm animals to directly generate and produce human sequence polyclonal sera.

Nelson PN, Reynolds GM, Waldron EE, et al.
Monoclonal antibodies.
Mol Pathol 2000;53:111–117.
Monoclonal antibodies are essential tools for many molecular immunology investigations. In particular, when used in combination with techniques such as epitope mapping and molecular modelling, monoclonal antibodies enable the antigenic profiling and visualisation of macromolecular surfaces. In addition, monoclonal antibodies have become key components in a vast array of clinical laboratory diagnostic tests. Their wide application in detecting and identifying serum analytes, cell markers, and pathogenic agents has largely arisen through the exquisite specificity of these unique reagents. Furthermore, the continuous culture of hybridoma cells that produce these antibodies offers the potential of an unlimited supply of reagent. In essence, when compared with the rather limited supply of polyclonal antibody reagents, the feature of a continuous supply enables the standardisation of both the reagent and the assay technique. Clearly, polyclonal and monoclonal antibodies have their advantages and disadvantages in terms of generation, cost, and overall applications. Ultimately, monoclonal antibodies are only produced when necessary because their production is time consuming and frustrating, although greatly rewarding (at least most of the time!). This is especially apparent when a monoclonal antibody can be applied successfully in a routine pathology laboratory or can aid in the clinical diagnosis and treatment of patients. In this article, the generation and application of monoclonal antibodies are demystified to enable greater understanding and hopefully formulate novel ideas for clinicians and scientists alike.

LANDMARK Hybridoma technology:
Köhler G, Milstein C.
Continuous cultures of fused cells secreting antibody of predefined specificity.

Nature 1975;256:495-497.

g. cytokine and mediator measurement

NOTE:

There are a number of cytokines and other mediators that may be released after a particular stimulus. A variety of methods are available to measure these cytokines and mediators individually such as ELISA-based methods, most of which are available in kit form. Quantitative RT-PCR allows for the measurement of numerous cytokines, chemokines, and other mediators, whose genes are actively transcribed after a stimulus. With quantitative RT-PCR it is possible to measure cytokines and other mediators from small samples of cells/tissues and to measure several cytokines/mediators at the same time. Below is an articles that describes the use of real-time RTPCR for the quantitation of cytokines and other mediators:

REVIEW:

Blaschke V, Reich K, Blaschke S, et al.

Rapid quantitation of proinflammatory and chemoattractant cytokine expression in small tissue samples and monocyte-derived dendritic cells: validation of a new real-time RT-PCR technology. J Immunol Methods 2000;246:79-90.

The analysis of cytokine profiles plays a central part in the characterization of disease-related inflammatory pathways and the identification of functional properties of immune cell subpopulations. Because tissue biopsy samples are too small to allow the detection of cytokine protein, the detection of mRNA by RT-PCR analysis is often used to investigate the cytokine milieu in inflammatory lesions. RT-PCR itself is a qualitative method, indicating the presence or absence of specific transcripts. With the use of internal or external standards it may also serve as a quantitative method. The most widely accepted method is quantitative competitive RT-PCR, based on internal shortened standards. Recently, online real-time PCR has been introduced (LightCycler), which allows quantitation in less than 30 min. Here, we have tested its use for the analysis of cytokine gene expression in different experimental in vitro and ex vivo settings. First, we compared quantitative competitive RT-PCR with real-time RT-PCR in the quantitation of transcription levels of the CD4(+) cell-specific chemoattractant Interleukin-16 during the maturation of monocyte-derived dendritic cells, and found a good correlation between both methods. Second, differences in the amounts of IL-16 mRNA in synovial tissue from patients with rheumatoid arthritis and osteoarthritis as assessed by real-time RT-PCR paralleled differences in the level of IL-16 protein in the synovial fluid. Finally, we employed real-time RT-PCR to study the cutaneous expression of several cytokines during experimental immunomodulatory therapy of psoriasis by Interleukin-10, and demonstrate that the technique is suitable for pharmacogenomic monitoring. In summary, real-time RT-PCR is a sensitive and rapid tool for quantifying mRNA expression even with small quantities of tissue. The results obtained do not differ from those generated by quantitative competitive RT-PCR.

2. Test-performance characteristics: Principles of sensitivity, specificity, predictive value and ROC analysis

WEB BASED STATISTICS:

Stephen Simon, PhD

A sixteen page booklet on basic statistics for health professionals. He has also developed two web sites that cover common topics taught in his statistics class. You can find a PDF of the booklet on

the web at http://www.childrensmercy.org/stats/Diagnostic.pdf, and new material at www.pmean.com

BOOK:
Stephen D. Simon
Statistical Evidence in Medical Trials: What Do the Data Really Tell Us?
Oxford University Press, 2006
Statistical Evidence in Medical Trials is a lucid, well-written and entertaining text that addresses common pitfalls in evaluating medical research. Including extensive use of publications from the medical literature and a non-technical account of how to appraise the quality of evidence presented in these publications, this book is ideal for health care professionals, students in medical or nursing schools, researchers and students in statistics, and anyone needing to assess the evidence published in medical journals.

REVIEW USE OF ROC ANALYSIS:
Anthony K Akobeng
Understanding diagnostic tests 3: receiver operating characteristic curves
Acta Paediatr 2007 May; 96(5):644-7. Epub 2007 Mar 21.
The results of many clinical tests are quantitative and are provided on a continuous scale. To help decide the presence or absence of disease, a cut-off point for 'normal' or 'abnormal' is chosen. The sensitivity and specificity of a test vary according to the level that is chosen as the cut-off point. The receiver operating characteristic (ROC) curve, a graphical technique for describing and comparing the accuracy of diagnostic tests, is obtained by plotting the sensitivity of a test on the *y* axis against 1-specificity on the *x* axis. Two methods commonly used to establish the optimal cut-off point include the point on the ROC curve closest to (0, 1) and the Youden index. The area under the ROC curve provides a measure of the overall performance of a diagnostic test. In this paper, the author explains how the ROC curve can be used to select optimal cut-off points for a test result, to assess the diagnostic accuracy of a test, and to compare the usefulness of tests. The ROC curve is obtained by calculating the sensitivity and specificity of a test at every possible cut-off point, and plotting sensitivity against 1-specificity. The curve may be used to select optimal cut-off values for a test result, to assess the diagnostic accuracy of a test, and to compare the usefulness of different tests.

3. Unproven and inappropriate diagnostic tests for allergic and immune deficiency diseases

REVIEW:
B. Niggemann, C. Grüber
Unproven diagnostic procedures in IgE-mediated allergic diseases
Allergy. 2004 Aug; 59(8):806-8.
A considerable body of literature on therapeutic aspects of complementary and alternative medicine has been published in recent years, but little is known on diagnostic procedures. This short review lists complementary and alternative diagnostic procedures for the diagnosis of allergic diseases and presents an assessment of their usefulness for the daily practice. The review of the literature revealed that neither the determination of specific immunoglobulin G-antibodies in serum, the hair-analysis, the cytotoxic test, kinesiology, iridology, or electrodermal testing represent useful tests for the daily practice. To date, no complementary or alternative diagnostic

procedure can be recommended as a meaningful element in the diagnostic work-up of allergic diseases. This is especially true for food allergy: properly performed oral food challenges still represent the gold standard for implementing specific diets in food allergic individuals. Ineffective diagnostic approaches may be costly for the consumer and delay appropriate therapy

REVIEW CHAPTER:
Abba I. Terr
Unconventional Theories and Unproved Methods in Allergy
in Middleton's Allergy: Principles and Practice, 7th ed., Copyright c 2008 Mosby, Inc.
There are numerous unproven theories of allergic disease that include allergic toxemia, multiple chemical sensitivity and candida hypersensitivity syndrome. These theories have in common a broad range of symptoms, presumed sensitivity of the offending agent, a delay in onset of symptoms after exposure, and lack of evidence for the pathogenesis of these diseases. Testing for these diagnoses includes unproven procedures such as specific IgG antibodies to food or environmental allergens, food immune complexes, chemical analysis of body fluids and tissues, pulse test, cytotoxic tests, end-point titration, provocation-neutralization, electrodermal testing and applied kinesiology. Proponents of these theories will make patients go through extreme measures to eliminate contact with an extensive list of environmental chemicals or to avoid multiple foods especially without appropriate testing or evaluation.

II. Anatomy and Physiology

A. Normal anatomy and physiology

1. Upper airway -nose, sinuses, middle ear

REVIEW:
Zeifer, B
Pediatric sinonasal imaging – normal anatomy and inflammatory disease
Neuroimaging Clinics of North America. 10(1):137-59, ix, 2000
Pediatric sinonasal anatomy changes and develops from birth to adolescence. This article elucidates the normal anatomy and patterns of development in the pediatric population. Issues in pediaric sinusitis include indications for imaging, the nonspecificity of sinus opacification, and the importance of clinical information. Sinonasal physiology is briefly discussed to offer insight into the interpretation of radiographic findings. Cystic fibrosis, polyps, and choanal atresia, representing the spectrum of common pediatric sinonasal inflammatory disorders are illustrated, and the spectrum of orbital and intracranial complications of sinusitis is reviewed.

REVIEW:
Neri E, Caramella D, Panconi M, Berrettini S, Sellari Franceschini S, Forli F, Bartolozzi C
Virtual endoscopy of the middle ear
European Radiology. 11(1):41-9, 2001
Virtual endoscopy is a computer-generated simulation of fiberoptic endoscopy, and its application to the study of the middle ear has been recently proposed. The need to represent the middle ear anatomy by means of virtual endoscopy arose from the increased interest of otolarygologists in transtympanic endoscopy. In fact, this imaging method allows the visualization of middle ear

anatomy with high detail, but it is evasive and is essentially used for surgical guidance. Virtual endoscopy provides similar perspectives of the tympanic cavity but does not require the tympanic perforation. In the study of the middle ear, specific attention is given to the retroperitoneum. This region contains elevations of the medial wall (pyramidal eminence and ridge, styloid eminence and ridge, subiculum, ponticulus) and depressions (sinus tympani, posterior sinus tympani, facial sinus, fossula of Grivot, oval window fossula), which can be effectively displayed by virtual endoscopy. Virtual endoscopy is foreseen as a useful tool in preoperative management of patients who are candidates for middle ear surgery, since it can predict with high detail the patient's specific anatomy by imaging perspectives familiar to otosurgeons.

REVIEW:
Rao, V M and el-Noueam, K I
Sinonasal imaging. Anatomy and pathology.
Radiologic Clinics of North America. 36(5):921-39, vi, 1998
This article provides a clear understanding of the pathophysiology of sinonasal inflammatory diseases and the rationale behind endoscopic surgery. Normal anatomy and pertinent anatomic variants that should be included in the radiology report are described. The relative role of CT and MR imaging in evaluation of inflammatory and neoplastic lesions is emphasized.

2. Lower airway

LANDMARK ARTICLE:
Magnussen JS. Chicco P. Palmer AW. Van der Wall H. Vu DH.
Creation of a three-dimensional model of human segmental lung anatomy
AJR. American Journal of Roentgenology. 174(5):1333-6, 2000
OBJECTIVE: The investigation of pulmonary embolism using scintigraphic tomography requires a model of the internal architecture of the segments and subsegments in the human lung. Such a model has been developed by the segmentation and subsegmentation of an existing whole-body tissue-segmented phantom. MATERIALS AND METHODS: By using information from suitably windowed human axial CT scans, combined with the information gained from the injection of color-coded dyes into the segmental bronchi of human cadaveric lungs, the lobar and segmental boundaries were added to the existing phantom. Further refinements were added from reports in the literature regarding the predominant pattern of subsegmental bronchi in a series of human cadavers, enabling the creation of subsegmental boundaries. RESULTS: A digitized model of the segmental and subsegmental anatomy of the human lung was successfully created. External, or pleural, projections of the complex internal arrangement of the segments closely corresponded with the projections of the best available authorities on the subject. CONCLUSION: The model provides the opportunity to address several issues germane to scintigraphy and important for diagnosing pulmonary embolic disease. In particular, the model allows the manipulation of three-dimensional data sets to explore issues of importance to tomographic lung scanning.

CUTTING EDGE:
Kitaoka H, Nieman GF, Fujino Y, Carney D, DiRocco J, Kawase I
A 4-dimensional model of the alveolar structure
Journal of Physiological Sciences: JPS. 57(3):175-85, 2007
The alveolar structure, a space-filling branching duct system with alveolar openings, is one of the most complicated structures in the living body. Although its deformation during ventilation is the

basic knowledge for lung physiology, there has been no consensus on it because of technical difficulties of dynamic 3-dimensional observation in vivo. It is known that the alveolar duct wall (primary septa) in the fetal lung is deformed so as to obtain the largest inner space and the widest surface area, and that the secondary septa grow just before birth and their free ridges form the alveolar entrance rings (mouths) containing abundant elastin fibers. We have constructed a 4-dimensional alveolar model according to this morphogenetic process, where the alveolar deformation is modeled by a combination of springs and hinges, corresponding to elastin fibers at alveolar mouths and junctions of alveolar septa, respectively. The model includes a hypothesis that alveolar mouths are closed at minimum volume and that closed alveoli are stabilized by the alveolar lining liquid film containing a surfactant. Morphometric characteristics of the model were consistent with previous reports. Furthermore, the model explained how the alveolar number and size could change during ventilation. Using in vivo microscopy, we validated our model by an analysis of the dynamic inflation and deflation of subpleural alveoli. Our model, including the alveolar mouth-closure hypothesis, can explain the origin of phase IV in a single breath nitrogen washout curve (closing volume) and mechanism of alveolar recruitment/derecruitment.

REVIEW:
Fahy, R J. Wewers, M D.
Pulmonary defense and the human cathelicidin hCAP-18/LL-37
Immunologic Research. 31(2):75-89, 2005
Antimicrobial peptides form an important component of the innate immune system. The cathelicidin family, a key member of the antimicrobial peptide defenses, has been highly conserved throughout evolution. Though widespread in mammals, there is currently only one identified human example, hCAP-18/LL-37. The cathelicidins have been found to have multiple functions, in addition to their known antimicrobial and lipopolysaccharide-neutralizing effects. As a result, they profoundly affect both innate and adaptive immunity. Currently, antimicrobial peptides are being evaluated as therapeutic drugs in disease states as diverse as oral mucositis, cystic fibrosis, and septic shock. One such peptide, the cathelicidin hCAP-18/LL-37, is reviewed in detail in the context of its role in lung physiology and defense.

3. Skin

REVIEW:
Wysocki, A B.
Skin anatomy, physiology, and pathophysiology
Nursing Clinics of North America. 34(4):777-97, 1999
Human skin is the largest multifunctional organ of the body, and knowledge of its structure and function is essential to clinicians and researchers. The skin has two layers, the epidermis and dermis, separated by a basement membrane zone. It provides protection, sensation, thermoregulation, biochemical/metabolic, and immune functions. Key and emerging concepts important to understanding pathophysiological mechanisms for practicing clinicians are: knowledge of differences between acute and chronic wounds; ability to evaluate depth and extent of injury; understanding stages of healing versus zones of activity; and knowledge of ischemic-reperfusion injury, the skin immune system, cytokines, growth factors and other biomolecules, and matrix synthesis and degradation. These concepts are addressed in this article.

CUTTING EDGE:

Xue M, Campbell D, Jackson CJ
Protein C is an autocrine growth factor for human skin keratinocytes.
Journal of Biological Chemistry. 282(18):13610-6, 2007
The protein C (PC) pathway plays an important role in coagulation and inflammation. Many components of the PC pathway have been identified in epidermal keratinocytes, including endothelial protein C receptor (EPCR), which is the specific receptor for PC/activated PC (APC), but the core member of this pathway, PC, and its function in keratinocytes has not been defined. In this study, we reveal that PC is strongly expressed by human keratinocytes at both gene and protein levels. When endogenous PC was blocked by siRNA the proliferation of keratinocytes was significantly decreased. This inhibitory effect was restored by the addition of recombinant APC. PC siRNA treatment also increased cell apoptosis by 3-fold and inhibited cell migration by more than 20%. When keratinocytes were pretreated with RCR252, an EPCR-blocking antibody, or PD153035, an epidermal growth factor receptor (EGFR) inhibitor, cell proliferation was hindered by more than 30%. These inhibitors also completely abolished recombinant APC (10 mug/ml)-stimulated proliferation. Blocking PC expression or inhibiting its binding to EPCR/EGFR decreased the phosphorylation of ERK1/2 but increased p38 activation. Furthermore, inhibition of ERK decreased cell proliferation by approximately 30% and completely abolished the stimulatory effect of APC on proliferation. Taken together, these results indicate that keratinocyte-derived PC promotes cell survival, growth, and migration in an autocrine manner via EPCR, EGFR, and activation of ERK1/2. Our results highlight a novel role for the PC pathway in normal skin physiology and wound healing.

4. Gastrointestinal Tract

REVIEW:
Kararli, T
Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals.
Biopharmaceutics & Drug Disposition. 16(5):351-80, 1995 Jul
In addition to metabolic differences, the anatomical, physiological, and biochemical differences in the gastrointestinal (G.I.) tract of the human and common laboratory animals can cause significant variation in drug absorption from the oral route. Among the physiological factors, pH, bile, pancreatic juice, and mucus and fluid volume and content can modify dissolution rates, solubility, transit times, and membrane transport of drug molecules. The microbial content of the G.I. tract can significantly affect the reductive metabolism and enterohepatic circulation of drugs and colonic delivery of formulations. The transit time of dosage forms can be significantly different between species due to different dimensions and propulsive activities of the G.I. tract. The lipid/protein composition of the enterocyte membrane along the G.I. tract can alter binding and passive, active, and carrier-mediated transport of drugs. The location and number of Peyer's patches can also be important in the absorption of large molecules and particulate matter. While small animals, rats, mice, guinea pigs, and rabbits, are most suitable for determining the mechanism of drug absorption and bioavailability values from powder or solution formulations, larger animals, dogs, pigs, and monkeys, are used to assess absorption from formulations. The understanding of physiological, anatomical, and biochemical differences between the G.I. tracts of different animal species can lead to the selection of the correct animal model to mimic the bioavailability of compounds in the human. This article reviews the anatomical, physiological, and biochemical differences between the G.I. tracts of humans and commonly used laboratory animals.

REVIEW:
Wershil BK. Furuta GT
Gastrointestinal mucosal immunity
Journal of Allergy & Clinical Immunology. 121(2 Suppl):S380-3
Mucosal surfaces constitute a large host-environmental interface that must be protected from pathogenic organisms. The mucosal immune system has evolved as a distinct immune organ functioning independently from its systemic counterpart. The mucosal immune system has the difficult task of mounting protective responses to invading microorganisms while maintaining a state of nonresponsiveness to commensal bacteria and food antigens. The system has unique cellular components and functional aspects that permit it to carry out this dual role.

5. Lymphoid Tissue

REVIEW:
Muthuchamy M. Zawieja D
Molecular regulation of lymphatic contractility.
Annals of the New York Academy of Sciences. 1131:89-99, 2008
The lymphatic system plays critical roles in body fluid and macromolecular homeostasis, lipid absorption, immune function, and metastasis. To accomplish these tasks, the lymphatics must move lymph and its contents from the interstitial space through the lymph vessels and nodes and into the great veins. Contrary to popular belief, lymph does not passively "drain" down this pathway, because the net pressure gradients oppose flow. Instead, the lymphatics must act as both the conduits that direct and regulate lymph flow and the pumps that generate the lymph flow. Thus, to regulate lymph transport and function, both lymphatic pumping and flow resistance must be controlled. Both of these processes occur via regulation of lymphatic muscle contractions, which are classically thought to occur via the interaction of cell calcium with regulatory and contractile proteins. However, our knowledge of this regulation of lymphatic contractile function is far from complete. In this chapter we review our understanding of the important molecular mechanisms, the calcium regulation, and the contractile/regulatory proteins that control lymphatic contractions. A better understanding of these mechanisms could provide the basis for the development of better diagnostic and treatment modalities for lymphatic dysfunction. While progress has been made in our understanding of the molecular biology of lymphangiogenesis as a result of the development of potential lymphangiogenic therapeutic targets, there are currently no therapeutic agents that specifically modulate lymphatic pump function and lymph flow via lymphatic muscle. However, their development will not be possible until the molecular basis of lymphatic contractility is more fully understood.

REVIEW:
Cesta MF
Normal structure, function, and histology of mucosa-associated lymphoid tissue
Toxicologic Pathology. 34(5):599-608, 2006
The mucosa-associated lymphoid tissue (MALT) initiates immune responses to specific antigens encountered along all mucosal surfaces. MALT inductive sites are secondary immune tissues where antigen sampling occurs and immune responses are initiated. Effector sites, present as diffuse lymphoid tissue along all mucosal surfaces are the sites of IgA transport across the mucosal epithelium. Though there are many differences between inductive sites in various organs, they all

contain the same basic compartments-follicles, interfollicular regions, subepithelial dome regions, and follicle-associated epithelium. The morphologic differences between MALT and other secondary lymphoid tissues, between the MALT sites of differing anatomic locations, and species differences among laboratory animals are described. The morphologic changes in MALT associated with aging, route of nutrition, and genetic mutation (i.e., the nude and SCID mutations) are also discussed. MALT tissues comprise the mucosal immune system which can function independently of the systemic immune system and are, therefore, an important and often overlooked aspect of immunopathology.

B. Pathology of primary atopic disorders

1. Asthma (including airway remodeling)

a. Children

REVIEW:
Apter AJ, Szefler SJ
Advances in adult and pediatric asthma
J Allergy Clin Immunol 2004;113:407-414
This review summarizes the highlights in the study of adult and pediatric asthma from October 2002 through October 2003. It is easiest to categorize this year's advances into physiologic, epidemiologic, therapeutic, and primarily pediatric developments. In physiology the identification of the ADAM33 gene as an asthma susceptibility gene has led to a new hypothesis concerning the pathogenesis of asthma. Understanding the integration of the upper and lower airways is likely to have important implications for patient management. Epidemiologic studies continue to show that asthma is a significant and costly disease, with medications comprising the most significant direct costs. Early intervention and improved management can significantly reduce the burden of illness. Research presented indicates there is an opportunity for allergist-immunologists to improve diagnostic and therapeutic approaches to asthma management. Our community has a strong commitment to health care quality, education, and delivery. The Journal will reflect this commitment with a new section devoted to these issues.

REVIEW:
Spahn JD, Szefler SJ
Childhood asthma: New insights into management
J Allergy Clin Immunol 2002;109:3-13
Recently, a concerted effort has been made to reverse the trend of increasing asthma mortality and morbidity. One additional strategy might be to recognize patients at risk for persistent asthma and to intervene early. This review summarizes new information on asthma pathogenesis that has helped shape a new direction in managing childhood asthma. At the core is the recognition that asthma is a chronic inflammatory disease. Subsequently, inhaled steroids, the most potent anti-inflammatory asthma medications, have emerged as the cornerstone of the management of persistent asthma. The recent report of the National Heart, Lung, and Blood Institute's Childhood Asthma Management Program provides a comprehensive "profile of performance" for 3 treatment choices for the management of persistent asthma. This study answers questions regarding the benefits and shortcomings of the medications evaluated and prompts a closer evaluation of the long-term effects of other treatment strategies, including medications currently being developed.

Although intervention with inhaled steroids offers new opportunities to control the development of asthma, one must be cognizant of potential risks in early and long-term therapeutic intervention. This review provides a perspective on our present knowledge, the rationale for early intervention, and opportunities for more aggressive therapy, as well as speculation on how ongoing clinical research will continue to play a role in advancing asthma care and moving toward a "cure" for this life-threatening disease.

b. Adults

PRACTICE PARAMETER:
Li JT, Oppenheimer J, Bernstein IL
Attaining optimal asthma control: A practice parameter
J Allergy Clin Immunol 2005;116:S3-S11

MANAGEMENT GUIDELINE:
National Asthma Education and Prevention Program Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma & Update 2002: Expert Panel Report
http://www.nhlbi.nih.gov/guidelines/asthma/index.htm

REVIEW:
Busse WW, Banks-Schlegel S, Wenzel SE
Pathophysiology of severe asthma
J Allergy Clin Immunol 2000;106:1033-1042.
Although asthma affects nearly 8% of the adult population, most of these patients have mild-to-moderate disease that can be controlled with appropriate treatment. It is estimated, however, that 5% to 10% of patients with asthma have severe disease that is unresponsive to typical therapeutics, including corticosteroids. Because patients with severe asthma are disproportionately affected by their disease, in terms of both impaired lifestyle and health care costs, the National Heart, Lung, and Blood Institute sponsored a workshop on the pathogenesis of severe asthma. The goals of this workshop were to begin to define the characteristics of severe asthma. In these discussions, it was clear that many characteristics need to be considered in defining this phenotype of asthma, including symptoms, intensity of therapy (including administration of systemic corticosteroids), and impairment of lung function. Also discussed were potential mechanisms of severe asthma including the role of allergic diseases, which may play less of a role in severe asthma than in mild-to-moderate disease, and infections. A major limitation to control of severe asthma is the recalcitrant response of these patients to usual therapy including systemic corticosteroids; the potential of other therapies was reviewed. From these discussions, recommendations were made for future research needs to gain insights into a difficult therapeutic and possibly novel mechanistic area of asthma.

2. Rhinitis and rhinosinusitis

a. Allergic

LANDMARK PAPER:
Meltzer EO, Hamilos DL, Hadley JA, et al
Rhinosinusitis: Establishing definitions for clinical research and patient care
J Allergy Clin Immunol 2004;114:155-212)

BACKGROUND: There is a need for more research on all forms of rhinosinusitis. Progress in this area has been hampered by a lack of consensus definitions and the limited number of published clinical trials. OBJECTIVES: To develop consensus definitions for rhinosinusitis and outline strategies useful in clinical trials. METHODS: Five national societies, The American Academy of Allergy, Asthma and Immunology; The American Academy of Otolaryngic Allergy; The American Academy of Otolaryngology Head and Neck Surgery; The American College of Allergy, Asthma and Immunology; and the American Rhinologic Society formed an expert panel from multiple disciplines. Over two days, the panel developed definitions for rhinosinusitis and outlined strategies for design of clinical trials. RESULTS: Committee members agreed to adopt the term "rhinosinusitis" and reached consensus on definitions and strategies for clinical research on acute presumed bacterial rhinosinusitis, chronic rhinosinusitis without polyposis, chronic rhinosinusitis with polyposis, and classic allergic fungal rhinosinusitis. Symptom and objective criteria, measures for monitoring research progress, and use of symptom scoring tools, quality-of-life instruments, radiologic studies, and rhinoscopic assessment were outlined for each condition. Conclusion -The recommendations from this conference should improve accuracy of clinical diagnosis and serve as a starting point for design of rhinosinusitis clinical trials

REVIEW:
Borish L
Allergic rhinitis: Systemic inflammation and implications for management
J Allergy Clin Immunol 2003;112:1021-1031
Allergic rhinitis triggers a systemic increase of inflammation. Within minutes of allergen exposure, immune cells release histamine, proteases, cysteinyl leukotrienes, prostaglandins, and cytokines. Some produce the early symptoms, while others augment the production, systemic circulation, and subsequent infiltration of the nasal mucosa with inflammatory cells that sustain the symptoms. Systemic circulation of inflammatory cells permits their infiltration into other tissues where chemoattractant and adhesion molecules already exist. Consequently, allergic rhinitis is linked to comorbid conditions: asthma, chronic hyperplastic eosinophilic sinusitis, nasal polyposis, and serous otitis media. Effective therapy should be directed at underlying inflammation and its systemic manifestations. It should improve the rhinitis and the comorbid conditions. Antihistamines relieve early symptoms by blocking basophil- and mast cell-generated histamine, but they do not significantly influence the pro-inflammatory loop. They are often little better than placebo. Oral corticosteroids provide the systemic anti-inflammatory efficacy, but their toxicity precludes such an approach. Intranasal corticosteroids effectively target the local inflammatory processes of rhinitis, reducing local inflammatory cells within the nares, but they do not directly access tissues involved in the comorbid conditions. Leukotriene modifiers have both systemic anti-inflammatory effects and an acceptable safety profile.

REVIEW:
Skoner DP
Allergic rhinitis: Definition, epidemiology, pathophysiology, detection, and diagnosis
J Allergy Clin Immunol 2001;108:2S-8S
Allergic rhinitis (AR) is a heterogeneous disorder that despite its high prevalence is often undiagnosed. It is characterized by one or more symptoms including sneezing, itching, nasal congestion, and rhinorrhea. Many causative agents have been linked to AR including pollens, molds, dust mites, and animal dander. Seasonal allergic rhinitis (SAR) is fairly easy to identify

because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure. Perennial AR is often more difficult to detect than SAR because of the overlap with sinusitis, respiratory infections, and vasomotor rhinitis. SAR can result in hyperresponsiveness to allergens such as cigarette smoke, once pollen season is over. Perennial AR is defined as occurring during approximately 9 months of the year. AR affects an estimated 20 to 40 million people in the United States alone, and the incidence is increasing; an estimated 20% of cases are SAR; 40% of cases are perennial rhinitis; and 40% of cases are mixed. The pathophysiology of SAR is complex. There is a strong genetic component to the allergic response, which is driven through mucosal infiltration and action on plasma cells, mast cells, and eosinophils. The allergic response occurs in two phases, which are considered the "early" and "late" phase responses. Early phase response occurs within minutes of exposure to the allergen and tends to produce sneezing, itching, and clear rhinorrhea; late phase response occurs 4 to 8 hours after allergen exposure and is characterized by congestion, fatigue, malaise, irritability, and possibly neurocognitive deficits. The key to diagnosis of AR is awareness of signs and symptoms. IgE antibody tests to detect specific allergens are the standard method used today; however, in addition, diagnosis must be confirmed with a positive history and demonstration that the symptoms are the result of IgE-mediated inflammation.

b. Infectious

PRACTICE PARAMETER:
Slavin RG, Spector SL, Bernstein IL, et al
The diagnosis and management of sinusitis:
A practice parameter update
J Allergy Clin Immunol 2005;116:S13-47.

Sinusitis is one of the most commonly diagnosed diseases in the United States, affecting an estimated 16% of the adult population annually. It extracts an overall direct annual health care cost of $5.8 billion. Total restricted activity days increased from 50 million per year during 1986 through 1988 to 73 million per year during 1990 through 1992. Sinusitis also significantly affects quality of life in some symptom domains even more than other chronic diseases, such as chronic obstructive pulmonary disease, angina, and back pain.Because of the importance of sinusitis, the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma and Immunology,developed the first set of ‘‘Parameters for the diagnosisand management of sinusitis,’’ which was published in 1998.3 Much has happened since then with respect to new concepts in diagnosis and management and new insights into pathogenesis. For these reasons, it was decided that a revision-update was indicated.

c. Nonallergic

REVIEW:
Ciprandi D
Treatment of nonallergic perennial rhinitis
Allergy 2004;76:16-22.

Nonallergic perennial rhinitis (also commonly referred to as vasomotor rhinitis) is a chronic non-IgE-mediated condition that is characterized by symptoms which are similar to those seen in allergic rhinitis, but which persist for over nine months each year. Although treatment of vasomotor rhinitis involves the use of either intranasal corticosteroids or antihistamines, the corticosteroids are generally not effective in treatment of all the symptoms of vasomotor rhinitis

and have generally been shown to be effective in patients with eosinophilia. With the exception of azelastine, the only topical antihistamine to be approved by the FDA for the treatment of nonallergic rhinitis, the antihistamines have also produced inconsistent results. While clinical studies of azelastine have demonstrated that this drug is highly efficacious in the treatment of all the symptoms of vasomotor rhinitis, mechanistic studies have demonstrated that azelastine has potent anti-inflammatory effects (in particular attenuation of the expression and synthesis of pro-inflammatory cytokines, leukotrienes, and cell adhesion molecules), which are likely to contribute to its clinical efficacy. Furthermore, pharamacokinetic studies have suggested that since azelastine has a more rapid onset of action, compared to most other antihistamines and intranasal corticosteroids, then azelastine nasal spray may be considered as primary therapy for patients with symptoms of both allergic and/or vasomotor (nonallergic perennial) rhinitis.

REVIEW:
Novak N, Bieber T
Allergic and nonallergic forms of atopic diseases
J Allergy Clin Immunol 2003;112:252-262
Atopic dermatitis, allergic rhinitis, and asthma are atopic diseases that develop on a complex genetic background, the so-called atopic diathesis. Although they target different organs, in most patients they are characterized by the presence of elevated total serum IgE levels. However, a subgroup of atopic patients exhibits normal IgE levels and mechanisms contributing to the so-called "intrinsic" or "nonallergic form" have been the matter of intensive research work in the last years. Because of the rapid advancements in the research field of atopic diseases, it now becomes possible for the first time to delineate a new disease classification of allergic and nonallergic subtypes of atopic diseases, thereby bringing hope to the clinician for a more specific treatment approach for each subgroup of these patients.

REVIEW:
Leynaert B, Bousquet J, Neukirch C, et al.
Perennial rhinitis:An independent risk factor for asthma in nonatopic subjects: Results from the European Community Respiratory Health Survey
J Allergy Clin Immunol 1999;104:301-304
BACKGROUND: Although clinical and experimental studies suggest that upper respiratory tract dysfunction may affect the lower airways, rhinitis is usually not studied as a potential risk factor for asthma. This is because both diseases share key elements of pathogenesis and are usually considered as different manifestations of the same underlying "atopic" state. OBJECTIVE: We sought to assess whether asthma is associated with rhinitis in the absence of immunologic disorders in a population study. METHODS: Data from 34 centers participating in the European Community Respiratory Health Survey were analyzed. Random samples of 20- to 44-year-old subjects were invited to complete a detailed questionnaire and undergo total and specific IgE measurements, skin prick tests to 9 allergens, and bronchoprovocation challenges with methacholine. RESULTS: Subjects with perennial rhinitis (n = 1412) were more likely than control subjects (n = 5198) to have current asthma. After adjustment for sex, age, smoking habit, family history of asthma, geographic area, and season at the time of examination, asthma was strongly associated with rhinitis among atopic subjects (odds ratio [OR] = 8.1; 95% confidence interval [CI] = 5.4-12.1) but also among nonatopic subjects (OR = 11.6; 95% CI = 6.2-21.9). Moreover, the association remained very strong when the analysis was restricted to nonatopic

subjects with IgE levels of 80 kIU/L or less (OR = 13.3; 95% CI = 6. 7-26.5). In nonasthmatic subjects bronchial hyperresponsiveness was also more frequent in subjects with rhinitis than in those without rhinitis (OR = 1.7; 95%CI = 1.2-2.6 in nonatopic subjects with IgE levels of </=80 kIU/L). CONCLUSION: The strong association between perennial rhinitis and asthma in nonatopic subjects with normal IgE levels is consistent with the hypothesis that rhinitis is an independent risk factor for asthma.

d. Nasal polyps

POSITION PAPER:
Fokkens W, Lund V, Bachert C
EAACI position paper on rhinosinusitis and nasal polyps executive summary
Allergy 2005; 60:583-601

REVIEW:
Bachert C. Robillard T.
Management of nasal polyposis.
B-ENT. Suppl 2005;1:77-84
These guidelines are modified from the recent EAACI Position Paper. Nasal polyposis is characterized by an inflammatory process, the factors of which are summarized. Recently, Staphylococcus aureus enterotoxins have been identified to modify the disease. A classification system for polyps, grading systems and epidemiologic data are given, frequent comorbidities are discussed. The diagnostic management is based on endoscopy and CT scanning. A score of severity is proposed. The therapeutic management consists of the medical treatment options, which are given with evidence-based recommendations. Surgical treatment is indicated after failure of medical treatment and commonly performed by endoscopy. Nevertheless medical therapy must be continued after surgery to prevent recurrences. Algorithms of decision are finally proposed

REVIEW:
Bikhazi NB
Contemporary management of nasal polyps,
Otolaryngol Clin North Am; 2004;37, 327-37,
Nasal polyposis is a multifactorial disease process resulting in a common pathologic structure. Better understanding of the pathophysiology has resulted in improved protocols for treatment. Different causes of polyposis are discussed with attention to both medical and surgical therapy. Recent advances in aspirin desensitization are detailed.

REVIEW:
Watanabe, Shirasaki, Kanaizumi and Himi,
Effects of glucocorticoids on infiltrating cells and epithelial cells of nasal polyps,
Ann Otol Rhinol Laryngol; 2004;113, 465-73,
Glucocorticoids are known to be effective in the treatment of nasal polyps (NPs). To examine the mechanisms of their effect, we evaluated 1) the ability of glucocorticoids to induce the apoptosis of eosinophils and T lymphocytes in NPs, and 2) the ability of dexamethasone to down-regulate epithelial cell functions that relate to eosinophilic inflammation. In vitro and in vivo, glucocorticoids increased the apoptosis of both eosinophils and T lymphocytes in NPs. Dexamethasone inhibited the production of

granulocyte-macrophage colony-stimulating factor (GM-CSF) from both NP epithelial cells that were unstimulated and NP epithelial cells that were stimulated with interleukin-4 or tumor necrosis factor alpha. These results suggest that the clinical efficacy of glucocorticoids on NPs may be due to 1) induction of apoptosis in both eosinophils and T lymphocytes that infiltrate NPs, and 2) down-regulation of epithelial GM-CSF production, which prolongs eosinophil survival.

KEY CLINICAL TRIAL:
Blomqvist EH, Lundblad L, Anggard A et al
A randomized controlled study evaluating medical treatment versus surgical treatment in addition to medical treatment of nasal polyposis.
J Allergy Clin Immunol 2001;107:224-8.
BACKGROUND: Controlled prospective studies are needed to determine whether surgical treatment in fact has an effect additive to that of medical treatment of nasal polyposis. OBJECTIVE: We sought to compare the effect of medical treatment versus combined surgical and medical treatment on olfaction, polyp score, and symptoms in nasal polyposis. METHODS: Thirty-two patients with nasal polyposis and symmetrical nasal airways were randomized to unilateral endoscopic sinus surgery after pretreatment with oral prednisolone for 10 days and local nasal budesonide bilaterally for 1 month. Postoperatively, patients were given local nasal steroids (budesonide). Patients were evaluated with nasal endoscopy, symptom scores, and olfactory thresholds. They were followed for 12 months. RESULTS: The sense of smell was improved by the combination of local and oral steroids. Surgery had no additional effect. Symptom scores improved significantly with medical treatment alone, but surgery had additional beneficial effects on nasal obstruction and secretion. After surgery, the polyp score decreased significantly on the operated side but remained the same on the unoperated side. Twenty-five percent of the patients were willing to undergo an operation also on the unoperated side at the end of the study. CONCLUSIONS: Medical treatment seems to be sufficient to treat most symptoms of nasal polyposis. When hyposmia is the primary symptom, no additional benefit seems to be gained from surgical treatment. If nasal obstruction is the main problem after steroid treatment, surgical treatment is indicated. Selection of those who will benefit from surgery should be based on the patient's symptoms and not on the examiner's polyp score.

KEY CLINICAL TRIAL:
Hissaria P, Smith W, Wormald PJ et al
Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures
J Allergy Clin Immunol 2006;118:128-33
BACKGROUND: Topical and systemic corticosteroids are the first choice in medical treatments for sinonasal polyposis, but surprisingly, there is no high-level evidence for the efficacy of oral corticosteroids. OBJECTIVE: The aim of this study was to establish the efficacy of a short course of oral prednisolone in ameliorating the symptoms of sinonasal polyposis, as well as reducing mucosal inflammation assessed by means of nasendoscopy and magnetic resonance imaging (MRI). A secondary aim was to evaluate the relationship between outcome measures. METHODS: Subjects with symptomatic endoscopically diagnosed sinonasal polyposis received 50 mg of prednisolone daily for 14 days or placebo. Outcome was quantified by using the modified 31-item Rhinosinusitis Outcome Measure questionnaire, physician's assessment, nasendoscopy with

photography, and MRI. RESULTS: There were 20 subjects in each treatment group. Only the prednisolone-treated group showed significant improvement in nasal symptoms (P < .001). The Rhinosinusitis Outcome Measure score improved in both groups, but the prednisolone-treated group had significantly greater improvement than the placebo group (P < .001). Objectively, there was significant reduction in polyp size, as noted with nasendoscopy (P < .001) and MRI (P < .001), only in the prednisolone-treated group. The outcome measures correlated with each other; the highest level of correlation was between the objective measures of nasendoscopy and MRI (R(2) = 0.76, P < .001). There were no significant adverse events. CONCLUSION: This trial clearly establishes clinically significant improvement in the symptoms and pathology of sinonasal polyposis with a short course of systemic corticosteroids. MRI scanning and quantitative nasendoscopic photography are objective and valid tools for assessing the outcome of treatment in this condition. CLINICAL IMPLICATIONS: A 14-day course of 50 mg of prednisolone is safe and effective therapy for symptomatic nasal polyposis.

REVIEW:
Bikhazi NB
Contemporary management of nasal polyps,
Otolaryngol Clin North Am; 2004;37, 327-37,
Nasal polyposis is a multifactorial disease process resulting in a common pathologic structure. Better understanding of the pathophysiology has resulted in improved protocols for treatment. Different causes of polyposis are discussed with attention to both medical and surgical therapy. Recent advances in aspirin desensitization are detailed.

REVIEW:
Watanabe, Shirasaki, Kanaizumi and Himi,
Effects of glucocorticoids on infiltrating cells and epithelial cells of nasal polyps,
Ann Otol Rhinol Laryngol; 2004;113, 465-73,
Glucocorticoids are known to be effective in the treatment of nasal polyps (NPs). To examine the mechanisms of their effect, we evaluated 1) the ability of glucocorticoids to induce the apoptosis of eosinophils and T lymphocytes in NPs, and 2) the ability of dexamethasone to down-regulate epithelial cell functions that relate to Eosinophilic inflammation. In vitro and in vivo, glucocorticoids increased the apoptosis of both eosinophils and T lymphocytes in NPs. Dexamethasone inhibited the production of granulocyte-macrophage colony-stimulating factor (GM-CSF) from both NP epithelial cells that were unstimulated and NP epithelial cells that were stimulated with interleukin-4 or tumor necrosis factor alpha. These results suggest that the clinical efficacy of glucocorticoids on NPs may be due to 1) induction of apoptosis in both eosinophils and T lymphocytes that infiltrate NPs, and 2) down-regulation of epithelial GM-CSF production, which prolongs eosinophil survival.

RESEARCH FRONTIER:
Bernstein, Ballow, Rich, Allen, Swanson and Dmochowski,
Lymphocyte subpopulations and cytokines in nasal polyps: is there a local immune system in the nasal polyp?
Otolaryngol Head Neck Surg; 2004;130, 526-35,
PURPOSE: The pathogenesis of chronic hyperplastic rhinosinusitis with massive nasal polyposis is still not entirely known. The present study evaluates the lymphocyte subpopulations and their

production of cytokines using a technique for detection of intracytoplasmic cytokines by flow cytometry. This information may allow us to determine whether the source of these lymphocytes is from peripheral blood, the common mucosal immune system, or both. METHODS: Detection of intracytoplasmic cytokines by flow cytometry was performed using a fluoresceinated monoclonal antibody directed against CD4+ and CD8+ lymphocytes and a rhodamine-labeled intracytoplasmic monoclonal antibody directed against four cytokines. In this way, the percentage of lymphocytes synthesizing TH1 and TH2 cytokines were identified in nasal polyp lymphocytes and the corresponding peripheral blood lymphocytes of 13 patients. RESULTS: Lymphocytes producing interferon-gamma and IL-2, as well as IL-4 and IL-5, were found in the nasal polyps, suggesting that the nasal polyp possesses both TH1 and TH2 cytokine expression. There are also significant differences between the percentage of lymphocytes producing these cytokines between nasal polyps and peripheral blood, suggesting that nasal polyp lymphocytes derive from at least another source than only peripheral blood lymphocytes. Statistical analysis of four groups of patients demonstrated that no statistically significant difference in the lymphocyte subpopulations in atopic versus non-atopic patients, nor aspirin-intolerant versus aspirin-tolerant patients. In general, CD8 cells always produce more interferon-gamma than IL-2 in both peripheral blood and nasal polyps. In contrast with this data, CD4 cells produce more IL-2 in the peripheral blood than in nasal polyps. CONCLUSIONS: Data support the concept that nasal polyp lymphocyte subpopulations may be derived from both the local mucosal immune system as well as from random migration of peripheral blood lymphocytes secondary to adhesion molecules and chemokines, which are known to be present in nasal polyps

3. Atopic Dermatitis

REVIEW:
Allam JP. Novak N.
The pathophysiology of atopic eczema.
Clin Exp Derm.2006 31:89-93.
Atopic eczema (AE) represents a pruritic chronic inflammatory skin disease with a complex background, triggered by genetic and environmental factors. Different dendritic cells subtypes, such as Langerhans cells, inflammatory dendritic epidermal cells and plasmacytoid dendritic cells, play a key role in AE and impact on the mechanisms underlying AE, such as the recruitment of inflammatory cells, T-cell priming, and cytokine and chemokine release. In addition, allergens in combination with bacterial and viral stimuli influence the course and severity of AE. In this review, we highlight the recent progress made in the pathophysiology of AE focusing on the latest research results published in this field

REVIEW PRACTICE GUIDELINE Atopic Dermatitis:
Akdis CA , MD, Akdis B, Bieber T, et al.
Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/ American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report
J Allergy Clin Immunol 2006;118:152-169
There are remarkable differences in the diagnostic and therapeutic management of atopic dermatitis practiced by dermatologists and pediatricians in different countries. Therefore, the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology nominated expert teams who were given the task of finding a consensus

to serve as a guideline for clinical practice in Europe as well as in North America. The consensus report is part of the PRACTALL initiative, which is endorsed by both academies.

4. Early and late responses to allergen challenge:

a. Nasal Challenge:

REVIEW:

Litvyakova LI, Baraniuk JN. Nasal provocation testing: a review.
Ann Allergy Asthma Immunol. 2001 Apr;86(4):355-64; quiz 364-5, 386.

OBJECTIVE: This review focuses on the uses of nasal provocation testing (NPT) for scientific investigations of the mechanisms of allergic and nonallergic rhinitis. It also describes the use of NPT as a diagnostic tool in clinical practice. The indications, contraindications, advantages, and limitations of different techniques for evaluation of nasal responses are reviewed. The paper familiarizes investigators with particulars of different nasal delivery systems, provocation agents, nasal patency measurements, secretion collection, and nasal lavage techniques. DATA SOURCES: Relevant publications obtained from a literature review. STUDY SELECTION: Relevant publications on the topics of NPT, allergic, and nonallergic rhinitis were critically evaluated. RESULTS AND CONCLUSIONS: To date, NPT has been used primarily as a research tool for the investigation of allergic and nonallergic rhinitis with a wide variety of techniques depending on the specific scientific purposes. NPT will continue to provide useful information about the pathogenesis of airway diseases. Standardized nasal provocation testing has the potential to become a more frequently used clinical test in the diagnosis of allergic and occupational rhinitis and for determination of the appropriate and focused therapy.

REVIEW:

Miyahara S, Miyahara N, Lucas JJ, Joetham A, Matsubara S, Ohnishi H, Dakhama A, Gelfand EW. Contribution of allergen-specific and nonspecific nasal responses to early-phase and late-phase nasal responses.
J Allergy Clin Immunol. 2008 Mar;121(3):718-24. Epub 2007 Dec 21.

BACKGROUND: The relative contributions of the allergen-specific early-phase nasal response and nonspecific nasal response and mast cells to the pathophysiology of allergic rhinitis are not well defined. OBJECTIVES**:** To determine the contributions of specific reactivity, nonspecific reactivity, and mast cells to the development of early-phase and late-phase responses using a mouse model of allergic rhinitis. METHODS**:** Sensitized wild-type and FcvarepsilonRI-deficient (FcvarepsilonRI-/-) mice were exposed to allergen for 3, 5, or 12 days. As indicators of nasal reactivity, respiratory frequency and nasal resistance were monitored. RESULTS**:** Sensitized mice exposed to 3 days of nasal allergen challenge showed a nonspecific early-phase response. As the number of allergen exposures increased, there was progressive diminution in nonspecific responses with increased allergen-specific early-phase responses and a late-phase response. Sensitized FcvarepsilonRI-/- mice did not develop nonspecific nasal responses or late-phase responses, but transfer of in vitro-differentiated wild-type mast cells into FcvarepsilonRI-/- mice restored nonspecific early-phase nasal responses but not the late-phase response. CONCLUSION**:** These data identify the nonspecific nasal response as a major contributor to the early-phase response, especially during initial allergen exposure, and is dependent on mast cells. Increasing allergen exposure results in increasing allergen-specific responses, converting the nonspecific early-phase response to a late-phase response that is allergen-specific and mast cell-independent.

REVIEW:

Malm, l, Gerth van Wijk R, Bachert C.

Guidelines for nasal provocations with aspects on nasal patency, airflow, and airflow resistance. International Committee on Objective Assessment of the Nasal Airways, International Rhinologic Society.

Rhinology. 2000;38:1-6

Under the auspices of the International Rhinologic Society (IRS) there is an 'International Committee on Objective Assessment of the Nasal Airways'. In 1984 Rhinology published the Committee's recommendations regarding rhinomanometry (Clement, 1984). During the last Congresses of the European Rhinologic Society (ERS) a subcommittee within that committee has discussed nasal provocations and the value of measuring nasal patency, airflow and airflow resistance to evaluate such provocations. The following is an effort to a consensus of indications and techniques for nasal provocation and to a critical analysis of methods to measure the effects. Only the most known methods will be discussed, i.e. acoustic rhinometry, rhinostereometry, nasal peak airflow and rhinomanometry with its different techniques. For graded responses after provocations the use of such methods is of clinical value only in combination with scores from symptoms such as sneezes and secretion, as allergic rhinitis symptoms consist of obstruction, sneezing, itching and concomitant symptoms of the neighbouring organs. For research all methods can be recommended to be used and their respective value is depending on the specific scientific purposes.

RESEARCH FRONTIER:

Nakaya M,Dohi M, Okunishi K, et al

Noninvasive system for evaluating allergen-induced nasal hypersensitivity in murine allergic rhinitis.

Lab Invest. 2006;86:917-26

Until now there has been no method for physiologically evaluating nasal hypersensitivity in mice.Enhanced pause (Penh) has been used as an indicator that reflects changes in the lower airway. Recently, however, there is disagreement regarding the significance of the Penh system; this isbecause Penh is not essentially a physiological parameter, and it might not necessarily represent a change in the lower respiratory tract. The purpose of the present study is to investigate whether Penh could be applicable for analyzing nasal hypersensitivity in mice. BALB/c mice were sensitized with ovalbumin (OVA) through a combination of intraperitoneal injection and daily intranasal challenge in an awake condition. Penh was measured at each time point during sensitization, or a serial change in Penh value was followed after the final nasal challenge and the effect of treatment was assessed. Following sensitization and nasal challenge, the Penh value gradually increased and showed a significant difference on day 14. Changes in IgE, eosinophil infiltration into nasal mucosa, and OVA-induced symptoms all strongly correlated with the increase in Penh. On day 19, after OVA nasal provocation, Penh gradually increased and reached maximal values 25 min after the challenge. Pretreatment with dexamethasone or a histamine H1 blocker significantly suppressed this increase in Penh. We confirmed that intranasal OVA challenge did not induce bronchoconstriction by measuring airway resistance and bronchoalveolar lavage fluid, andthrough histological examination. These results clearly demonstrate that Penh could be a useful noninvasive indicator for studying nasal hypersensitivity.

LANDMARK PUBLICATION:

Raphael GD, Igarashi Y, White MV, Kaliner MA.
The pathophysiology of rhinitis. Sources of protein in allergen-induced nasal secretions.
J Allergy Clin Immunol. 1991;88:33-42.

Allergic rhinitis is characterized by a profuse rhinorrhea in addition to paroxysms of sneezing, nasal congestion, and pruritus. To define better the sources of nasal secretion produced during rhinitis, nasal allergen challenges were performed on nine atopic subjects with seasonal rhinitis. A single dose of allergen was sprayed into one side of the nose, and nasal lavages were collected bilaterally for 7 hours. Nasal lavages were assayed for protein (total protein, albumin, lactoferrin, and lysozyme) and mediator (histamine and prostaglandin D2) content. Protein concentrations increased and remained elevated above baseline levels in both ipsilateral and contralateral secretions for up to 3 hours after allergen challenge. The proportion of albumin relative to total protein (the albumin percent) increased on the ipsilateral side, whereas the relative proportions of lactoferrin and lysozyme (the lactoferrin percent and lysozyme percent) increased on the contralateral side. Prostaglandin D2, but not histamine, increased selectively on the ipsilateral side. These data suggest that the ipsilateral protein secretory response is due to allergen-induced mast cell mediator release causing increased vascular permeability, whereas the contralateral protein secretory response is primarily a reflex-induced glandular secretion.

Proud D, Riker DK, Togias A. Reproducibility of nasal allergen challenge in evaluating the efficacy of intranasal corticosteroid treatment.Clin Exp Allergy. 2010 May;40(5):738-44. Epub 2010 Mar 12.

BACKGROUND**:** Although nasal challenge with allergen has often been used to evaluate the efficacy of therapeutic modalities used for the treatment of allergic rhinitis, the reproducibility of this model in quantitatively evaluating efficacy has not been rigorously examined. OBJECTIVE: To examine the reproducibility of the suppressive effects of an intranasal corticosteroid on the clinical and biochemical outcomes of a nasal allergen challenge during two identical treatment periods using the same subjects. METHODS: In a single-blind study, 25 seasonal allergic subjects with positive skin tests to grass or ragweed were studied outside of their pollen season. Subjects underwent a baseline, three-dose allergen challenge. Beginning 1 week later, subjects received two 7-day courses of intranasal beclomethasone (168 microg b.i.d.) separated by a 1-month washout period. Nasal challenges with allergen were performed after each treatment period. The nasal allergic response was evaluated by counting sneezes, recording symptom scores and measuring levels of albumin (an index of vascular permeability), lysozyme (an index of serous glandular secretion) and kinins (proinflammatory peptides) in recovered nasal lavages. RESULTS: Compared with the baseline challenge, each course of beclomethasone significantly reduced sneezing, symptom scores, albumin and kinins, but not lysozyme. Reproducibility analysis of the net changes from diluent challenge in the two beclomethasone treatment periods, showed the following intraclass correlation coefficients: sneezing (0.92), lysozyme (0.82), symptom scores (0.72), albumin (0.64) and kinins (0.28). CONCLUSION: We conclude that the nasal challenge model is a reproducible method to evaluate the efficacy of anti-allergic medications. For nasal corticosteroid trials, sneezing, symptom scores and albumin levels are recommended as the most reproducibly suppressive outcome measures.

b. Bronchial Challenge:

REVIEW:

Anderson SD. Curr Opin Pulm Med. 2008 Jan;14(1):39-45.
PURPOSE OF REVIEW: To review bronchial provocations tests used in the measurement of bronchial hyperresponsiveness to help in the diagnosis of asthma. RECENT FINDINGS: The bronchial provocations tests reviewed include exercise, methacholine, AMP and mannitol, with reference to methodology and monitoring of treatment. SUMMARY**:** Methacholine is used for identifying bronchial hyperresponsiveness and to guide treatment. Exercise is used as a bronchial provocation test because demonstrating prevention of exercise-induced asthma is an indication for use of a drug. Both of these tests are being used to study tolerance to beta2 agonists. There is increasing use of eucapnic voluntary hyperpnea as a surrogate bronchial provocation test for exercise to identify exercise-induced asthma, particularly in athletes. For methacholine and AMP there is concern about the different breathing patterns used to inhale these aerosols and the impact they have on the cutoff point for identifying bronchial hyperresponsiveness. A new test that uses a kit containing prepacked capsules of different doses of mannitol and a delivery device is discussed. There is increasing interest in using tests that act indirectly by release of mediators because the bronchial hyperresponsiveness itself is an indicator of the presence of inflammation. Since treatment of inflammation leads to loss of bronchial hyperresponsiveness to indirect stimuli, these tests are well suited to identify success of treatment.

REVIEW:
Covar RA. Bronchoprovocation testing in asthma.
Immunol Allergy Clin North Am. 2007 Nov;27(4):633-49; vi-vii.
Bronchial hyperresponsiveness (BHR) is an important feature of asthma and is useful in diagnosis, monitoring, and prognostication. It probably represents inherent elements of the disease process such as genetic predisposition, airway inflammation, and airway remodeling. Airway inflammation likely accounts for the variable component of BHR, whereas the persistent component of BHR correlates significantly with structural changes in the airway, such as basement membrane thickness and epithelial damage. It might be this component that is resistant or refractory to the effects of available interventions. A few trials of immunomodulatory therapy have shown considerable improvements in markers of airway inflammation, without significantly modifying airway reactivity. Interventions to impact the more permanent feature of BHR are needed.

LANDMARK PUBLICATION:
Cockcroft DW, Murdock KY, Kirby J, Hargreave F.
Prediction of airway responsiveness to allergen from skin sensitivity to allergen and airway responsiveness to histamine.
Am Rev Respir Dis. 1987;135:264-7
Previous data have indicated that airway responsiveness to allergen, expressed as the provocation concentration causing a 20% FEV1 fall (PC20), was dependent on nonallergic airway responsiveness (histamine PC20) and sensitivity to allergen (skin sensitivity or end-point titration). From retrospective data in 24 subjects, we developed a formula to predict allergen PC20 and examined its accuracy prospectively in 26 new subjects undergoing allergen inhalation test with doubling allergen concentrations. Allergen PC20 (APC20) was predicted from histamine PC20 (HPC20) and skin sensitivity (SS) by the formula: Log10 (APC20) = 0.69 Log10 (HPC20 X SS) + 0.11 (r = 0.85). Allergen PC20 was accurately predicted in 6, and overestimated or underestimated by 1 doubling concentration in 11, by 2 concentrations in 6, by 3 concentrations in 3, and by greater than 3 concentrations in none. From the total of 50 subjects, a new relationship was

developed: Log10 (APC10) = 0.68 log10 (HPC20 X SS) (r = 0.82) from which 46 of 50 (92%) of allergen PC20 values fall within 2 doubling concentrations of the regression line (and all within 3). Early airway responsiveness to a given allergen can be predicted within a +/- 8-fold range, which is better than some investigator's test reproducibility of +/- 1 log (10-fold). Allergen inhalation tests to determine early asthmatic responsiveness to different IgE-mediated allergens can probably be replaced by the simpler and safer determinations of allergen sensitivity (SS, RAST) and histamine or methacholine airway responsiveness.

RESEARCH FRONTIER:
Cockcroft DW,Davis BE, Boulet LP, Deschesnes F,Gauvreau GM, O'Byrne PM, Watson RM.
The links between allergen skin test sensitivity, airway responsiveness and airway response to allergen.
Allergy. 2005;60:56-9
BACKGROUND: The allergen-induced early asthmatic response [provocation concentration (PC)20, the concentration causing a 20% forced expiratory volume in 1 s (FEV)1 fall] depends on the level of IgE sensitivity and the degree of nonallergic airway hyperresponsiveness (AHR) and can be predicted from histamine PC20 and allergen skin test endpoint. OBJECTIVES: We examined the relationships between allergen PC20, methacholine PC20, and allergen skin test endpoint and assessed the accuracy of both the histamine PC20-based prediction of allergen PC20 (using methacholine) and a new methacholine PC20-based prediction equation. METHODS: From 158 allergen challenges, the allergen PC20, the methacholine PC20, and the skin test endpoint were recorded and relationships between these three were sought. We compared the measured allergen PC20 to that predicted from the previous histamine PC20-based and the new methacholine-based formulae. RESULTS: In single regressions, allergen PC20 correlated with both methacholine PC20 (r=0.25, P=0.0015) and skin test endpoint (r=0.52, P <0.00005). The relationship was improved by multiple regression of log-allergen PC20vs. log-methacholine PC20 and log-endpoint (r=0.61, P <0.00005). The histamine-based formula predicted allergen PC20 to within 2 doubling concentrations in 80% and within 3 in 92%. The new methacholine-based formula to within 2 and 3 concentrations in 81% and 94%, respectively; only nine of 158 subjects were outside the 3 concentrations. CONCLUSIONS: We have confirmed the dependence of the allergen-induced early asthmatic response upon the level of allergic sensitivity and the degree of AHR, the latter as assessed by methacholine challenge. The allergen PC20 can be predicted to within 3 doubling concentrations in 94% of cases.

LANDMARK PUBLICATION:
Killian D, Cockcroft DW, Hargreave FE, Dolovich J.
Factors in allergen induced asthma: Relevance of the intensity of the airways allergic reactionand non-specific bronchial reactivity.
Clin Allergy 1976; 6:219–225.
Early asthmatic responses (EAR) of similar severity were produced by allergen inhalation challenges in nine asthmatic subjects. The severity of the airways allergic reaction was estimated by measuring the skin test weal size produced by the same dilution of allergen which caused the EAR. The non-specific bronchial reactivity was assessed by inhalation of incresing concentrations of histamine acid phosphate. Possible relationships between the severtiy of the airways allergic reaction, the level of non-specific bronchial hyper-reactivity and the pattern of asthmatic response

were examined. There was a marked inverse correlation between the required severity of the airways allergic reaction and the non-specific bronchial reactivity (log10) of the individual (r = -0-96, P less than 0-001). The EAR was followed by a late asthmatic response (LAR) in five subjects. There was no evident correlation between the magnitude of the EAR and that of the LAR. In addition, no correlation was obtained between the pattern of response interms of EAR or LAR and the severity of the allergic reaction, or the level of non-specific bronchial reactivity. These results indicate that the allergic reaction and the non-specific bronchial reactivity are interrelated in the production of allergen-induced asthma. Thus a mild allergic reaction will induce and EAR in patients with markedly increased non-specific bronchial reactivity, whereas a severe allergic reaction is required to produce an EAR in those with only slightly increased non-specific reactivity. The lack of correlation between the occurrence of the LAR and the intensity of the airways allergic reaction, the non-specific bronchial reactivity and the intensity of the EAR indicates that other factors are involved in the development of LAR.

c. Cutaneous

RESEARCH FRONTIER

He R, Oyoshi MK, Wang JY, Hodge MR, Jin H, Geha RS.

The prostaglandin D_2 receptor CRTH2 is important for allergic skin inflammation after epicutaneous antigen challenge.

J Allergy Clin Immunol. 2010 Oct;126(4):784-90. Epub 2010 Aug 14.

BACKGROUND: Cutaneous prostaglandin (PG) D_2 levels increase after scratching. Chemoattractant receptor-homologous molecule expressed on receptor on T(H)2 cells (CRTH2) mediates chemotaxis to PGD_2 and is expressed on T(H)2 cells and eosinophils, which infiltrate skin lesions in patients with atopic dermatitis. OBJECTIVE: We sought to examine the role of CRTH2 in a murine model of atopic dermatitis. METHODS: CRTH2(-/-) mice and wild-type control animals were epicutaneously sensitized by means of repeated application of ovalbumin (OVA) to tape-stripped skin for 7 weeks and then challenged by means of OVA application to tape-stripped previously unsensitized skin for 1 week. Skin histology was assessed by means of hematoxylin and eosin staining and immunohistochemistry. Cytokine mRNA expression was examined by means of quantitative RT-PCR. Levels of PGD_2, antibody, and cytokines were measured by means of ELISA. RESULTS: PGD_2 levels significantly increased in skin 24 hours after tape stripping, although not in skin subjected to repeated sensitization with OVA. Allergic skin inflammation developed normally at sites of chronic epicutaneous sensitization with OVA in CRTH2(-/-) mice but was severely impaired in previously unsensitized skin challenged with OVA, as evidenced by significantly decreased skin infiltration with eosinophils and CD4(+) cells and impaired T(H)2 cytokine mRNA expression. Impaired skin inflammation at sites of acute OVA challenge in CRTH2(-/-) mice was not due to an impaired systemic response to epicutaneous sensitization because OVA-specific IgG1 and IgE antibody levels and OVA-driven splenocyte secretion of cytokines in these mice were comparable with those seen in wild-type control animals. CONCLUSIONS: CRTH2 promotes allergic skin inflammation in response to cutaneous exposure to antigen in previously sensitized mice.

RESEARCH FRONTIER:

He R, Oyoshi MK, Jin H, Geha RS.

Epicutaneous antigen exposure induces a Th17 response that drives airway inflammation after inhalation challenge.

Proc Natl Acad Sci U S A. 2007 Oct 2;104(40):15817-22. Epub 2007 Sep 24.
IL-17 has been implicated in a number of inflammatory diseases, but the conditions of antigen exposure that drive the generation of Th17 responses have not been well defined. Epicutaneous (EC) immunization of mice with ovalbumin (OVA), which causes allergic skin inflammation with many characteristics of the skin lesions of atopic dermatitis, was found to also drive IL-17 expression in the skin. EC, but not i.p., immunization of mice with OVA drove the generation of IL-17-producing T cells in draining lymph nodes and spleen and increased serum IL-17 levels. OVA inhalation by EC-sensitized mice induced IL-17 and CXCL2 expression and neutrophil influx in the lung along with bronchial hyperreactivity, which were reversed by IL-17 blockade. Dendritic cells trafficking from skin to lymph nodes expressed more IL-23 and induced more IL-17 secretion by naïve T cells than splenic dendritic cells. This was inhibited by neutralizing IL-23 in vitro and by intradermal injection of anti-TGFbeta neutralizing antibody in vivo. Our findings suggest that initial cutaneous exposure to antigens in patients with atopic dermatitis may selectively induce the production of IL-17, which, in turn, drives inflammation of their airways.

REVIEW:
Simons FE, Johnston L, Gu X, Simons KJ.
Suppression of the early and late cutaneous allergic responses using fexofenadine and montelukast.
Ann Allergy Asthma Immunol. 2001 Jan;86(1):44-50
BACKGROUND: The relative contribution of histamine and the cysteinyl leukotrienes to the early and late cutaneous allergic responses (ECAR and LCAR) can be studied using antagonists of these mediators. OBJECTIVE: To determine the relative suppression of the ECARs and LCARs using standard doses of an H1-receptor antagonist, a cysteinyl leukotriene1-receptor antagonist, and the two antagonists administered concurrently. METHODS: We carried out a prospective, randomized, double-blind, placebo-controlled, four-way crossover study in 12 highly allergic participants. Intradermal tests with standardized allergen, and with histamine phosphate, LTD4, and saline controls were performed on 5 different test days as follows: pretreatment baseline and at steady state immediately after the seventh and last dose of a 1-week course of treatment with once-daily fexofenadine, 120 mg; montelukast, 10 mg; fexofenadine and montelukast administered concurrently; or placebo. On each test day, the skin test results were read at intervals from 0.25 to 24 hours after the intradermal injections were performed. RESULTS: After allergen injection, compared with baseline, all treatment regimens significantly decreased the ECAR and LCAR. After allergen injection, compared with placebo, fexofenadine significantly decreased the ECAR and the LCAR from 0.25 to 2 hours and at 8 hours. Montelukast did not significantly decrease the ECAR or LCAR. Fexofenadine and montelukast administered concurrently were not more effective than fexofenadine alone at any time. In the control skin tests, compared with placebo, fexofenadine, but not montelukast, significantly decreased the histamine-induced response, and montelukast, but not fexofenadine, significantly decreased the LTD4-induced response. CONCLUSIONS: Fexofenadine and montelukast administered concurrently were not significantly more effective than fexofenadine alone in decreasing the ECAR and LCAR. Montelukast does not need to be discontinued before allergen skin testing. Further studies of the effect of concurrent treatment with higher doses of a histamine antagonist and a leukotriene modifier on the allergic response in the skin are needed.

5. Role of Structural Cells:

a. Epithelium:

REVIEW:
Takizawa H.
Bronchial epithelial cells in allergic reactions.
Curr Drug Targets Inflamm Allergy. 2005 Jun;4(3):305-11.
Bronchial epithelial cells (BEC) are known to play an integral role in the airway defense mechanism via mucociliary system as well as mechanical barriers. Recent studies further indicate that BEC produce and release biologically active compounds including lipid mediators, growth factors, endothelin and a variety of cytokines/chemokines important in the pathogenesis of airway disorders. Cytokines and chemokines produced by BEC include IL-6, IL-8, G-CSF, GM-CSF, RANTES, eotaxin and TARC. Pro-inflammatory cytokines IL-1 and TNF-alpha, generally upregulate expression and release these cytokines/chemokines. BEC from patients with bronchial asthma showed increased levels of mRNA for these potent inflammatory peptides. BEC also interact with immune and inflammatory cells by direct adhesion as well as by humoral factors including cytokines. For example, eosinophil adhesion to BEC may be an important signal for the activation and degranulation of eosinophils. BEC is also believed to take part in the airway mucosal immunity via Toll-like receptors. Finally, BEC may play a crucial role in the processes of airway remodeling by cross-talk with mesenchymal cells. These findings strongly suggest that BEC are actively involved as regulators of allergic inflammatory responses, and become a target for therapeutic intervention.

RESEARCH FRONTIER:
Wu CA, Peluso JJ, Zhu L, Lingenheld EG, Walker ST, Puddington L.
Bronchial epithelial cells produce IL-5: implications for local immune responses in the airways.
Cell Immunol. 2010;264(1):32-41. Epub 2010 May 5.
IL-5 is a pleiotropic cytokine that promotes eosinophil differentiation and survival. While naïve bronchial epithelial cells (BEC) produce low levels of IL-5, the role of BEC-derived IL-5 in allergic airway inflammation is unknown. We now show that BEC, isolated from mice with OVA-induced allergic airway disease (AAD), produced elevated levels of IL-5 mRNA and protein as compared to BEC from naïve mice. To determine the contribution of BEC-derived IL-5 to effector responses in the airways, IL-5 deficient bone marrow chimeric mice were generated in which IL-5 expression was restricted to stromal (e.g. BEC) or hematopoietic cells. When subjected to AAD, IL-5 produced by BECs contributed to mucous metaplasia, airway eosinophilia, and OVA-specific IgA levels. Thus, IL-5 production by BEC can impact the microenvironment of the lung, modifying pathologic and protective immune responses in the airways.

KEY INVESTIGATION:
Erez Salik, Max Tyorkin, Savita Mohan et al.
Antigen Trafficking and Accessory Cell Function in Respiratory Epithelial Cells
Am. J. Respir. Cell Mol. Biol. 1999;21: 365-379
We investigated accessory cell function, antigen (Ag) trafficking, and uptake of immune complexes in isolated nasal epithelial cells (NEC) and airway epithelial cells (AEC), as well as in

the two respiratory epithelial cell lines A549 and BEAS-2B. The NEC and AEC were capable of supporting Ag-specific as well as phytohemagglutinin-induced and anti-CD3 antibody-induced T-cell proliferation. We colocalized fluorescein isothiocyanate (FITC)-labeled Ags with human leukocyte antigen (HLA)-DR in A549 and BEAS-2B, utilizing laser confocal microscopy. Respiratory epithelial cells stimulated and unstimulated with interferon (IFN)- were pulsed with FITC-labeled Ags for varying periods and evaluated for their ability to internalize Ag. In the unstimulated cells, intracellular punctate staining was evident at 60 min and persisted up to 120 min. In the IFN stimulated cells (100 U/ml for 48 h), uptake occurred at 30 min, was maximal at 60 min, and diminished at 120 min. We conducted kinetic studies in the A549 and BEAS-2B cells, utilizing electron microscopy with colloidal gold-conjugated Ags (Au-OVA). At 15 min, Au-OVA was evident in the early compartments resembling the compartment of uncoupling of receptor and ligand. At 30 min, multivesicular bodies were labeled with Au-OVA, and by 60 min Au-OVA was present in the primary and secondary lysosomes. The FITC-labeled Ags colocalized with an early endosomal marker (anti-cathepsin D), a late endosomal marker (M6PR), a lysosomal marker (CD63), and with 3-(2,4-dinitroanilino)-3'-aminomethyldipropylamine, a marker of acidic vesicles. The BEAS-2B and A549 cells, and NEC and AEC, expressed surface Fc receptor and internalized IgG immune complexes. The NEC and AEC also expressed the costimulatory molecules CD80 and CD86 as determined with flow cytometry, the reverse transcription-polymerase chain reaction for RNA, and immunohistochemistry, and T-cell proliferation could be blocked by treating NEC andAEC with anti-CD80 and anti-CD86 antibodies. Our findings suggest that respiratory epithelial cells may have a role in local Ag presentation.

RESEARCH FRONTIER:
Duncan W. Borthwick, Mariam Shahbazian, et al.
Evidence for Stem-Cell Niches in the Tracheal Epithelium
Am. J. Respir. Cell Mol. Biol., 2001;24:662-670
It is generally important to elucidate airway epithelial cell lineages and to identify multipotent progenitors as targets for gene therapy. Stem (S) cells are typically present in specialized compartments spatially proximal to their differentiated progeny, but an equivalent paradigm has not been demonstrated in the airway. We discovered a distinct population of cells displaying high levels of keratin expression in murine tracheal submucosal gland ducts, and tested the hypothesis that bromodeoxyuridine (BrdU) label-retaining cells (LRCs), thought to represent the S-cells, were present in this compartment. Mice received weekly epithelial damage by intratracheal detergent or SO2 inhalation for 4 wk and received intraperitoneal injections of BrdU every 48 h during the injury and repair period. At 3 and 6 d after injury, BrdU-positive epithelial cells were noted along the entire tracheal length in both basal and lumenal cell positions. At later time points (20 and 95 d) LRCs were localized to gland ducts in the upper trachea and to systematically arrayed foci in the lower trachea, typically near the cartilage-intercartilage junction. LRCs were not pulmonary neuroendocrine cells. Heterotopic tracheal grafts after surface epithelial removal demonstrated reconstitution of a surface-like epithelium from gland remnants. These results suggest that airway epithelial S cells are localized to specific niches.

b. Endothelium:

REVIEW:
Tabuchi A, Kuebler WM.
Endothelium-platelet interactions in inflammatory lung disease.

Vascul Pharmacol. 2008 Oct-Dec;49(4-6):141-50. Epub 2008 Jun 24.
In addition to their established role in hemostasis, recent studies have identified platelets as key regulators of inflammatory reactions. Upon activation, platelets interact with both endothelial cells and circulating leukocytes. By receptor-mediated activation of interacting cell types and by release of mitogenic, pro-inflammatory and -coagulatory mediators, platelets contribute crucially to the initiation and propagation of pathological conditions and processes such as inflammatory bowel disease or atherosclerosis. In inflammatory lung disease, platelets play a critical role in the recruitment of neutrophils, eosinophils and lymphocytes as shown in experimental models of acute lung injury and allergic airway inflammation. Circulating platelet-leukocyte aggregates have been detected in patients with allergic asthma and cystic fibrosis, and in experimental lung injury. Here, we discuss the molecular mechanisms regulating the interaction of platelets with leukocytes, endothelial cells, and the subendothelial matrix with special regard to platelet kinetics in pulmonary microvessels and the putative role of platelets in inflammatory lung disorders. In light of the existing data from experimental and clinical studies it is conceivable that platelet adhesion molecules and platelet mediators provide promising targets for novel therapeutic strategies in inflammatory lung diseases.

KEY INVESTIGATION:
Shasby DM, Shasby SS, Sullivan JM, Peach MJ
Role of endothelial cell cytoskeleton in control of endothelial permeability.
Circ Res. 1982;51:657-61.
Increased permeability of the pulmonary microvasculature is felt to cause acute noncardiogenic lung edema, and histological studies of edematous lungs show gaps between apparently healthy endothelial cells. To determine whether alterations in endothelial cell cytoskeletons would alter endothelial permeability, we exposed monolayers of pulmonary artery endothelial cells grown on micropore filters to cytochalasin B or D. Cytochalasin exposed monolayers demonstrated a 2- to 3-fold increase in endothelial permeability that was readily reversible by washing the monolayers freeof cytochalasins. Parallel phase contrast and fluorescence microscopy demonstrated retraction of cell cytoplasm and disruption of bundles of microfilaments in cytochalasin exposed cells. These changes also were readily reversed after washing the cells free from cytochalasins. To test the relevance of these findings to an in situ microvasculature, we added cytochalasin B to the perfusate of isolated rabbit lungs and observed that cytochalasin B caused a high permeability lung edema. These studies suggest that endothelial cell cytoskeletons may be important determinants of endothelial permeability.

c. Smooth Muscle:

RESEARCH FRONTIER:
Leclere M, Lavoie-Lamoureux A, Gélinas-Lymburner E, David F, Martin JG, Lavoie JP.
Effect of Antigen Exposure on Airway Smooth Muscle Remodeling in an Equine Model of Chronic Asthma.
Am J Respir Cell Mol Biol. 2010 Oct 8. [Epub ahead of print]
Rationale: Recent studies suggest that airway smooth muscle remodeling is an early event in asthma but it is unknown whether it remains a dynamic process late in the course of the disease. Little is known of the effect of an antigenic exposure on chronically established smooth muscle remodeling. Objectives: To measure the effect of antigen exposure on airway smooth muscle in central and peripheral airways of horses with heaves, a naturally occurring airway disease that

shares similarities with chronic asthma. Methods: Heaves-affected horses (6) and age-matched controls (5) were kept on pasture before being exposed to indoor antigens for 30 days to induce airway inflammation and bronchoconstriction. Peripheral lung and endobronchial biopsies were collected before and after antigen exposure by thoracoscopy and bronchoscopy, respectively. Immunohistochemistry and enzymatic labeling were used for morphometric analysis of airway smooth muscle mass and proliferative and apoptotic myocytes. Measurements and Main Results: In peripheral airways, heaves-affected horses had twice as much smooth muscle as controls. Remodeling was associated with smooth muscle hyperplasia and in situ proliferation without reduced apoptosis. Further antigen exposure had no effect on morphometric data. In central airways, proliferating myocytes were increased compared to controls only after antigen exposure. Conclusions: Peripheral airway smooth muscle mass is stable in chronically affected animals subjected to antigenic exposure. This increased mass is maintained in a dynamic equilibrium by an elevated cellular turnover, suggesting that targeting smooth muscle proliferation could be effective at decreasing chronic remodeling.

AT A GLANCE COMMENTARY:

Scientific Knowledge on the Subject:

Recent studies suggest that airway smooth muscle remodeling is an early event in asthma but it is unknown whether it remains a dynamic process late in the course of the disease and how antigen exposure affects established remodeling.

What This Study Adds to the Field:

We showed that a 30-day antigen exposure had little effect on established remodeling in diseased animals, despite the development of inflammation and bronchoconstriction. In peripheral airways, airway smooth muscle remodeling appears to be maintained in a dynamic equilibrium by an elevated turnover with *in situ* proliferation, suggesting that targeting airway smooth muscle proliferation could be effective at decreasing its mass.

REVIEW:

James A and N Carroll

Airway smooth muscle in health and disease; methods of measurement and relation to function

Eur Respir J 2000;15:782-789

Smooth muscle is present and probably functional in the airways in utero and increases in absolute area during growth with little further change during adulthood. It encircles the entire airway below the level of the main bronchus, in a roughly circular orientation, except at high lung volumes. It occupies relatively more of the airway wall in the peripheral airways, reaching a maximum in the membranous bronchioles. Measurement of smooth muscle area in the airway wall is confounded by clinical classification of cases, methods of tissue retrieval and preparation, staining and orientation of sections, magnification, image analysis and statistical methods of comparison between groups. Airway smooth muscle area is pathologically increased in inflammatory conditions of the airways such as chronic obstructive pulmonary disease, in relation to airways obstruction, and asthma, in relation to severity and airway size (between 25 and 250% compared with control cases). It is increased in sudden infant death syndrome, but there are few studies in

other conditions such as bronchiectasis. In asthma, smooth muscle must shorten (not necessarily to an abnormal degree) for the structural abnormalities of the airway to manifest as excessive airway narrowing. Not surprisingly there is renewed interest in the relationships between the mechanical and contractile properties of smooth muscle, parenchymal properties and lung volume and how these interact to determine smooth muscle length. The relative importance of smooth muscle area and mechanical properties, altered airway structure and airway inflammation in disease are yet to be determined.

RESEARCH FRONTIER:
SJ Hirst, TR Walker, and ER Chilvers
Phenotypic diversity and molecular mechanisms of airway smooth muscle proliferation in asthma
Eur Respir J 2000;16:159-177
Chronic persistent asthma is characterized by poorly reversible airflow obstruction and airways inflammation and remodelling. Histopathological studies of airways removed at post mortem from patients with severe asthma reveal marked inflammatory and architectural changes associated with airway wall thickening. Increased airway smooth muscle content, occurring as a result of hyperplastic and/or hypertrophic growth, is believed to be one of the principal contributors to airway wall thickening. In recent years, significant advances have been made in elucidating the mediators and the intracellular pathways that regulate proliferation of airway smooth muscle. The contribution that smooth muscle makes to persistent airflow obstruction may not, however, be limited simply to its increased bulk within the airway wall. Interest is growing in the possibility that reversible phenotypic modulation and increased heterogeneity of airway smooth muscle function may also be a feature of the asthmatic airway. This review focuses on possible mechanisms controlling smooth muscle phenotype heterogeneity as well as on the mediators and intracellular pathways implicated in its cellular proliferation. Particular attention is paid to mechanisms involving activation of the extracellular signal regulated kinase-, protein kinase C- and phosphoinositide 3-kinase-dependent pathways, since these appear to be the major candidate second messenger pathways for G protein- and tyrosine kinase-coupled receptor-stimulated proliferation.

d. Fibroblasts:

RESEARCH FRONTIER:
Borowski A, Kuepper M, Horn U, Knüpfer U, Zissel G, Höhne K, Luttmann W, Krause S, Virchow JC Jr, Friedrich K. Interleukin-13 acts as an apoptotic effector on lung epithelial cells and induces pro-fibrotic gene expression in lung fibroblastsClin Exp Allergy. 2008 Apr;38(4):619-28. Epub 2008 Feb 11.
BACKGROUND: IL-13 promotes acute allergic asthma and is discussed to play a role in late asthmatic features such as fibrotic processes and airway remodelling. The contributions of IL-13-mediated mechanisms to subepithelial events related to fibrosis are not yet settled. OBJECTIVE: We investigated the impact of IL-13 on lung epithelial cells as apoptotic effector and on lung fibroblasts as inducer of pro-fibrotic gene expression. METHODS: Using the two lung epithelial cell lines A549 and BEAS-2B as well as primary lung epithelial cells, we investigated the capability of IL-13 to induce apoptosis by both flow-cytometry and ELISA. The ability of IL-13 to increase the expression of pro-fibrotic genes and to exert influence on the expression of its own receptor was investigated by real-time quantitative PCR measurement of mRNAs encoding

collagen I, collagen III, basic fibroblast growth factor (bFGF), alpha-smooth muscle actin (alpha-SMA) and the IL-13 receptor alpha1 (IL-13Ralpha1) chain in human primary lung fibroblasts. The specificity of IL-13-mediated cellular responses was confirmed by means of an inhibitory monoclonal antibody directed to the IL-13 receptor. RESULTS: IL-13 induces apoptosis in lung epithelial cell lines as well as in primary lung epithelial cells. Furthermore, IL-13 increases the expression of mRNA for alpha-SMA and collagen III, but not for bFGF in human primary lung fibroblasts. The susceptibility of lung fibroblasts to IL-13-induced up-regulation of pro-fibrotic genes is associated with the regulation of IL-13 receptor expression. IL-13-dependent fibrosis-associated effects could be inhibited by antibody-mediated blockade of the IL-13Ralpha1 subunit. CONCLUSION: Our findings indicate a function of IL-13 as a mediator in fibrotic processes leading to loss of functional airway tissue in asthma. They also highlight the therapeutic potential of specifically targeting the interaction between IL-13 and its receptor.

REVIEW:
Levine SJ
Bronchial epithelial cell-cytokine interactions in airway inflammation
J Investig Med. 1995;43:241-9
A variety of cytokine bronchial cell interactions may play an important role in normal host defense as well as in the pathogenesis of inflammatory airway disorders such as asthma, cystic fibrosis, acute and chronic bronchitis, and bronchiectasis. First, airway epithelial cells may participate in local cytokine networks by synthesizing interleukins, chemokines, colony stimulating factors and growth factors in response to inflammatory mediators. Bronchial epithelial cell derived cytokines may thereby amplify ongoing inflammatory processes via the recruitment and activation of specific subsets of inflammatory cells, as well as by prolonging their survival in the airway microenvironment. Second, airway epithelial cells can initiate inflammatory cascades by generating cytokines in direct response to viral and bacterial products, noxious gases, and sensitizing chemicals. Third, airway epithelial cells represent targets for paracrine acting cytokines, which may then modulate bronchial epithelial cell functions. Finally, airway epithelial cells may modulate ongoing inflammatory events in the airway microenvironment via the shedding of soluble TNF receptors. Cytokine-bronchial epithelial cell interactions represent an important mechanism by which inflammatory events in the airway microenvironment can be regulated and represent potential targets for novel anti-inflammatory therapies in airway disorders.

e. Mucociliary cells:

RESEARCH FRONTIER:
Lachowicz-Scroggins ME, Boushey HA, Finkbeiner WE, Widdicombe JH.
Interleukin-13 Induced Mucous Metaplasia Increases Susceptibility of Human Airway Epithelium to Rhinovirus Infection.
Am J Respir Cell Mol Biol. 2010 Jan 15. [Epub ahead of print]
Infection of airway epithelium by rhinovirus is the commonest cause of asthma exacerbations. Even in mild asthma, airway epithelium shows mucous metaplasia, and this increases with increasing severity of disease. We have earlier shown that squamous cultures of human airway epithelium have many times higher levels of rhinoviral infection than are well-differentiated cultures of mucociliary phenotype. Here we have tested the hypothesis that mucous metaplasia is also associated with increased levels of rhinoviral infection. Mucous metaplasia was induced with IL-13, which doubled the numbers of goblet cells. In both control (mucociliary) and IL-13- treated

(mucous metaplastic) cultures, goblet cells were preferentially infected by rhinovirus. IL-13 doubled the numbers of infected cells by increasing the numbers of infected goblet cells. Furthermore, IL-13 also increased both the maturity of the goblet cells and the probability that a goblet cell would be infected. Infection of cells that were not goblet cells were unaltered by IL-13. IL-13 treatment did not alter the levels of rhinovirus receptor ICAM-1, nor did the proliferative effects of IL-13 enhance infection, as rhinovirus did not colocalize with dividing cells. However, induction of mucous metaplasia caused changes in the apical membrane structure, notably a marked decrease in overall ciliation and an increase in the overall flatness of the apical surface. We conclude that the presence of mucous metaplasia in asthma increases the susceptibility of airway epithelium to infection by rhinovirus due to changes in the overall architecture of the apical surface.

KEY INVESTIGATION:
O'Riordan TG, Zwang J, Smaldone GC
Mucociliary clearance in adult asthma.
Am. J. Respir. Cell Mol. Biol., Volume 21, Number 3, September 1999 365-379
Severe impairment of mucociliary clearance (MC) in hospitalized asthmatics has recently been demonstrated in peripheral and central airways. MC was also shown to improve with clinical recovery and hospital discharge (2). In the present study, we measure MC in chronic, stable asthma in subjects with a wide range of obstruction to see if MC was related to the severity of chronic disease. We separated the subjects into those with severe obstruction with expiratory flow limitation during tidal breathing (FL subjects) and those without tidal flow limitation (NFL subjects) to see if the presence of chronic flow limitation was associated with regional MC abnormalities. Seventeen asthmatic patients were studied. Mucociliary clearance was assessed using inhaled radioaerosol and serial measurements of the retention of radioactivity over 2 h. By controlling breathing pattern, the initial pattern of deposition in the lungs was matched, with all subjects having a predominance of particles in the central airways. This pattern was normalized for regional lung volume using a xenon equilibrium scan and expressed as a specific central to peripheral (sC/P) ratio. The percentage retention of deposited radioactivity at 120 min ranged from 19 to 83% (mean, 52%). FL subjects had a mean retention at 120 min of 66% (range, 55 to 83%). The NFL subjects had a mean retention at 120 min of 33% (range, 19 to 51%). Throughout the 2-h study period, retention by the FL group was significantly greater than that of the NFL group with separation of 95% confidence intervals.

C. Measurements and interpretation of lower airway function

1. Spirometry: FVC, FEV1, FEV/FVC, FEF 25-75, Flow volume loop, pre-and post-bronchodilator values

Am J Respir Crit Care Med.
An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children.
2007 Jun 15;175(12):1304-45.
Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, Bisgaard H, Davis GM, Ducharme FM, Eigen H, Gappa M, Gaultier C, Gustafsson PM, Hall GL, Hantos Z, Healy MJ, Jones MH, Klug B, Lødrup Carlsen KC, McKenzie SA, Marchal F, Mayer OH, Merkus PJ, Morris MG, Oostveen E, Pillow JJ, Seddon PC, Silverman M, Sly PD, Stocks J, Tepper RS, Vilozni D,

Wilson NM; American Thoracic Society/European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing.

Respir Care.
2009 Dec;54(12):1717-26.
The physiologic basis of spirometry.
Hayes D Jr, Kraman SS.
Department of Pediatrics, University of Kentucky College of Medicine, Lexington KY
Spirometry is the most useful and commonly available tests of pulmonary function. It is a physiological test that measures individual inhalation and exhalation volumes of air as a function of time. Pulmonologists and general-practice physicians commonly use spirometry in their offices in the assessment and management of lung disease. Spirometric indices are well validated and easily interpreted by comparison with established normal values. The remarkable reproducibility of spirometry results from the presence of compliant intrathoracic airways that act as air flow regulators during forced expiration. Because of this anatomic arrangement, expiratory flow becomes dependent solely on the elasticity of the lungs and airway resistance once a certain degree of expiratory force is exerted. Insight into this aspect of resistance once a certain degress of expiratory force is exerted. Insight into this aspeci of respiratory physiology can help in the interpretation of spirometry.

Chest.
2009 Aug;136(2):608-14.
Spirometry: don't blow it!
Lange NE, Mulholland M, Kreider ME.
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA.
Spirometry is a useful test of pulmonary function and can be safely performed in a variety of clinical situations. Although the technique for performing the maneuver is straightforward, there are many sources of variability in results. Specific criteria must be met in order for the test to be considered valid. For the best results, proper instruction and coaching is essential, and patient understanding and effort must be maximized. Appropriate interpretation of spirometry requires several steps, including recognition and reporting of technically sound maneuvers, comparison to an appropriate reference population, and finally application of a well-developed interpretation scheme utilized in the context of patient symptoms and findings. Failure at any point along this path from performance to interpretation can yield misleading results that may ultimately poorly impact patient care. A clear understanding by the provider of proper coding and billing for spirometry is necessary to receive appropriate reimbursement from payers

REVIEWS:
Miller MR et al.
ATS/ERS Standardization of Lung Function Testing: General Considerations for Lung Function Testing.
Eur Respir J 2005;26:153-161.
This is the first in a series of statements on the standardization of lung function testing.

Miller MR et al.

ATS/ERS Standardization of Lung Function Testing: Standardization of Spirometry.
Eur Respir J 2005;26:319-338.
This is the second document in a series of statements on lung function testing.

Pellegrino R et al.
ATS/ERS Standardization of Lung Function Testing: Interpretative Strategies for lung function tests.
Eur Respir J 2005;26: 948-968.
This is the final document in a series of five statements on pulmonary function testing.

2. Provocative challenges (exercise, methacholine, allergen, other): indications, performance, and interpretation, predictive value of asthma

REVIEW:
Curr Opin Pulm Med. 2008 Jan;14(1):39-45.
Anderson SD.
Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital Camperdown, New South Wales, Australia.
PURPOSE OF REVIEW: To review bronchial provocations tests used in the measurement of bronchial hyperresponsiveness to help in the diagnosis of asthma. RECENT FINDINGS: The bronchial provocations tests reviewed include exercise, methacholine, AMP and mannitol, with reference to methodology and monitoring of treatment. SUMMARY: Methacholine is used for identifying bronchial hyperresponsiveness and to guide treatment. Exercise is used as a bronchial provocation test because demonstrating prevention of exercise-induced asthma is an indication for use of a drug. Both of these tests are being used to study tolerance to beta2 agonists. There is increasing use of eucapnic voluntary hyperpnea as a surrogate bronchial provocation test for exercise to identify exercise-induced asthma, particularly in athletes. For methacholine and AMP there is concern about the different breathing patterns used to inhale these aerosols and the impact they have on the cutoff point for identifying bronchial hyperresponsiveness. A new test that uses a kit containing prepacked capsules of different doses of mannitol and a delivery device is discussed. There is increasing interest in using tests that act indirectly by release of mediators because the bronchial hyperresponsiveness itself is an indicator of the presence of inflammation. Since treatment of inflammation leads to loss of bronchial hyperresponsiveness to indirect stimuli, these tests are well suited to identify success of treatment.

Guidelines for Methacholine and Exercise Challenge Testing-1999.
Am J Respir Crit Care Med 2000;116:309-329.
This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999.

REVIEW:
Crapo et al.
Guidelines for Methacholine and Exercise Challenge Testing-1999.
Am J Respir Crit Care Med 2000;116:309-329.
This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999.

III. Pharmacology

A. Pharmacology and pharmacokinetics of drugs used in allergy/immunology

1. Glucocorticoids

REVIEW:

Hubner M. Hochhaus G. Derendorf H.

Comparative pharmacology, bioavailability, pharmacokinetics, and pharmacodynamics of inhaled glucocorticosteroids.

Immunol Allergy Clin North Am. 2005;25:469-88.

A comparison of the pharmacodynamics and pharmacokinetics of inhaled corticosteroids is necessary for their assessment. A good knowledge of these two aspects allows the optimization of efficacy and safety. The currently available inhaled corticosteroids already show some of the desired PK/PD parameters. The local adverse effects are decreased as soon as the inhaled corticosteroid is administered as an inactive prodrug or shows a better lung deposition. HFA-MDI beclomethasone dipropionate (BDP) and ciclesonide are two agents that illustrate this. Low oral bioavailability, rapid systemic clearance, and high plasma protein binding can minimize systemic adverse effects. Mometasone furoate, ciclesonide, and fluticasone propionate possess those characteristics. The pulmonary efficacy is maximized by high lung deposition and long pulmonary residence times. This effect can be achieved by slow dissolution in the lungs, as is the case for fluticasone propionate or lipid conjugation and has been shown for budesonide and ciclesonide. Furthermore, the lung deposition depends on the inhalation device, the particle size, and the inhalation technique. Therefore, improvement in the design of MDIs, DPIs, and nebulizers, and the development of more effective drug particles will lead to an optimized pulmonary targeting. Much progress has been made in the treatment of asthma. The available inhaled corticosteroids show a high safety profile and a good pulmonary selectivity. Development of newer compounds showed that improvement is possible as the result of a complete understanding of the PK/PD concepts. However, the introduction of further improved formulations with a better efficacy/safety profile will be difficult and protracted because the existing drugs are already highly efficient.

KEY INVESTIGATION:

Schuh, et al.

A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma.

N Engl J Med 2000;343:689-94

BACKGROUND: Inhaled corticosteroids are effective in the treatment of children with asthma. It is uncertain how inhaled corticosteroids compare with oral corticosteroids in the management of severe acute disease. METHODS: We performed a double-blind, randomized trial involving 100 children five years of age or older who had severe acute asthma (indicated by a forced expiratory volume in one second [FEV1] that was less than 60 percent of the predicted value) and in whom the results could be evaluated. All were treated with an aggressive bronchodilator regimen and received one dose of either 2 mg of inhaled fluticasone through a metered-dose inhaler with a spacer or 2 mg of oral prednisone per kilogram of body weight. They were assessed hourly for up to four hours. RESULTS: The mean (+/-SD) base-line FEV1 as a percentage of the predicted value

was 46.3+/-12.5 in the fluticasone group (51 subjects) and 43.9+/-9.9 in the prednisone group (49 subjects). The FEV1 increased by a mean of 9.4+/-12.5 percentage points in the fluticasone group and by 18.9+/-9.8 percentage points in the prednisone group four hours after therapy (P< 0.001). None of the children in the prednisone group had a reduction in FEV1 as a percentage of the predicted value from base line to four hours, as compared with 25 percent of those in the fluticasone group (P<0.001). Sixteen (31 percent) of the children treated with fluticasone were hospitalized, as compared with five (10 percent) of those treated with prednisone (P=0.01). CONCLUSIONS: Children with severe acute asthma should be treated with oral prednisone and not with inhaled fluticasone or a similar inhaled corticosteroid.

KEY INVESTIGATION –GROWTH:

Agertoft and Pedersen. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma.

N Engl J Med 2000;343:1064-9

BACKGROUND: Short-term studies have shown that inhaled corticosteroids may reduce the growth of children with asthma. However, the effect of long-term treatment on adult height is uncertain. METHODS: We conducted a prospective study in children with asthma to examine the effect of long-term treatment with inhaled budesonide on adult height. We report on 211 children who have attained adult height: 142 budesonide-treated children with asthma, 18 control patients with asthma who have never received inhaled corticosteroids, and 51 healthy siblings of patients in the budesonide group, who also served as controls. RESULTS: The children in the budesonide group attained adult height after a mean of 9.2 years of budesonide treatment (range, 3 to 13) at a mean daily dose of 412 microg (range, 110 to 877). The mean cumulative dose of budesonide was 1.35 g (range, 0.41 to 3.99). The mean differences between the measured and target adult heights were +0.3 cm (95 percent confidence interval, -0.6 to + 1.2) for the budesonide-treated children, -0.2 cm (95 percent confidence interval, -2.4 to +2.1) for the control children with asthma, and +0.9 cm (95 percent confidence interval, -0.4 to +2.2) for the healthy siblings. The adult height depended significantly (P<0.001) on the child's height before budesonide treatment. Although growth rates were significantly reduced during the first years of budesonide treatment, these changes in growth rate were not significantly associated with adult height. CONCLUSIONS: Children with asthma who have received long-term treatment with budesonide attain normal adult height.

REVIEW GROWTH:

Allen DB.

Inhaled steroids for children: effects on growth, bone, and adrenal function.

Endocrinol Metab Clin North Am.. 2005;34:555-64.

Inhaled corticosteroids are the first-line therapy for persistent asthma in children. Major safety concerns of long-term inhaled corticosteroid therapy include suppression of adrenal function and impaired growth and bone development. Proper interpretation of inhaled corticosteroid safety requires knowledge of differences among various drug devices. Dosage, type of inhaler device used, patient technique, and characteristics of the individual drug influence systemic effects of inhaled corticosteroids. Systemic side effects can occur when continuous high-dose treatment is required for severe asthma or when prescribed dosage is excessive and compliance is unusually good. Recent studies confirm that benefits of inhaled corticosteroids outweigh potential adverse effects and the risks associated with poorly controlled asthma.

KEY INVESTIGATION OSTEOPOROSIS:

Johannes CB et al.

The Risk of Nonvertebral Fracture Related to Inhaled Corticosteroid Exposure Among Adults With Chronic Respiratory Disease

Chest 2005; 127: 89 – 97.

OBJECTIVE: To examine nonvertebral fracture risk in relation to inhaled corticosteroid (ICS) exposure among adults with respiratory disease. DESIGN AND PATIENTS: Nested case-control study within a cohort of 89,877 UnitedHealthcare members aged ≥40 years with physician insurance claims for COPD or asthma, enrolled for ≥1 year from January 1, 1997 to June 30, 2001. METHODS: Cases (n = 1,722) represented patients with a first treated nonvertebral fracture (the index date is the first fracture claim). Control subjects (n = 17,220) were randomly selected from the person-time and assigned a random index date. ICS exposure was ascertained 1 month, 3 months, 6 months, and 12 months before the index date, with estimated cumulative dose through 0 to 6 months, 7 to 12 months, and 0 to 12 months. Covariates included demographics, oral corticosteroid and other medication exposure, comorbidities, and indicators of respiratory disease severity. Odds ratios (ORs) adjusted for all covariates were estimated by logistic regression. Results: No increased fracture risk with ICS exposure as a class or with fluticasone propionate alone was detected. ORs for exposure in the preceding 30 days were 1.05 (95% confidence interval [CI], 0.89 to 1.24), 1.13 (95% CI, 0.90 to 1.40), and 0.97 (95% CI, 0.78 to 1.21) for all ICS, fluticasone propionate, and other ICS, respectively. No dose-response effect was present. Among patients with COPD only (n = 6,932), no increased risk was found for recent ICS exposure (OR, 0.86; 95% CI, 0.59 to 1.25). CONCLUSIONS: Concern about nonvertebral fracture risk should not strongly influence the decision to use recommended doses of ICS for adult patients with asthma or COPD in managed-care settings in the United States. This study could not evaluate very-high ICS dose, long-term ICS exposure, or vertebral fracture risk.

REVIEW OSTEOPOROSIS:

Richy, F, Bousquet, J, Ehrlich, GE, et al

Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systematic review.

Osteoporos Int 2003;14,179-190

Deleterious effect of oral corticosteroids on bone has been well documented, whereas this remains debated for inhaled ones (ICS). Our objectives were to analyze the effects of ICS on bone mineral density, fracture risk and bone markers. We performed an exhaustive systematic research of all controlled trials potentially containing pertinent data, peer-reviewed by a dedicated WHO expert group, and comprehensive meta-analyses of the data. Inclusion criteria were ICS, and BMD/markers/fractures in asthma/chronic obstructive pulmonary diseases (COPD) and healthy patients. Analyses were performed in a conservative fashion using professional dedicated softwares and stratified by outcome, study design and ICS type. Results were expressed as standardized mean difference/effect size (ES), relative risk (RR) or odds ratio (OR), depending on study design and outcome units. Publication bias was investigated. Twenty-three trials were reviewed; 11 papers fit the inclusion criteria and were assessed for the main analysis. Quality scores for the randomized controlled trials (RCTs) were 80%, 71% for the prospective cohort studies, and 78% for the retrospective cohort and cross-sectional studies. We globally assessed ICS effects on BMD and found deleterious effects: ES=0.61 (p=0.001) for healthy subjects, and

ES=0.27 (p<0.001) for asthma/COPD patients. For these patients, this effect was 0.21 (p<0.01) at the lumbar spine, and 0.26 (p<0.001) at the hip or femoral neck. A single study evaluated the impact of ICS on hip fracture and reported an increased OR of 1.6 (1.24; 2.03). Lumbar fracture rate differences did not reach the level of statistical significance: 1.87 (0.5; 6.94). Osteocalcin and PICP were decreased and ICTP, pyridinoline and deoxypyridinoline levels were not significantly affected. Budesonide (BUD) appeared to be the ICS inducing the less deleterious effects on bone, followed by beclomethasone dipropionate (BDP) and triamcinolone (TRI). Publication bias investigation provided non-significant results. In our meta-analyses, BUD at a mean daily dose (SD) of 686 &mgr;g (158 &mgr;g), BDP at 703 &mgr;g (123 &mgr;g) and TRI at 1000 &mgr;g (282 &mgr;g) were found to affect bone mineral density and markers in patients suffering from the two major respiratory diseases. These findings could have practical implication in the long-term management of asthmatic and COPD patients.

REVIEW OSTEONECROSIS:

Powell C, Chang C, Naguwa SM, Cheema G, Gershwin ME. Steroid induced osteonecrosis: an analysis of steroid dosing risk. Autoimmun Rev 2010;9:721-43.

This review assessed case studies, retrospective studies and prospective studies in humans on different corticosteroids and varied dosages. Most cases of osteonecrosis are secondary to systemically administered corticosteroidsgh and/or high dose daily therapy, particularly in patients with underlying comorbidities including connective tissue diseases, hyperlipidemia, or previous trauma. Previous case reports of osteonecrosis related to inhaled or topical use of steroids are complicated by the fact that in the great majority of cases, the patients are also treated with systemic steroids prior to the development of osteonecrosis. Based on the literature, a set of recommendations regarding the risk of osteonecrosis in patients on steroids was formulated.

REVIEW OSTEONECROSIS MECHANISMS:

Kerachian MA, Seguin C, Harvey EJ. Glucosteroids in osteonecrosis of the femoral head: a new understanding of the mechanisms of action. J Steroid Biochem Mol Biol 2009;114:121-8.

Glucocorticoid (GC) usage is the most common non-traumatic cause of osteonecrosis of the femoral head (ON). Investigators have proposed both direct and indirect effects of GC on cells. Indirect and direct mechanisms remain intimately related and often result in positive feedback loops to potentiate the disease processes. However, the direct effects, in particular apoptosis, have recently been shown to be increasingly important. Suppression of osteoblast and osteoclast precursor production, increased apoptosis of osteoblasts and osteocytes, prolongation of the lifespan of osteoclasts and apoptosis of endothelial cells (EC) are all direct effects of GC usage. Elevated blood pressure through several pathways may raise the risk of clot formation. High-dose GC also decreases tissue plasminogen activator activity (t-PA) and increases plasma plasminogen activator inhibitor-1 (PAI-1) antigen levels increasing the procoagulant potential of GC. Inhibited angiogenesis, altered bone repair and nitric oxide metabolism can also result. Also, GC treatment modulates other vasoactive mediators such as endothelin-1, noradrenalin and bradykinin. Thus, GCs act as a regulator of local blood flow by modulating vascular responsiveness to vasoactive substances. Vasoconstriction induced in intraosseous femoral head arteries causes femoral head ischemia. GCs also cause ischemia through increased intraosseous pressure, which subsequently decreases the blood flow to the femoral head by apoptosis of ECs as well as elevating the level of adipogenesis and fat hypertrophy in the bone marrow. It is difficult to predict which patients receiving a specific dose of GC will develop ON, indicating individual differences in steroid

sensitivity and the potential of additional mechanisms. The textbook model of ON is a multiple hit theory in which, with a greater number of risk factors, the risk of ON increases.

REVIEW STEROID MECHANISMS AND RESISTANCE:
Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. J Steroid Biochem Mol Biol 2010;120:76-85.
Glucocorticoids suppress inflammation by several mechanisms. Glucocorticoids suppress the multiple inflammatory genes that are activated in chronic inflammatory diseases, such as asthma, by reversing histone acetylation of activated inflammatory genes through binding of liganded glucocorticoid receptors (GR) to coactivator molecules and recruitment of histone deacetylase-2 (HDAC2) to the activated transcription complex. At higher concentrations of glucocorticoids GR homodimers interact with DNA recognition sites to activate transcription through increased histone acetylation of anti-inflammatory genes and transcription of several genes linked to glucocorticoid side effects. Decreased glucocorticoid responsiveness is found in patients with severe asthma and asthmatics who smoke, as well as in all patients with COPD and cystic fibrosis. Several molecular mechanisms of glucocorticoid resistance have now been identified. HDAC2 is markedly reduced in activity and expression as a result of oxidative/nitrative stress so that inflammation becomes resistant to the anti-inflammatory actions of glucocorticoids. Dissociated glucocorticoids have been developed to reduce side effects but so far it has been difficult to dissociate anti-inflammatory effects from adverse effects. In patients with glucocorticoid resistance alternative anti-inflammatory treatments are being investigated as well as drugs that may reverse the molecular mechanism of glucocorticoid resistance.

REVIEW:
Marques AH, Silverman MN, Sternberg EM. Glucocorticoid dysregulations and their clinical correlates. From receptors to therapeutics. Ann N Y Acad Sci 2009;1179:1-18.
Clinicians have long known that a substantial proportion of patients treated with high-dose glucocorticoids experience a variety of serious side effects, including metabolic syndrome, bone loss, and mood shifts, such as depressive symptomatology, manic or hypomanic symptoms, and even suicide. Emerging literature is beginning to shed light on possible mechanisms of these effects. This paper reviews the basic biology of glucocorticoid release and molecular mechanisms of glucocorticoid receptor function, and discusses how dysregulation of glucocorticoid action at all levels could contribute to such side effects. A framework for assessment of patients is proposed that incorporates functional, physiological, and molecular biomarkers to identify subgroups of patients at risk for depressive symptomatology associated with glucocorticoid treatment, and for prevention of side effects, which in many cases can be life-threatening.

REVIEW:
Nicolaides NC, Galata Z, Kino T,Chrousos GP, Charmandari E. The human glucocorticoid receptor: molecular basis of biologic function. Steroids 2010;75:1-12.
This review summarizes the basic aspects of the structure and actions of the human glucocorticoid receptor and the molecular basis of its biologic functions.

REVIEW:
Black JL, Oliver BG, Roth M. Molecular mechanisms of combination therapy with inhaled corticosteroids and long-acting beta-agonists. Chest 2009;136:1095-1100.

Use of corticosteroids (CSs) and beta(2) agonists in combination delivered either separately or through one device has provided some clear and important clinical advantages. Beta(2)-Agonists can stimulate the glucocorticoid receptor (GR) and promote its translocation to the nucleus, resulting in increased CS-mediated gene transcription. In structural airway cells, such as fibroblasts and smooth muscle, this gene transcription is associated with the formation of a complex between the GR and another transcription factor, CCAAT enhancer-binding protein (C/EBP)-alpha. Airway smooth muscle cells from persons with asthma are deficient in C/EBP-alpha, which may explain the finding that CSs do not inhibit the proliferation of these cells in vitro. Whether this deficiency can explain the increased bulk of muscle in the asthmatic airway remains to be established. Beta(2)-agonists can inhibit mast cell mediator release, but this response is susceptible to attenuation, a process that CSs can inhibit. CSs also can increase the transcription of the beta(2)-receptor gene in the lung and the nasal mucosa. These effects of CSs mitigate against the reduced transcription of beta(2)-receptors, which occurs as a consequence of long-term beta(2)-agonist administration.

2. Beta-Agonists and Antagonists

KEY INVESTIGATION:

Wechsler M et al.

beta-Adrenergic receptor polymorphisms and response to salmeterol

Am J Respir Crit Care Med. 2006 Mar 1;173(5):519-26 .

RATIONALE: Several studies suggest that patients with asthma who are homozygous for arginine at the 16th position of the beta2-adrenergic receptor may not benefit from short-acting beta-agonists. OBJECTIVES: We investigated whether such genotype-specific effects occur when patients are treated with long-acting beta-agonists and whether such effects are modified by concurrent inhaled corticosteroid (ICS) use. METHODS: We compared salmeterol response in patients with asthma homozygous for arginine at B16 (B16Arg/Arg) with those homozygous for glycine at B16 (B16Gly/Gly) in two separate cohorts. In the first, subjects were randomized to regular therapy with salmeterol while simultaneously discontinuing ICS therapy. In the second, subjects were randomized to regular therapy with salmeterol while continuing concomitant ICS. RESULTS: In both trials, B16Arg/Arg subjects did not benefit compared with B16Gly/Gly subjects after salmeterol was initiated. In the first cohort, compared with placebo, the addition of salmeterol was associated with a 51.4 L/min lower A.M. peak expiratory flow (PEF; $p = 0.005$) in B16Arg/Arg subjects(salmeterol, $n = 12$; placebo, $n = 5$) as compared with B16Gly/Gly subjects (salmeterol, $n = 13$; placebo, $n = 13$). In the second cohort, B16Arg/Arg subjects treated with salmeterol and ICS concurrently ($n = 8$) had a lower A.M. PEF (36.8 L/min difference, $p = 0.048$) than B16Gly/Gly subjects ($n = 22$) treated with the same regimen. In addition, B16 Arg/Arg subjects in the second cohort had lower FEV1 (0.42 L, $p = 0.003$), increased symptom scores (0.2 units, $p = 0.034$), and increased albuterol rescue use (0.95 puffs/d, $p = 0.004$) compared with B16Gly/Gly subjects. CONCLUSIONS: Relative to B16Gly/Gly patients with asthma, B16Arg/Arg patients with asthma may have an impaired therapeutic response to salmeterol in either the absence or presence of concurrent ICS use. Investigation of alternate treatment strategies may benefit this group.

REVIEW:

Nelson HS.

Is there a problem with inhaled long-acting beta-adrenergic agonists?.

J Allergy Clin Immunol 2006;117(1):3-16.
Short-acting β2-agonists are effective in relieving acute symptoms of asthma and in the short-term prevention of symptoms from stimuli, such as exercise. They are ineffective when used on a regular schedule to improve asthma control. Long-acting β2-agonists, on the other hand, provide sustained bronchodilation and improve asthma control. Regular use of long-acting β2-agonists is not associated with significant tolerance to their bronchodilator action, impairment in the response to albuterol, decreased baseline pulmonary function, increased response to methacholine, or increased risk of adverse cardiac events. Case-control studies do not suggest an increased risk for death or intensive care unit admissions with use of long-acting β2-agonists. In prospective studies in which there has been an increase in asthma deaths or serious asthma exacerbations, this increased risk has not been observed in subjects using inhaled corticosteroids. Where increased deaths have occurred in relation to either short- or long-acting β2-agonists, the events have not occurred equally throughout the exposed population. This suggests that these outcomes were not a direct toxic effect of the drugs and increases the possibility that they resulted from an interaction between relief of symptoms by β2-agonists and delay in seeking medical care.

KEY INVESTIGATION:
Bleecker ER, Yancey SW, Baitinger LA, et al.
Salmeterol response is not affected by β2-adrenergic receptor genotype in subjects with persistent asthma
J Allerg Clin Immunol 2006;118:809-816
BACKGROUND: Recent studies suggest that there might be an association between albuterol use and worsening asthma in patients homozygous for arginine (Arg/Arg) at codon 16 of the β-receptor. However, it is not known whether similar responses occur in Arg/Arg patients receiving long-acting β2-agonists. OBJECTIVE: We sought to evaluate the effects of variation in the β2-adrenergic receptor gene (ADRB2) on clinical response to salmeterol administered with fluticasone propionate. METHODS: Subjects (n = 183) currently receiving short-acting β2-agonists were randomized to twice-daily therapy with salmeterol, 50 μg, administered with fluticasone propionate, 100 μg, in a single inhaler or daily therapy with montelukast for 12 weeks, followed by a 2- to 4-day run-out period. RESULTS: There was sustained and significant improvement ($P < .001$) over baseline in all measures of asthma control in subjects receiving salmeterol, regardless of Arg16Gly genotype. Morning peak expiratory flow in subjects with the Arg/Arg genotype showed 89.0 ± 16.1 L/min improvement over baseline compared with 93.7 ± 12.7 L/min for Gly/Gly subjects and 92.5 ± 11.9 L/min for Arg/Gly subjects. Pairwise changes were similar for Arg/Arg compared with Gly/Gly or Arg/Gly genotypes (estimated differences, 4.7 L/min and 3.5 L/min, respectively). Responses did not appear to be modified by haplotype pairs. During the run-out period, all subjects had predictable and similar decreases in measures of asthma control, with no differences between genotypes. CONCLUSION: Response to salmeterol does not vary between ADRB2 genotypes after chronic dosing with an inhaled corticosteroid.
Clinical implications: Analyses from this study indicate that genetic polymorphisms leading to Arg16Gly sequence changes within the β2-adrenergic receptor do not affect patients' responses to recommended asthma therapy with salmeterol and fluticasone propionate.

REVIEW:
Dickey BF, Walker JK, Hanania NA, Bond RA.
Beta-Adrenoceptor inverse agonists in asthma.

Curr Opin Pharmacol 2010;10:254-9.
Recent data suggest that certain beta-blockers, specifically beta-adrenoceptor (beta-AR) inverse agonists, may be useful in the chronic treatment of asthma. This article reviews the data and the signaling pathways that may be involved. Data suggest that beta(2)-AR signaling is required to produce maximal airway inflammation and hyperresponsiveness, and the signaling pathway responsible for these effects is likely the non-canonical beta-arrestin-2 pathway. Therefore, beta-AR inverse agonists may produce their beneficial chronic effects by inhibiting constitutive or ligand-induced activation of this pathway.

EVIDENCE-BASED REVIEW
Welsh EJ, Cates CJ.
Formoterol versus short-acting beta-agonists as relief medication for adults and children with asthma.
Cochrane Database Syst Rev 2010;(9):CD008418.
Two authors independently selected trials for inclusion in the review. Randomised, parallel-arm trials of at least 12 weeks duration in patients of any age and severity of asthma. Studies randomised patients to any dose of as-needed formoterol versus short-acting beta(2)-agonist. Concomitant use of inhaled corticosteroids or other maintenance medication was allowed, as long as this was not part of the randomised treatment regimen.This review includes eight studies conducted in 22,604 participants (mostly adults). Six studies compared formoterol as-needed to terbutaline whilst two studies compared formoterol with salbutamol as-needed. Background maintenance therapy varied across the trials. Asthma exacerbations and serious adverse events showed a direction of treatment effect favouring formoterol, of which one outcome reached statistical significance (exacerbations requiring a course of oral corticosteroids). In patients on short-acting beta(2)-agonists, 117 people out of 1000 had exacerbations requiring oral corticosteroids over 30 weeks, compared to 101 (95% CI 93 to 108) out of 1000 for patients on formoterol as-needed. In patients on maintenance inhaled corticosteroids there were also significantly fewer exacerbations requiring a course of oral corticosteroids on formoterol as-needed (Peto OR 0.75; 95% CI 0.62 to 0.91). There was one death per 1000 people on formoterol or on short-acting beta(2)-agonists. In summary, formoterol in adults was similar to short-acting beta(2)-agonists when used as a reliever, and showed a reduction in the number of exacerbations requiring a course of oral corticosteroids. Clinicians should weigh the relatively modest benefits of formoterol as-needed against the benefits of single inhaler therapy and the potential danger of long-term use of long-acting beta(2)-agonists in some patients. We did not find evidence to recommend changes to guidelines that suggest that long-acting beta(2)-agonists should be given only to patients already taking inhaled corticosteroids.There was insufficient information reported from children in the included trials to come to any conclusion on the safety or efficacy of formoterol as relief medication for children with asthma.

3. Mast Cell Active Agents (Cromolyn / Nedocromil)

EVIDENCE BASED REVIEW:
Guevara JP. Ducharme FM. Keren R, et al.
Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma.
Cochrane Database Syst Rev. 2006;19:CD003558.
BACKGROUND: Inhaled corticosteroids (ICS) and sodium cromoglycate (SCG) have become established as effective controller medications for children and adults with asthma, but their

relative efficacy is not clear. OBJECTIVES: To compare the relative effectiveness and adverse effects of ICS and SCG among children and adults with chronic asthma. SEARCH STRATEGY: Systematic search of the Cochrane Airways Group's special register of controlled trials (to Feb. 2004), hand searches of the reference lists of included trials and relevant review papers, and written requests for identification of additional trials from pharmaceutical manufacturers. SELECTION CRITERIA: Randomized controlled trials comparing the effect of ICS with SCG in children and adults with chronic asthma. DATA COLLECTION AND ANALYSIS: All studies were assessed independently for eligibility by three review authors. Disagreements were settled by consensus. Trial authors were contacted to supply missing data or to verify methods. Eligible studies were abstracted and fixed- and random-effects models were implemented to pool studies. Separate analyses were conducted for paediatric and adult studies. Subgroup analyses and meta-regression models were fit to explore heterogeneity of lung function outcomes by type of RCT, category of ICS or SCG dosage, asthma severity of participants, and study quality on outcomes. MAIN RESULTS: Of 67 identified studies, 17 trials involving 1279 children and eight trials involving 321 adults with asthma were eligible. Thirteen (76%) of the paediatric studies and six (75%) of the adult studies were judged to be high quality. Among children, ICS were associated with a higher final mean forced expiratory volume in 1 second [FEV1] (weighted mean difference [WMD] 0.07 litres, 95% confidence interval [CI] 0.02 to 0.11) and higher mean final peak expiratory flow rate [PEF] (WMD 17.3 litres/minute, 95% CI 11.3 to 23.3) than SCG. In addition, ICS were associated with fewer exacerbations (WMD -1.18 exacerbations per year, 95% CI -2.15 to - 0.21), lower asthma symptom scores, and less rescue bronchodilator use than SCG. There were no group differences in the proportion of children with adverse effects. Among adults, ICS were similarly associated with a higher mean final FEV1 (WMD 0.21 litres, 95% CI 0.13 to 0.28) and a higher final endpoint PEF (WMD 28.2 litres/minute, 95% CI 18.7 to 37.6) than SCG. ICS were also associated with fewer exacerbations (WMD -3.30 exacerbations per year, 95% CI -5.62 to -0.98), lower asthma symptom scores among cross-over trials but not parallel trials, and less rescue bronchodilator use than SCG. There were no differences in the proportion of adults with adverse effects. In subgroup analyses involving lung function measures, paediatric and adult studies judged to be of high quality had results consistent with the overall results. Lung function measures in children were higher in studies with medium BDP-equivalent steroid dosages than low BDP-equivalent dosages, while adult studies could not be compared by steroid dosage since they all incorporated similar dosages. There were no significant differences in lung function by the asthma severity of participants for adult or child studies. AUTHORS' CONCLUSIONS: ICS were superior to SCG on measures of lung function and asthma control for both adults and children with chronic asthma. There were few studies reporting on quality of life and health care utilization, which limited our ability to adequately evaluate the relative effects of these medications on a broader range of outcomes. Although there were no differences in adverse effects between ICS and SCG, most trials were short and may not have been of sufficient duration to identify long-term effects. Our results support recent consensus statements in the U.S. and elsewhere that favour the use of ICS over SCG for control of persistent asthma.

EVIDENCE-BASED REVIEW:
Sridhar AV, McKean M.
Nedocromil sodium for chronic asthma in children. Cochrane Database Syst Rev 2006;3:CD004108.

Two authors independently assessed trial quality and extracted data of randomized placebo controlled trials comparing nedocromil sodium to placebo in the treatment of chronic asthma in children (0-18 years). Fifteen trials (twelve parallel group studies; three crossover trials recruiting 1422 children (837 males and 585 females)) were included. The studies were generally of good methodological quality. Two large long term studies used nedocromil for six months and four to six years and showed conflicting results in symptom free days. Short term studies (duration between 4 weeks to 12 weeks) showed that nedocromil sodium produced some improvement in a number of efficacy measures compared to placebo including FEV(1), FVC, FEV(1) % predicted, PC20 FEV(1), evening PEF and symptom scores. The parent's assessment of efficacy was in favour of nedocromil (odds ratio (OR) 0.5 (95% CI 0.3 to 0.8). Nedocromil sodium has a good safety profile. The only significant side effect observed was unpleasant taste. There was little evidence for a clinically dose response effect and only a few studies recruited participants with severe asthma. In summary, a limited number of small studies have shown that nedocromil is of benefit in improving lung function and some measures of symptoms, but the evidence with regard to the primary outcome of the review was conflicting. Two long-term trials did not show consistent effects on lung function outcomes, whereas several small short-term trials have shown benefit in these outcomes. Differing severities at baseline may explain this difference with milder participants experiencing less benefit, although the discrepancy between study findings may also reflect publication bias. Nedocromil sodium is associated with a very good safety profile with no significant short term or long- term adverse side effects. Although nedocromil may have advantages over inhaled corticosteroids in terms of side effects, there is a need for head to head trials of nedocromil and inhaled corticosteroids to establish whether asthma control is similar, especially in mild asthma.

4. Cyclooxygenase and Leukotriene Pathway Modulators

SURVEY REPORT:

Barnes N, Thomas M, Price D, et al.

The national montelukast survey.

J Allergy Clin Immunol 2005; 115:47-54

BACKGROUND: Randomized controlled trials have demonstrated the efficacy of montelukast for treating asthma; whether this can be extrapolated to clinical effectiveness in routine practice has yet to be established. OBJECTIVE: To examine the use, effectiveness, and tolerability of montelukast in clinical practice for treating asthma and to explore prognostic factors that could predict a favorable response to the drug. METHODS: This was a retrospective, cross-sectional, observational study of clinical outcomes seen in patients prescribed montelukast for asthma that used routinely collected clinical information. Data were collected on all consenting patients who had been prescribed montelukast for asthma irrespective of the continuation or duration of treatment. Independent observers, treating physicians, and patients assessed certain outcomes after the initiation of montelukast, including the general asthma response and changes in activity-related symptoms. RESULTS: Fifty-six centers in the United Kingdom (20 primary care and 36 secondary care) participated. The analysis was based on 1351 eligible patients for whom essential data were available. Eight hundred thirty patients (66.4%; 95% CI, 63.8% to 69.0%) were recorded as having shown an improvement in their asthma control, and 103 (8.2%; 95% CI, 6.8% to 9.9%) experienced a dramatic improvement. The greatest proportion of patients responding was seen in those with mild to moderate asthma. Montelukast was well tolerated; no new adverse events were recorded. CONCLUSIONS: Montelukast is an effective, well-tolerated treatment for asthma in

routine practice. The overall response rate and tolerability seen in this survey are similar to those reported in randomized clinical trials.

EVIDENCE BASED REVIEW:
Currie GP. Lee DK. Srivastava P.
Long-acting bronchodilator or leukotriene modifier as add-on therapy to inhaled corticosteroids in persistent asthma?.
Chest 2005;128:2954-62.
Despite the widespread use of inhaled corticosteroids, many asthmatic patients experience persistent symptoms. In such individuals, the addition of a long-acting beta2-agonist (LABA) is frequently more effective than doubling the dose of inhaled corticosteroid. However, the role of additional therapy with a leukotriene receptor antagonist (LTRA) as an alternative to an LABA has been the focus of attention in recent studies. In order to determine the overall efficacy of the pharmacologic armamentarium used in asthma, it is imperative that a combination of end points, including lung function, airway hyperresponsiveness, effects on underlying inflammation, symptoms, and more long-term sequelae such as exacerbations, are assessed. This evidence-based systematic review outlines the pharmacologic properties of LABAs and LTRAs and the importance of evaluating end points in addition to lung function when assessing these drugs. We also highlight the results of all published studies that have performed direct comparisons of both LABAs and LTRAs as add-on therapy to inhaled corticosteroids.

REVIEW:
Scadding GW, Scadding GK. Recent advances in antileukotriene therapy. Curr Opin Allergy Clin Immunol 2010;10:370-6.
This review discusses recent advances concerning the molecular mechanisms of antileukotrienes as well as their efficacy in various clinical scenarios and patient groups.

REVIEW:
Duroudier NP, Tulah AS, Sayers I.
Leukotriene pathway genetics and pharmacogenetics in allergy.
Allergy 2009;64:823-39.
Cysteinyl leukotrienes (LTC(4), LTD(4) and, LTE(4)) and the dihydroxy leukotriene LTB(4) are generated by a series of enzymes/proteins constituting the LT synthetic pathway or 5-lipoxygenase (5-LO) pathway. Their function is mediated by interacting with multiple receptors. Leukotriene receptor antagonists (LTRA) and LT synthesis inhibitors (LTSI) have shown clinical efficacy in asthma and more recently in allergic rhinitis. Despite growing knowledge of leukotriene biology, the molecular regulation of these inflammatory mediators remains to be fully understood. Genes encoding enzymes of the 5-LO pathway (i.e. ALOX5, LTC4S and LTA4H) and encoding for LT receptors (CYSLTR1/2 and LTB4R1/2) provide excellent candidates for disease susceptibility and severity; however, their role remains unclear. Preliminary data also suggest that 5-LO pathway/receptor gene polymorphism can predict patient responses to LTSI and LTRA; however, the exact mechanisms require elucidation. The aim of this review was to summarize the recent advances in the knowledge of these important mediators, focusing on genetic and pharmacogenetic aspects in the context of allergic phenotypes.

REVIEW:

Schuligoi R, Sturm E, Luschnig P, et al.
CRTH2 and D-type prostanoid receptor antagonists as novel therapeutic agents for inflammatory diseases.
Pharmacology 2010;85:372-82.
Prostaglandin (PG)D(2) is generated by activated mast cells after allergen exposure and subsequently orchestrates the recruitment of inflammatory cells to the tissue. PGD(2) induces the chemotaxis of Th2 cells, basophils and eosinophils, stimulates cytokine release from these cells and prolongs their survival, and might hence indirectly promote IgE production. PGD(2) mediates its biologic functions via 2 distinct G protein-coupled receptors, D-type prostanoid receptor (DP), and the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). DP and CRTH2 receptors are currently being considered as highly promising therapeutic targets for combating allergic diseases and asthma.

REVIEW:
Spina D.
PDE4 inhibitors: current status.
Br J Pharmacol 2008;155:305-15.
The rationale for the development of phosphodiesterase-4 (PDE4) inhibitors stems from an understanding of the role of PDE4 in suppressing the function of a range of inflammatory and resident cells thought to contribute toward the pathogenesis of respiratory diseases such as asthma and chronic obstructive pulmonary disease. Similarly, numerous preclinical in vivo studies have shown that PDE4 inhibitors suppress characteristic features of these diseases, namely, cell recruitment, activation of inflammatory cells and physiological changes in lung function in response to a range of insults to the airways. These potentially beneficial actions of PDE4 inhibitors have been successfully translated in phase II and III clinical trials with roflumilast and cilomilast. However, dose limiting side effects of nausea, diarrhoea and headache have tempered the enthusiasm of this drug class for the treatment of these respiratory diseases. Strategies are being pursued in attempts to improve efficacy and reduce side effects.

5. Anticholinergics

EVIDENCE BASED REVIEW:
Rodrigo GJ. Rodrigo C.
The role of anticholinergics in acute asthma treatment: an evidence-based evaluation.
Chest 2002;121:1977-87.
The role for anticholinergic medications in acute asthma is not well-defined. Thus, the use of therapy with anticholinergics and beta(2)-agonists, either simultaneously or in sequence, has produced positive as well as negative results in trials. Therefore, the current recommendations for the use of these drugs in the emergency department (ED) and hospital management of asthma exacerbations are not precise. This review answers the following question: what level of evidence is available in the literature to support the use of anticholinergic medications in combination with beta(2)-agonists in acute asthma patients? We limited the search on our therapy question to systematic reviews of randomized trials and/or randomized controlled trials not included in the reviews. After an extensive review of the most relevant evidence, the following conclusions may be emphasized. (1) The use of multiple doses of ipratropium bromide are indicated in the ED treatment of children and adults with severe acute asthma. The studies reported a substantial reduction in hospital admissions (30 to 60%; number needed to treat, 5 to 11) and significant

differences in lung function favoring the combined treatment. No apparent increase in the occurrence of side effects was observed. (2) The use of single-dose protocols of ipratropium bromide with beta(2)-agonist treatment produced, particularly in children with more severe acute asthma, a modest improvement in pulmonary function without reduction in hospital admissions; in adults, the data showed a similar increase in pulmonary function with an approximately 35% reduction in the hospital admission rate. In patients with mild-to-moderate acute asthma, there is no apparent benefit from adding a single dose of an anticholinergic medication.

KEY INVESTIGATION:
Peters SP, Kunselman SJ, Icitovic N, Moore WC, et al.
Tiotropium bromide step-up therapy for adults with uncontrolled asthma.
N Engl J Med 2010;363:1715-26.
In a three-way, double-blind, triple-dummy crossover trial involving 210 patients with asthma, the authors evaluated the addition of tiotropium bromide (a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease but not asthma) to an inhaled glucocorticoid, as compared with a doubling of the dose of the inhaled glucocorticoid (primary superiority comparison) or the addition of the LABA salmeterol (secondary noninferiority comparison). The use of tiotropium resulted in a superior primary outcome, as compared with a doubling of the dose of an inhaled glucocorticoid, as assessed by measuring the morning peak expiratory flow (PEF), with a mean difference of 25.8 liters per minute ($P<0.001$) and superiority in most secondary outcomes, including evening PEF, with a difference of 35.3 liters per minute ($P<0.001$); the proportion of asthma-control days, with a difference of 0.079 ($P=0.01$); the forced expiratory volume in 1 second (FEV1) before bronchodilation, with a difference of 0.10 liters ($P=0.004$); and daily symptom scores, with a difference of -0.11 points ($P<0.001$). The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and increased the prebronchodilator FEV1 more than did salmeterol, with a difference of 0.11 liters ($P=0.003$). In summary, tiotropium added to an inhaled glucocorticoid improved symptoms and lung function in patients with inadequately controlled asthma. Its effects appeared to be equivalent to those with the addition of salmeterol.

6. Theophylline

REVIEW:
Barnes PJ.
Theophylline: new perspectives for an old drug.
Am J Respir Crit Care Med. 2003;167:813-8.
Theophylline has been used in the treatment of asthma and chronic obstructive pulmonary disease (COPD) for over 60 years and remains one of the most widely prescribed drugs for the treatment of airway diseases worldwide as it is inexpensive. In many industrialized countries, however, theophylline has recently become a third-line treatment that is only used in some poorly controlled patients. This has been reinforced by various guidelines to therapy. It has even been suggested that theophylline is not indicated in any patients with asthma. The frequency of side effects and the relatively low efficacy of theophylline have recently led to reduced usage because inhaled $ß_2$-agonists are far more effective as bronchodilators and inhaled corticosteroids have a greater anti-inflammatory effect. Despite the long history of theophylline in asthma therapy, there has been considerable uncertainty about its mode of action in the management of airway diseases and its logical place in therapy. Because of problems with side effects, there have been attempts to

improve on theophylline, and recently there has been increasing interest in the development of selective phosphodiesterase (PDE) inhibitor. Selective PDE4 inhibitors have the possibility of improving the beneficial and reducing the adverse effects of theophylline, although existing inhibitors appear to be limited by the same side effects as theophylline.

INVESTIGATION:
Yasui K, Kondo Y, Wada T, et al.
Theophylline inhibits the differentiation of human monocyte into dendritc cell potentially via adenosine receptor antagonism.
Clin Exp Allergy 2009;39:1857-65.
The purpose of this study was to investigate the effects of theophylline on human monocyte differentiation into DCs and whether this involved antagonism of adenosine receptors. Peripheral human blood monocytes were cultured in the presence of granulocyte/macrophage-colony stimulating factor and IL-4 to induce DC differentiation. The cells were incubated with theophylline, KF17837 (a selective A2a receptor antagonist) and enprofylline (A2b receptor antagonist) and co-incubated with selective adenosine A1 and A2a receptor agonists, a phosphodiesterase inhibitor (rolipram) and adenosine deaminase (ADA) to determine their effects on DC differentiation. In addition, depletion of adenosine receptors by small interfering RNA (siRNA) was also examined.Monocytes differentiated into myeloid DCs in the culture system. The number of DCs was reduced by 60-70% when theophylline was administered at a therapeutic concentration. This effect was concentration-dependently exacerbated, was partly mediated by cellular apoptosis and was effectively reversed by the addition of the A1 agonists [2-chloro-N(6)-cyclopentyladenosin, N(6)-cyclohexyladenosine, and N-ethylcarboxamidoadenosine (NECA)] or the A2a agonist (CGS-21680, NECA). The depletion of the adenosine A1 receptor by siRNA and addition of ADA remarkably reduced DC differentiation. Meanwhile, both enprofylline and rolipram had little effect.The authors suggest that the adenosine A1 (and possibly coordinated with A2a) receptors contribute to DC differentiation and survival.

7. Antihistamines

REVIEW:
Criado PR, Criado RF, Maruta CW, Machado Filho C.
Histamine, histamine receptors and antihistamines: new concepts.
An Bras Dermatol. 2010 Apr;85(2):195-210.
Drugs with antihistamine action are the most commonly prescribed medication in daily dermatologic practice, both to adults and children. This article addresses new concepts of the role of histamine receptors (H1 receptors) and discusses the anti-inflammatory effects of these drugs. Second generation antihistamines differs from first generation because of their high specificity and affinity for peripheral H1-receptors. Second generation antihistamines are also less likely to produce sedation because they have less effect on the central nervous system. Although the efficacy of the various H1-antihistamines in the treatment of allergic patients is similar, even when comparing first- and second-generation drugs, these drugs are still very different in terms of their chemical structure, pharmacology and toxic properties. Consequently, knowledge of their pharmacokinetic and pharmacodynamic characteristics is essential for a better medical care, especially that offered to pregnant women, children, the elderly, and patients with comorbidities.

REVIEW:

Simons FE.
Advances in H1 – Antihistamines.
N Engl J Med 2004 November: 351: 21: 2203-2217.
More than 30,000 peer-reviewed articles on histamine and the H1-antihistamines have been publishedsince this subject was last reviewed in the *Journal* a decade ago. The role of histamine in neurotransmission, allergic inflammation, and immune modulation has been further elucidated sincethat time. The human H1-histamine and H2-histamine receptors were cloned and characterized in the early 1990s, as were the human H3-histamine and H4-histamine receptors several years ago. H1-antihistamines, historically known as histamine H1-receptor blockers or antagonists, are specific for the H1-receptor. In addition, some H1-antihistamines inhibit transmission through the muscarinic, - adrenergic, and serotonin receptors and through ion channels. The H1-antihistamines have recently been reclassified as inverse agonists, rather than as H1-receptor antagonists, which is consonant with an increased understanding of their molecular pharmacologic features. More than 40 H1-antihistamines are available worldwide — indeed, these agents are among the most widely used of all medications. The H1-antihistamines astemizole and terfenadine, which are associated with cardiac toxic effects, are no longer approved for use. New H1-antihistamines have been developed and introduced. Both health care professionals and consumers generally assume that all approved H1-antihistamines have been shown to be efficacious and safe, but many medications in this class, in particular those introduced before 1985, have not been optimally studied in randomized, double-blind, controlled trials. This discussion of the differences in the clinical pharmacology and the similarities in efficacy and safety of the H1-antihistamines is based on a review of the literature published since 1994.

REVIEW:
O'Donoghue M, Tharp MD.
Antihistamines and their role as antipruritics.
Dermatology Therapy. Vol 18, 2005: 333-340.
Antihistamines that bind to the histamine 1 receptor (H1) serve as important therapeutic agents to counter the effects of histamine in the skin. Two generations of antihistamines exist: however, second generation agents are more advantageous because they cause less sedation, have a longer life and are more selective for the H1 receptor. While H1 antihistamines have proven to be effective at reversing the pruritus and cutaneous lesions of chronic urticaria, their ability to treat pruritus associated with other cutaneous and systemic disease is unproven.

REVIEW:
Akdis CA, Simons FER.
Histamine receptors are hot in immunopharmacology.
Eur J of Pharmacology 533 (2006): 69-76.
In addition to its well-characterized effects in the acute allergic inflammatory responses, histamine has been demonstrated to affect chronic inflammation and regulate several essential events in the immune response. Histamine can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization, and other functions leading to chronic inflammation. Histamine also regulates dendritic cells, T cells and B cells, as well as related antibody isotype responses. In addition, acting through its receptor 2, histamine positively interferes with the peripheral antigen tolerance induced by T regulatory cells in several pathways. The diverse effects of histamine on immune regulation appear to be due to differential expression

and regulation of 4 types of histamine receptors and their distinct intracellular signals. In addition, differences in affinities of these receptorsfor histamine is highly decisive for the biological effects of histamine and drugs that target histamine receptors. This article highlights recent discoveries in histamine immunobiology and discusses their relevance in allergic inflammation.

8. Immunosuppressive Agents

REVIEW:
Kazlow Stern D, Tripp JM, Ho VC, Lebwohl M.
The use of Systemic Immune Moderators in Dermatology: An Update.
Dermatology Clinics 2005; 23(2): 259-300
In addition to corticosteroids, dermatologists have access to an array of immunomodulatory therapies. Azathioprine, cyclophosphamide, methotrexate, cyclosporine, and mycophenolate mofetil are the systemic immunosuppressive agents most commonly used by dermatologists. In addition, new developments in biotechnology have spurred the development of immunobiologic agents that are able to target the immunologic process of many inflammatory disorders at specific points along the inflammatory cascade. Alefacept, efalizumab, etanercept, and infliximab are the immunobiologic agents that are currently the most well known and most commonly used by dermatologists. This article reviews the pharmacology, mechanism of action, side effects, and clinical applications of these therapies.

REVIEW sirolimus:
Bond Stenton S, Partovi N, Ensom HH.
Sirolimus, The Evidence for Clinical Pharmacokinetic Monitoring.
Clin Pharmacokinet 2005; 44(8): 769-786.
This review seeks to apply a decision-making algorithm to establish whether clinical pharmacokinetic monitoring (CPM) of sirolimus (rapamycin) in solid organ transplantation is indicated in specific patient populations. The need for CPM of sirolimus, although a regulatory requirement in Europe, has not yet been firmly established in North America and other parts of the world.Sirolimus has demonstrated immunosuppressive efficacy in renal, pancreatic islet cell, liver and heart transplant recipients. The pharmacological response of immunosuppressive therapy with sirolimus cannot be readily evaluated; however, a relationship between trough blood sirolimus concentrations, area under the plasma concentration-time curve (AUC) and the incidence of rejection has been proposed. Furthermore, sirolimus can be measured in whole blood by several assays--high-performance liquid chromatography with detection by tandem mass spectrometry, or with ultraviolet detection, radioreceptor assay or microparticle enzyme immunoassay. Both experimental animal and clinical data suggest that adverse events and their associated severity are correlated with blood concentrations. To prevent rejection and minimise toxicity, a therapeutic range of 4-12 microg/L (measured via chromatographic assays) is recommended when sirolimus is used in conjunction with ciclosporin. If ciclosporin therapy is discontinued, a target trough range of 12-20 microg/L is recommended. Sirolimus pharmacokinetics display large inter- and intrapatient variability, which may change in specific patient populations due to disease states or concurrent immunosuppressants or other interacting drugs. Due to the long half-life of sirolimus, dosage adjustments would ideally be based on trough levels obtained more than 5-7 days after initiation of therapy or dosage change. Once the initial dose titration is complete, monitoring sirolimus trough concentrations weekly for the first month and every 2 weeks for the second month appears to be appropriate. After the first 2 months of dose titration, routine CPM of

sirolimus is not necessary in all patients, but may be warranted to achieve target concentrations in certain populations of patients, but the frequency of further monitoring remains to be determined and should be individualized.

9. Immunomodulatory medications

REVIEW:
Liossis SNC, Tsokos GC.
Monoclonal antibodies and fusion proteins in medicine
J Allergy Clin Immunol 2005; 116(4): 721-729
Humanized antibodies and decoy receptors have been introduced in clinical practice to treat malignancies and systemic autoimmune disease because they ablate specific cells or disrupt pathogenic processes at distinct points. Reported clinical responses offer hope to treatment-resistant patients, particularly those with lymphomas and rheumatic diseases. Side effects from the use of biologic agents include lymphokine release syndrome, reactivation of tuberculosis, and immunosuppression. Further insights are needed regarding limitation of adverse effects, correct use in conjunction with existing drugs, and treatment of patients in whom resistance develops.

REVIEW omalizumab:
Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y,Reisner C.
The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation
J Allergy Clin Immunol 2005; 115(3):459-465.
Anti-IgE therapy with omalizumab reduces serum levels of free IgE and downregulates expression of IgE receptors (FcεRI) on mast cells and basophils. In the airways of patients with mild allergic asthma, omalizumab reduces FcεRI+ and IgE+ cells and causes a profound reduction in tissue eosinophilia, together with reductions in submucosal T-cell and B-cell numbers. In patients with seasonal allergic rhinitis, omalizumab inhibits the allergen-induced seasonal increases in circulating and tissue eosinophils. Omalizumab decreases FcεRI expression on circulating dendritic cells, which might lead to a reduction in allergen presentation, TH2 cell activation, and proliferation. As a systemic anti-IgE agent, omalizumab has demonstrated clinical efficacy in patients with moderate and severe allergic asthma and in those with seasonal and perennial allergic rhinitis, as well as in patients with concomitant allergic asthma and allergic rhinitis. The anti-inflammatory effects of omalizumab at different sites of allergic inflammation and the clinical benefits of anti-IgE therapy in patients with allergic asthma and allergic rhinitis emphasize the fundamental importance of IgE in allergicinflammation.

REVIEW:
Yamagata T, Ichinose M.
Agents against cytokine synthesis or receptors.
Eur J Pharmacol 2006; 533(1-3): 289-301
Various cytokines play a critical role in pathophysiology of chronic inflammatory lung diseases including asthma and chronic obstructive pulmonary disease (COPD). The increasing evidence of the involvement of these cytokines in the development of airway inflammation raises the possibility that these cytokines may become the novel promising therapeutic targets. Studies concerning the inhibition of interleukin (IL)-4 have been discontinued despite promising early

results in asthma. Although blocking antibody against IL-5 markedly reduces the infiltration of eosinophils in peripheral blood and airway, it does not seem to be effective in symptomatic asthma, while blocking IL-13 might be more effective. On the contrary, anti-inflammatory cytokines themselves such as IL-10, IL-12, IL-18, IL-23 and interferon-gamma may have a therapeutic potential. Inhibition of TNF-alpha may also be useful in severe asthma or COPD. Many chemokines are also involved in the inflammatory response of asthmaand COPD through the recruitment of inflammatory cells. Several small molecule inhibitors of chemokine receptors are now in development for the treatment of asthma and COPD. Antibodies that block IL-8 reduce neutrophilic inflammation. Chemokine CC3 receptor antagonists, which block eosinophil chemotaxis, are now in clinical development for asthma therapy. As many cytokines areinvolved in the pathophysiology of inflammatory lung diseases, inhibitory agents of the synthesis of multiple cytokines may be more useful tools. Several such agents are now in clinical development.

RESEARCH FRONTIER:
Corry DB, Kheradmand F.
Control of allergic airway inflammation through immunomodulation.
J Allergy Clin Immunol 2006; 117(2): S487-S464
Among the asthma clinical trials published over the last several years, a unique subset has focused on novel means for inhibiting the airway inflammation that is believed to cause airway obstruction in many patients. Such interventions, broadly considered here as immune-modifying or immunomodulatory therapies, include several new drugs omalizumab, suplatast tosilate, anti-cytokine antibodies, soluble receptors, and recombinant cytokines and bacterial extracts. In this chapter we review the major findings with these clinical trials and indicate which have changed the management of asthma, which have not, and those that deserve further study.

10. Agents and principles of aerosolized respiratory treatments

REVIEW:
Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, Smaldone GC, Guyatt G
Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Asthma, Allergy, and Immunology
Chest 2005; 127(1): 335-71
BACKGROUND: The proliferation of inhaler devices has resulted in a confusing number of choices for clinicians who are selecting a delivery device for aerosol therapy. There are advantages and disadvantages associated with each device category. Evidence-based guidelines for the selection of the appropriate aerosol delivery device in specific clinical settings are needed. AIM: (1) To compare the efficacy and adverse effects of treatment using nebulizers vs pressurized metered-dose inhalers (MDIs) with or without a spacer/holding chamber vs dry powder inhalers (DPIs) as delivery systems for betaagonists, anticholinergic agents, and corticosteroids for several commonly encountered clinical settings and patient populations, and (2) to provide recommendations to clinicians to aid them in selecting a particular aerosol delivery device for their patients. METHODS: A systematic review of pertinent randomized, controlled clinical trials (RCTs) was undertaken using MEDLINE, EmBase, and the Cochrane Library databases. A broad search strategy was chosen, combining terms related to aerosol devices or drugs with the diseases of interest in various patient groups and clinical settings. Only RCTs in which the same drug was

administered with different devices were included. RCTs (394 trials) assessing inhaled corticosteroid, beta2-agonist, and anticholinergic agents delivered by an MDI, an MDI with a spacer/holding chamber, a nebulizer, or a DPI were identified for the years 1982 to 2001. A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested beta2-agonists) proved to have useable data. RESULTS: None of the pooled metaanalyses showed a significant difference between devices in any efficacy outcome in any patient group for each of the clinical settings that was investigated. The adverse effects that were reported were minimal and were related to the increased drug dose that was delivered. Each of the delivery devices provided similar outcomes in patients using the correct technique for inhalation. CONCLUSIONS: Devices used for the delivery of bronchodilators and steroids can be equally efficacious. When selecting an aerosol delivery device for patients with asthma and COPD, the following should be considered: device/drug availability; clinical setting; patient age and the ability to use the selected device correctly; device use with multiple medications; cost and reimbursement; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference.

REVIEW Inhaled Corticosteroids:
Allen DB, Bielory L, Derendorf H, Dluhy R, Colice GL, Szefler SJ
Inhaled Corticosteroids: Past Lessons and Future Issues
J Allergy Clin Immunol 2006; 112(3): S1-140
Inhaled corticosteroids play a pivotal role in the treatment of asthma. Inhalation permits effective delivery of the corticosteroid in high concentration to target sites within the lung while minimizing systemic exposure. Consequently, the safety profile of inhaled corticosteroids is markedly better thanthat of oral corticosteroid therapy. However, although it was first thought that direct delivery mighteliminate systemic adverse effects, this has not been confirmed by clinical trials and experience. Inhaled corticosteroids are absorbed from the lungs into the systemic circulation, in which they can acutely decrease growth velocity in children, an effect that fortunately appears to be temporary and might have no effect on final adult height. In sufficient dosages, they also produce bone mineral loss leading to osteoporosis and might increase the risk of cataracts, glaucoma, skin atrophy, and vascular changes that increase the risk of ecchymoses. Effective evaluation of the severity and significance of these complications is challenging because highly sensitive tests do not reliably predict clinically significant events, and short-term observations do not predict long-term consequences. Also, compliance wanes with long-term treatment, and susceptibility to a particular adverse event can vary over time, even in the same individual, because of developmental or hormonal changes. This journal supplement will review what has been learned about the safety of inhaled cortico-steroids during the past decade, discussing some of the questions that remain and considering the characteristics of an "ideal" inhaled corticosteroid: one with high local activity in the lung and minimal or no adverse systemic effects.

11. Topical Dermatologic and Ophthalmologic Therapy

a. dermatologic

REVIEW topical calcineurin inhibitors:
Hultsch T, Kapp A, Spergel J.
Immunomodulation and Safety of Topical Calcineurin Inhibitors for the treatment of Atopic Dermatitis.

Dermatology 2005; 211: 174-187.
Atopic dermatitis (AD) is a chronic or chronically relapsing inflammatory skin condition that primarily affects children. Topical corticosteroids have been the mainstay of treatment since the late 1950s. While providing excellent short-term efficacy, topical corticosteroid usage is limited by potential adverse effects, including impairment of the function and viability of Langerhans cells/dendritic cells. The recently introduced topical calcineurin inhibitors pimecrolimus cream 1% (Elidel) and tacrolimus ointment 0.03 and 0.1% (Protopic) exhibit a more selective mechanism of action and do not affect Langerhans cells/dendritic cells. For the immune system of young children 'learning' to mount a balanced Th1/Th2 response, this selective effect has particular benefits. In clinical experience, topical calcineurin inhibitors have been shown to be a safe and effective alternative to topical corticosteroids in almost 7 million patients (>5 million on pimecrolimus; >1.7 million on tacrolimus). Topical pimecrolimus is primarily used in children with mild and moderate AD, whereas tacrolimus is used preferentially in more severe cases. None of the topical calcineurin inhibitors have been associated with systemic immunosuppression-related malignancies known to occur following long-term sustained systemic immunosuppression with oral immunosuppressants (e.g., tacrolimus, cyclosporine A, and corticosteroids) in transplant patients. Preclinical and clinical data suggest a greater skin selectivity and larger safety margin for topical pimecrolimus.

SAFETY REPORT calcineurin inhibitors:
Berger TG, Duvic M, Van Voorhees AS, Frieden IJ
The use of topical calcineurin inhibitors in dematology:Safety concerns
Report of the American Academy of Dematology Task Force
J Am Acad Derm 2006; 54(5):818-823
OUTLINE: Introduction and background; Food and Drug Administration concerns; American Academy of Dermatology Association conference, July 2005; review of information presented at the FDA hearing; Specific disease-state concerns; Cutaneous T-cell lymphoma and related conditions; States of immunosuppression and diseases with increased skin cancer susceptibility; Diseases associated with enhanced percutaneous absorption; Risk of cutaneous malignancies; Discussion and interpretation of information presented; Label and off-label use of TCIs; Education of patients and parents; Monitoring for AEs; Conclusions; Addendum; Long-term safety of topical calcineurin inhibitors has not been established

KEY INVESTIGATION topical steroids:
Furue M, Terao H, Terao H,Urabe K, Kinukawa N, Nose Y, Koga T
Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis.
Br J Dermatol 2003;148: 128-133
BACKGROUND: Topical steroids are used as the first-line therapy for atopic dermatitis. OBJECTIVES: To determine the clinical doses of topical steroids for the daily treatment of atopic dermatitis in clinics and to elucidate their adverse effects. PATIENTS AND METHODS: A multicentre retrospective analysis of a series of 1271 patients (210 infants, 546 children, and 515 adolescents and adults) with atopic dermatitis. RESULTS: Less than 89.5 g, 135 g and 304 g of topical steroid were applied in 90% of the patients in the infant, childhood, and adolescent and adult AD groups, respectively, on the entire body during the 6-month treatment period. The majority of patients were controlled well; however, 7% of infant, 10% of childhood and 19% of adolescent and adult patients remained in a very severe or severe state or experienced exacerbation even though they applied larger amounts of topical steroids. With regard to adverse effects, the

incidence of telangiectasia on cheeks tended to increase in patients who had a longer duration of disease and who applied more than 20 g to the face during the 6-month treatment period. The steroid-induced atrophy of the antecubital and popliteal fossae was more frequently observed in males than in females. CONCLUSIONS: Topical steroids are useful for treating atopic dermatitis, but a substantial percentage of patients cannot be satisfactorily treated with topical steroids. For such patients, adjustments of dose and rank of topical steroids and other therapeutic adjuncts are necessary.

b. ophthalmologic

REVIEW antihistamines:
Bielory L, Lien KW, Bigelsen S
Efficacy and Tolerability of Newer Antihistamines in the Treatment of Allergic Conjunctivitis
Drugs 2005; 65(2): 215-228

Treatment for allergic conjunctivitis has markedly expanded in recent years, providing opportunities for more focused therapy, but often leaving both physicians and patients confused over the variety of options. As monotherapy, oral antihistamines are an excellent choice when attempting to control multiple early-phase, and some late-phase, allergic symptoms in the eyes, nose and pharynx. Unfortunately, despite their efficacy in relief of allergic symptoms, systemic antihistamines may result in unwanted adverse effects, such as drowsiness and dry mouth. Newer second-generationantihistamines (cetirizine, fexofenadine, loratadine and desloratadine) are preferred over older firstgeneration antihistamines in order to avoid the sedative and anticholinergic effects that are associated with first-generation agents. When the allergic symptom or complaint, such as ocular pruritus, is isolated, focused therapy with topical (ophthalmic) antihistamines is often efficacious and clearly superior to systemic antihistamines, either as monotherapy or in conjunction with an oral or intranasal agent.Topical antihistaminic agents not only provide faster and superior relief than systemic antihistamines, but they may also possess a longer duration of action than other classes including vasoconstrictors, pure mast cell stabilisers, NSAIDs and corticosteroids. Many antihistamines have anti-inflammatory properties as well. Some of this anti-inflammatory effect seen with 'pure' antihistamines (levocabastine and emedastine) may be directly attributed to the blocking of the histamine receptor that has been shown to downregulate intercellular adhesion molecule-1 expression and, in turn, limit chemotaxis of inflammatory cells. Some topical multiple-action histamine H(1)- receptor antagonists (olopatadine, ketotifen, azelastine and epinastine) have been shown to prevent activation of neutrophils, eosinophils and macrophages, or inhibit release of leukotrienes, plateletactivating factors and other inflammatory mediators. Topical vasoconstrictor agents provide rapid relief, especially for redness; however, the relief is often short-lived, and overuse of vasoconstrictors may lead to rebound hyperaemia and irritation. Another class of topical agents, mast cell stabilizers (sodium cromoglicate [cromolyn sodium], nedocromil and lodoxamide), may be considered; however, they generally have a much slower onset of action. The efficacy of mast cell stabilisers may be attributed to anti-inflammatory properties in addition to mast cell stabilisation. In the class of topical NSAIDs, ketorolac has been promoted for ocular itching but has been found to be inferior for relief of allergic conjunctivitis when compared with olopatadine and emedastine. Lastly, topical corticosteroids may be considered for severe seasonal ocular allergy symptoms, although long-term use should be avoided because of risks of ocular adverse effects, including glaucoma and cataract formation.

REVIEW Immunosuppressive and non-steroidal agents:
Hemady, RK, Chan, AS, Nguyen, ATQ
Immunosuppressive Agents and Nonsteroidal Anti-inflammatory Drugs for Ocular Immune and Inflammatory Disorders
Ophthalmology Clinics of North America 2005; 18(4): 511-528
We now have at our disposal several nonsteroidal immunosuppressive and anti-inflammatory agentsthat may be used in addition to or instead of corticosteroids to treat ocular diseases. This articlediscusses some of the nonsteroidal immunosuppressive and anti-inflammatory agents available to theophthalmologist. OUTLINE: Systemic cytotoxic immunosuppressive agents (antimetabolites and alkylating agents); Systemic non-cytotoxic immunosuppressive (calcineurin inhibitors and biologics); Topical immunosuppressive agents (cyclosporine, tacrolimus); Topical non-steroidal anti-inflammatories (ketorolac, flurbiprofen, diclofenac). NOTE: The class and mechanisms, pharmacokinetics, indications, dose and route, adverse effects, monitoring are discussed for each drug.

REVIEW:
Histamine Receptors and the Conjunctiva
Bielory L, Ghafoor S
Curr. Opinion All. Clin. Immunol. 2005; 5(5): 437-440
PURPOSE OF REVIEW: The purpose of this review is to evaluate the effect of histamine on various receptors in the conjunctiva. A Medline search from 1980 was performed on the histamine receptor subtypes H1, H2 and H3 in the human conjunctiva. RECENT FINDINGS: In the conjunctiva, histamine has been shown to induce various physiological and immunological changes through both H1 and H2 receptor stimulation. Histamine binding to conjunctival H1 receptors through the phospholipase C-dependent inositol phosphate pathway leads to the symptom of pruritus while histamine stimulation of the conjunctival H2 receptors has been indirectly shown to cause vasodilation. SUMMARY: The effect of histamine on conjunctival H1 receptors appears to be the primary target for ocular allergy treatment as it is primarily involved in ocular pruritus. The exact interaction of the conjunctival H2 receptors appears to work in a complementary fashion to the H1 receptor in controlling other features of ocular allergy such as vasodilation and injection. Thus, oral and topical antihistamines with multiple histamine receptor binding activities may provide an improved treatment paradigm for the various signs and symptoms of ocular allergy. The histamine H1, H2 and H3 receptor affinities of ketotifen, pyrilamine, and epinastine appear to have the strongest H1 and H2 affinities.

12 . Vaccines against transmissible agents

REVIEW:
Moylett EH, Hanson IC
The Immune System. Immunization
J Allergy Clin Immunol 2003; 111(2), S754-65
The medical dictionary defines immunization as the "protection of susceptible individuals from communicable diseases by the administration of a living modified agent, a suspension of killed organisms, or an inactivated toxin." This elegant description can be expanded to include twenty-first century approaches to immunization that include recombinant technology, reassortment virus techniques, live vectors, DNA vaccines, and the expansion of the field to encompass

noncommunicable diseases such as Alzheimer's disease, autoimmunity, and tumor immunogenetics. Integral to the success of immunization is our knowledge of the immune system's memory of antigens, yet our understanding of this fundamental feature remains limited. On a global scale, communicable diseases remain the number-one cause of morbidity and mortality; hence Jenner's pioneering work with its birth in 1796 still has a challenging and exciting future.

REVIEW:
Wu JJ, Huang DB, Pang KR, Tyring SK
Vaccines and immunotherapies for the prevention of infectious diseases having cutaneous manifestations
J Am Acad Dermatol 2004; 50:495-528.
Although the development of antimicrobial drugs has advanced rapidly in the past several years, such agents act against only certain groups of microbes and are associated with increasing rates of resistance. These limitations of treatment force physicians to continue to rely on prevention, which is more effective and cost-effective than therapy. From the use of the smallpox vaccine by Jenner in the 1700s to the current concerns about biologic warfare, the technology for vaccine development has seen numerous advances. The currently available vaccines for viral illnesses include Dryvax for smallpox; the combination measles, mumps, and rubella vaccine; inactivated vaccine for hepatitis A; plasmaderived vaccine for hepatitis B; and the live attenuated Oka strain vaccine for varicella zoster. Vaccines available against bacterial illnesses include those for anthrax, Haemophilus influenzae, and Neisseria meningitidis. Currently in development for both prophylactic and therapeutic purposes are vaccines for HIV, herpes simplex virus, and human papillomavirus. Other vaccines being investigated for prevention are those for cytomegalovirus, respiratory syncytial virus, parainfluenza virus, hepatitis C, and dengue fever, among many others. Fungal and protozoan diseases are also subjects of vaccine research. Among immunoglobulins approved for prophylactic and therapeutic use are those against cytomegalovirus, hepatitis A and B, measles, rabies, and tetanus. With this progress, it is hoped that effective vaccines soon will be developed for many more infectious diseases with cutaneous manifestations.

13. Drug interactions

BRIEF REVIEW:
Tom Revzon, C.
Drug Interactions
Pediatrics in Review 2006; 27: 315-317
Short overview of the pharmacology of drug interactions; a list of references (articles, books, web sites and PDA programs on drug interactions).

REVIEW:
Shapiro LE, Knowles, SR, Shear NH
Drug Interactions of Clinical Significance for the Dermatologist
Am J Clin Dermatol 2003; 4(9): 623-639
While it would be impossible for any dermatologist to remember all potential drug interactions, knowledge of the mechanisms of drug interactions can help reduce the risk of serious adverse outcomes. Most drugs are associated with interactions but the majority do not produce significant outcomes. Dealing with drug interactions is a challenge in all clinical practice, including dermatology. New information continues to appear, and dermatologists need to know about the

drugs they use. This article focuses on the mechanisms of drug interactions. In particular, the life of a drug in terms of absorption, distribution, metabolism and excretion are reviewed with the focus on points of importance and relevance to drug interactions. The most clinically important drug interactions in dermatological practice are caused by alterations in drug metabolism. The contributions of P-glycoprotein, pharmacogenetic variation and genetic polymorphisms to drug interactions are highlighted, and the best evidence for drug interactions involving drug classes relevant to the dermatologist is presented. Since the initial evidence for clinically relevant drug interactions comes from case reports, prescribing physicians can have a major role in collating information on interactions. By understanding the mechanisms behind drug interactions and staying alert for toxicities, we can help make drug therapy safer and reduce the fear of drug interactions.

REVIEW:
Manzi SF, Shannon M.
Drug Interactions – a review
Clin Ped Emerg Med 2005; 6:93-102
The incidence and severity of drug interactions are on the rise as more medications are brought to market. Following the absorption, distribution, metabolism and excretion model of pharmacokinetics, this review will provide an overview of the varied mechanisms of drug-drug, drug-herb, and drug-food interactions with emphasis placed on the interactions most likely to cause harm. This information is intended to assist the pediatric emergency physician in recognizing drug interactions to identify and remove the offending agent when appropriate. Understanding the mechanisms of drug interactions will assist all clinicians in avoiding these serious, often preventable, events.

REVIEW:
Warringon JS, Shaw LM.
Pharmacogenetic differences and drug-drug interactions in immunosuppressive therapy.
Expert Opin. Metab. Toxicol 2005; 1(3): 487-503.
With the advent of new immunosuppressants and formulations, the elucidation of molecular targets and the evolution of therapeutic drug monitoring, the field of organ transplantation has witnessed significant reductions in acute rejection rates, prolonged graft survival and improved patient outcome. Nonetheless, challenges persist in the use of immunosuppressive medications. Marked interindividual variability remains in drug concentrations and drug response. As medications with narrow therapeutic indices, variations in immunosuppressant concentrations can result in acute toxicity or transplant rejection. Recent studies have begun to identify factors that contribute to this variability with the promise of tailoring immunosuppressive regimens to the individual patient. These advances have uncovered differences in genetic composition in drug-metabolising enzymes, drug transporters and drug targets. This review focuses on commonly used maintenance immunosuppressants (including cyclosporin, mycophenolate mofetil, tacrolimus, sirolimus, everolimus, azathioprine and corticosteroids), examines current studies on pharmacogenetic differences in drug-metabolising enzymes, drug transporters and drug targets and addresses common drug-drug interactions with immunosuppressant therapies. The potential role of drug-metabolising enzymes in contributing to these drug-drug interactions is briefly considered.

B. Allergenic Proteins and Extracts for Diagnosis and Treatment

1. Inhalant Allergenic Protein Sources

Allergens are distributed into few protein families and possess a restricted number of biochemical functions.
Radauer C
J Allergy Clin Immunol 2008; 121: 847-52.e7

Guilt by intimate association: what makes an allergen an allergen?
Karp CL
J Allergy Clin Immunol-2010; 125(5): 955-60; quiz 961-2.

a. Pollen and Mold/Fungi

REVIEW:
Thompson J.L., Thompson J.E.,
The urban jungle and allergy.
Immunol Allergy Clin North Am (2003) 23 : 371-387.
A major component of the urban jungle is the urban forest—the assemblage of trees, shrubs, and other plants that occupy the urban and suburban zones. Many of these species, planted in abundance by humans, produce powerful allergens that exist in high numbers. The overriding theme of the urban jungle is that it is an artificial structure that exists solely because of the activities of humans.

REVIEW:
Weber RW
Patterns of pollen cross-allergenicity.
J Allergy Clin Immunol 2003; 112: 229-39; quiz 240
There are many proteins, presumably performing vital functions, that are tightly preserved throughout the evolutionary tree from plants to animals, such as profilins, lipid transfer proteins, and pathogenesis-related proteins. These might function as panallergens. The small differences that exist between these ubiquitous proteins explain why these are frequently minor allergens not reacting in the majority of allergic sera. This review summarizes cross-reactivity studies with both crude pollen extracts and purified or recombinant allergenic proteins and the techniques used to assess the differences and similarities among extracts. The patterns of cross-allergenicity that emerge should be helpful in guiding both diagnostic and therapeutic decisions.

REVIEW:
Robert E. Esch, PhD
Manufacturing and standardizing fungal allergen products
Journal of Allergy and Clinical Immunology. 2004;113: 210-15
A wide variety of fungal species have been demonstrated to elicit allergic symptoms and to sensitize patients. The quality of fungal allergen preparations might have a significant effect on the specificity and sensitivity of diagnostic tests. The clinical relevance of the varying degrees of cross-reactivity among the fungal antigens has been neither fully appreciated nor

applied to clinical practice. In addition, an increasing number of potentially new fungal allergen sources for which commercial extracts are not available are being identified. Currently there are no standardized fungal allergen products available in the United States because of inherent difficulties with manufacturing and standardizing fungal extracts. This article reviews the extraction process, the protein and carbohydrate composition of fungal extracts from the major manufacturers, and the barriers that exist in achieving standardization.

RESEARCH FRONTIER:
Kaul S
Monoclonal IgE antibodies against birch pollen allergens: novel tools for biological characterization and standardization of allergens.
J Allergy Clin Immunol 2003; 111: 1262-8
Although this article concentrates on birch allergens, the clinical utility may be are broad applicable. Allergen characterization and standardization is usually based on the sera of allergic patients, whereas monoclonal IgE antibodies specific for clinically relevant allergens are very rare. The aim of this study was to establish IgE mAbs specific for birch pollen allergens, using IgE hybridomas.because these are important inhalant allergens. The obtained IgE mAbs were characterized by immunologic methods and by cDNA sequencing. Seven IgE mAbs specific for the birch pollen allergens Bet v 1 or Bet v 6 were obtained and were all biologically active in mast cell-based assays. Mediator release experiments with mAb combinations indicated that 2 different epitope regions were recognized on Bet v 1, whereas the 2 Bet v 6-specific mAbs bound to the same epitope region. After sensitization of rat basophilic leukemia cells with IgE mAbs, different amounts of Bet v 1 or Bet v 6 were detected in commercial diagnostic allergen reagents, whereas sensitization with polyclonal IgE resulted in similar allergenic potency of all products: IgE mAbs represent promising novel tools for allergen characterization and component-resolved standardization of allergen extracts.

Cross-reactivity among fungal allergens: a clinically relevant phenomenon?
Crameri R
Mycoses 2009; 52: 99-106
This is a review of recent progress in molecular cloning of fungal allergens and the availability of more than 40 completely sequenced fungal genomes. The recent technology facilitates characterization, cloning, and production of highly pure recombinant allergens, identification of homologous and orthologous allergens widespread among the fungal kingdom. These studies indicate that cross-reactivity is an important component of fungal sensitization.

Fungal allergens.
Vijay HM - Clin Allergy Immunol 2008; 21: 141-60. A comprehensive review of fungal allergens

Aspergillus and Penicillium allergens: focus on proteases.
Shen HD
Curr Allergy Asthma Rep 2007; 7: 351-6
Penicillium and Aspergillus species are prevalent airborne fungi. Alkaline and/or vacuolar serine proteases are major allergens of several prevalent Penicillium and Aspergillus species. This paper

reports on studies of the allergenic, and immunogenic proerties of the serine protease major allergens.

b. Insects and Arachnids

RESEARCH FRONTIER:

Satinover SM

Specific IgE and IgG antibody-binding patterns to recombinant cockroach allergens.

J Allergy Clin Immunol. 2005; 115: 803-9

BACKGROUND: The specificity of serum antibody responses to different cockroach allergens has not been studied. OBJECTIVE: We sought to quantitate serum IgE and IgG antibodies to a panel of purified cockroach allergens among cockroach-sensitized subjects. METHODS: IgE antibodies to recombinant cockroach allergens (rBla g 1, rBla g 2, rBla g 4, rBla g 5, and rPer a 7) were measured in sera containing IgE antibodies to Blattella germanica extract (n = 118) by using a streptavidin CAP assay and a multiplex flow cytometric assay. Specific IgG antibodies were determined by using radioimmunoprecipitation techniques. RESULTS: Specific IgE antibodies measured by means of CAP assay and multiplex assay were strongly correlated (r = 0.8, P < .001). The sum of IgE antibodies (in international units per milliliter) against all 5 allergens equated to IgE antibodies to cockroach extract. Although the prevalence of IgE antibodies was highest for rBla g 2 (54.4%) and rBla g 5 (37.4%), patterns of IgE antibody binding were unique to each subject. Surprisingly, only 16% of cockroach-sensitized subjects with IgE antibodies to house dust mite exhibited IgE antibody binding to cockroach tropomyosin (rPer a 7). Specific IgE antibodies were associated with increased IgG antibody levels, although detection of IgG in the absence of IgE was not uncommon. CONCLUSION: The techniques described offer a new approach for defining the hierarchy of purified allergens. IgE antibodies directed against 5 allergens constitute the majority of the IgE antibody repertoire for cockroach. Such distinct patterns of IgE-IgG responsiveness to different cockroach allergens highlight the complexity of B-cell responses to environmental allergens.

RESEARCH FRONTIER:

Hoffman DR

Sol i 1, the phospholipase allergen of imported fire ant venom.

J Allergy Clin Immunol. 2005; 115: 611-6

BACKGROUND: Sol i 1, the venom phospholipase of imported fire ant venom is an important allergen and exhibits some cross-reactivity with IgE antibodies from patients sensitized to other Hymenoptera venoms. OBJECTIVE: To determine the primary structure of Sol i 1 and evaluate the roles of protein and carbohydrate epitopes in its cross-reactivity. METHODS: Sol i 1 was purified from venom, proteolytic peptides prepared and amino acid sequences obtained. The cDNA for Sol i 1 was cloned, sequenced, and compared with sequences of other wasp venom phospholipases. The role of carbohydrate epitopes in the cross-reactivity with other Hymenoptera venoms was studied by RAST inhibition. RESULTS: The sequence identified Sol i 1 as a lipase of the GX class, lipoprotein lipase superfamily, pancreatic lipase homologous family and RP2 subgroup phospholipases as are the vespid venom phospholipases. The 148 residues identified by amino acid sequencing represent about 48% of the translated cDNA sequence. Sol i 1 was 31-32% identical to yellow jacket phospholipases. The identical regions of sequence were clustered in the domain which forms the serine hydrolase active site. Mannosylated N-glycans could completely inhibit binding of IgE from honeybee venom sensitized patients to Sol i 1. Inhibition by glycan of

IgE binding from yellow jacket venom sensitized patients was low or absent for three of eight sera and substantial, but not complete for five sera. CONCLUSIONS: Sol i 1 is related to wasp venom phospholipases. Cross-reactivity with honeybee venom is caused by carbohydrate, whereas cross-reactivity with yellow jacket venom involves reactivity with both carbohydrate determinants of hyaluronidase and high molecular weight proteins and phospholipase protein determinants.

RESEARCH FRONTIER:
Kussebi F et al
A major allergen gene-fusion protein for potential usage in allergen-specific immunotherapy.
J Allergy Clin Immunol. 2005; 115: 323-9
Specific immunotherapy is a common treatment of allergic diseases and could potentially be applied to other immunologic disorders. Despite its use in clinical practice, more defined and safer allergy vaccine preparations are required. Differences between epitopes of IgE that recognize the 3-dimensional structure of allergens and T cells that recognize linear amino acid sequences provide a suitable tool for novel vaccine development for specific immunotherapy. The aim of the study was to delete B-cell epitopes and prevent IgE crosslinking, but to preserve T-cell epitopes by fusion of 2 major allergens of bee venom because of a change in the conformation.

Reassessing the role of hyaluronidase in yellow jacket venom allergy.
Jin C
J Allergy Clin Immunol- 2010; 125: 184-90.e1
Hyaluronidase is a minor yellow jacket venom allergen, and only 10% to 15% of patients with yellow jacket allergy are estimated to have IgE against the hyaluronidase protein. Peptide-specific cross-reactivity with Api m 2 occurs in half of these sera. Component-resolved diagnosis with antigen 5 and phospholipase would detect virtually all patients with yellow jacket venom allergy.

Structural biology of allergens from stinging and biting insects.
Hoffman DR
Curr Opin Allergy Clin Immunol - 2008; 8: 338-42.
A number of new venom and salivary allergens have been characterized. The structures and significance of several insect allergens have been updated. Investigations continue into distinguishing venom crossreactivity from multiple sensitization. Further studies are clarifying the significance of carbohydrate epitopes. Genomic and proteomic techniques are being used in the investigation of proteins and peptides insect venom and saliva.

Biting insect allergens.
Hoffman DR
Clin Allergy Immunol 2008; 21: 251-60.
A good review.

c. Animals

REVIEW:
Erwin EA, Woodfolk JA, et al
Animal danders.

Immunol Allergy Clin North Am 2003; 23(3): 469-81
This review characterizes the indoor aeroallergens from animal and insect sources, immune responses to these allergens and environmental control measures.

Indoor allergens: relevance of major allergen measurements and standardization.
Van Ree R.
Journal of Allergy and Clinical Immunology 2007; 119(2): 270-7; quiz 278-9
Major allergen measurements have relevance for the standardization of allergen extracts for immunotherapy and for epidemiologic studies into the cause of allergic diseases. It is necessary to add major allergen measurements to standardization requirements to design adequate dosage schemes and elucidate the dose-response relation between major allergen dose and therapeutic effect. This will also help clarify to what extent sublingual immunotherapy requires higher doses of major allergen. Standardization should be based on certified major allergen references and accompanying assays that are cross-reactive enough to recognize all variants to facilitate comparability.

Characterization of dog allergens Can f 1 and Can f 2. 1.
Preparation of their recombinant proteins and antibodies.
Kamata Y
Int Arch Allergy Immunol 2007; 142: 291-300
Recombinant allergens and antibodies for Can f 1 and Can f 2 are available for immunological and biochemical characterization of dog allergens. The molecular weight of the natural Can f 1 and Can f 2 in dog saliva and hair/dander extracts showed a higher molecular weight than that of rCan f 1 and rCan f 2. The significance of dog skin as the tissue producing dog allergens, especially Can f 2, should be considered in further studies.

d. Aerobiology and environmental assessment of allergens, irritants and pollutants

REVIEW:
Portnoy J, Barnes C
Clinical relevance of spore and pollen counts.
Immunol Allergy Clin North Am -AUG-2003; 23: 389-410
A comprehensive and well referenced review of the aerobiology of pollens and mold spores.

REVIEW:
Nelson HS
How ill the wind? Issues in aeroallergen sampling.
J Allergy Clin Immunol. 2003; 112: 3-8.
The effective size of bioaerosols is the principal determinant of their behavior during takeoff, transport, and deposition. Collection methods involving impaction, impingement, and filtration allow recovery of increasingly small aerosol units and do so "per unit volume of processed air" with more or less well-defined efficiency. These principles offer direction in choosing sampling devices for specific applications; similarly, a particle's appearance, growth potential, and assayability define the scope of relevant analyses. Where a variety of aerosol types occur, multiple collection and/or analytic approaches might be required. The development of a sampling grid in

North America makes possible studies of distribution, transport, and climatic effects in ways never previously possible; however, some directive planning and oversight are essential to realize these goals. Methods sensitive to paucimicronic and submicronic particles should be included increasingly in new and ongoing survey protocols. Similarly, available means now facilitate study of aerosols at specific sites, both indoors and outdoors, with estimates of personal exposure during defined events. Resulting data describing airborne prevalence gain special value in light of competent inspection of implicated venues and consideration of alternative sources, such as incursion of bioaerosols into enclosed spaces

REVIEW:
Muilenberg ML
Sampling devices.
Immunol Allergy Clin North Am. AUG-2003; 23(3): 337-55
This is a terrific review of the commercial aerobiosol and particulate sampling devices with their specifications and manufacturer sources. The article also reviews analytical techniques such as visual particle counting, and immunochemical analysis.

Longitudinal evaluation of allergen and culturable fungal concentrations in inner-city households.
Cho SJ
J Occup Environ Hyg 2008; 5: 107-18
Seasonal variation of cat and cockroach allergens was negligible compared with the variability associated with residential characteristics such as race/ethnicity, family income, and the presence of cats. Fungal concentrations showed significant seasonal variation that outweighed the variability associated with residential characteristics. The authors conclude that a single measurement of cat allergen is a reasonable surrogate for long-term average exposure, since repeated measurements over time were highly correlated. Total culturable fungi require greater than nine repeated measurements for robust assessment of long-term exposures because of low correlations in fungal measures over time.

Projections of the effects of climate change on allergic asthma: the contribution of aerobiology.
Cecchi L
Allergy 2010; 65(9): 1073-81.
Climate has already had an impact on living organisms, including plants and fungi with current scenarios projecting further effects by the end of the century. Over the last three decades, studies have shown changes in production, dispersion and allergen content of pollen and spores, which may be region- and species-specific. In addition, these changes may have been influenced by urban air pollutants interacting directly with pollen. Data suggest an increasing effect of aeroallergens on allergic patients over this period, which may also imply a greater likelihood of the development of an allergic respiratory disease in sensitized subjects and exacerbation of symptomatic patients.

Collection of air samples to quantify exposure to airborne allergens.
Gordon S
Methods Mol Med 2008; 138: 209-15.

Methods that have been applied to quantify animal airborne allergens are described. By careful selection of the air sampling equipment and conditions, samples can be collected which quantify, for example, the personal exposure of an individual when performing a specific task or changes in exposure when allergen control methods are implemented. Portions of this article are very technical, but it is a good review of basic principles.

2. Allergen Extract Preparation and Standardization Methods

REVIEW:
Larsen JN
Manufacturing and Standardizing Allergen Vaccines
Immunol Allergy Clin North Am 2000. 20:609-623
This article describes the procedures used to select source materials and the preparation and standardization of allergen vaccines. Concise review with good references.

LANDMARK ARTICLE:
Turkeltaub PC
A standardized quantitative skin-test assay of allergen potency and stability: studies on the allergen dose-response curve and effect of wheal, erythema, and patient selection on assay results.
J Allergy Clin Immunol 1982; 70(5): 343-52
This classic article describes the methodology which is the current basis for standardizing allergen extracts.

Preparation and Standardization of Allergen Extracts
Jay E. Slater, Robert E. Esch, Richard F. Lockey
Adkinson: Middleton's Allergy: Principles and Practice, 7th ed.
Chapter 34 Mosby, St Louis, Mo 2008.
Comprehensive and well-referenced summary or see the next citation for a detailed description.

Also see:
Standardization of allergen extracts.
Larsen JN
Methods Mol Med-2008; 138: 133-45

Potential, pitfalls, and prospects of food allergy diagnostics with recombinant allergens or synthetic sequential epitopes.
Steckelbroeck S
J Allergy Clin Immunol 2008; 121(6): 1323-30
Recombinant allergens and synthetic sequential epitopes enabled detection of sensitization profiles, with IgE specific to several allergens and substructures now being suggested as markers of severity, persistence, or both. Microarray technology permits simultaneous measurement of multiple IgE reactivities regarding specificity, abundance, reactivity, or interaction. Improved functional tests might enable reliable estimation of the clinical relevance of IgE sensitizations.

European allergen extract units and potency: review of available information.
Larenas-Linnemann D

Ann Allergy Asthma Immunol - 2008; 100: 137-45
All but 1 of the European allergen extract manufacturers use in-house reference standards that are based on titrated skin prick testing of allergic patients and. in vitro tests compare the potency of commercial batches with the in-house reference. Potency is assigned as arbitrary units. Most manufacturers measure major allergens content of their standardized products. Diversity in major allergen content was found. Micrograms of major allergens given in articles on sublingual immunotherapy to express the dose administered cannot be used to translate the dose to US extracts. Extract potency can only be compared if uniform test methods and reference extracts are used.

A hypoallergenic variant of Der p 1 as a candidate for mite allergy vaccines.
Walgraffe D
J Allergy Clin Immunol 2009; 123(5): 1150-6
The recombinant proform of Der p 1 (ProDer p 1) was expressed in Escherichia coli (ProDer p 1 coli). In mice ProDer p 1 forms were able to retain the Der p 1-specific T-cell reactivity but direct ELISA, competitive inhibition, and rat basophil leukemia assays clearly showed that ProDer p 1 coli displays a very weak IgE reactivity. ProDer p 1 coli treatment in mice inhibited the development of airway eosinophilia and airway hyperresponsiveness to inhaled methacholine

Impact of native, recombinant, and cross-reactive allergens on humoral and T-cell-mediated immune responses.
Crameri R
Immunol Allergy Clin North Am - FEB-2007; 27(1): 65-78
Many native allergens have been purified to homogeneity from natural sources, and whole arrays of recombinant and cross-reactive allergens have been produced in large amounts as biologically active molecules. These allergens offer potent research tools to investigate humoral and T cell-mediated immune responses to allergens in healthy and allergic individuals, providing methods for verifying the responses in a reproducible and dose-dependent manner. Dissecting the immune responses to allergens at cellular and molecular levels provides models for studying the different aspects of T-cell activation and the development of immunologic memory and effector functions.

The European Union CREATE project: a model for international standardization of allergy diagnostics and vaccines.
Chapman MD
J Allergy Clin Immunol 2008; 122(5): 882-889.e2.
The aims of the European Union CREATE project were to develop international standards with verifiable allergen content. Purified natural and recombinant allergens were analyzed by means of SDS-PAGE, mass spectrometry, circular dichroism spectra, and small-angle x-ray scattering. IgE reactivity was assessed by means of direct RAST, RAST inhibition, immunoblotting, and basophil histamine. . The CREATE project has provided a major step forward in allergen standardization and a model for the development of a comprehensive panel of international reference preparations that will harmonize allergen measurements worldwide.

3. Clinical Use of Allergenic Extracts as Therapeutic Agents
REVIEW:
Nelson HS, Iklé D, Buchmeier A.

Studies of allergen extract stability: the effects of dilution and mixing.
J Allergy Clin Immunol 1996;98:382-8.
This is an excellent review of the factors that can affect allergen potency. The study was performed to assess separately the deterioration during storage in allergen extract potency caused by dilution or by mixture with allergen extracts that have been reported to contain proteases. Bermuda grass, cat, and house dust mite extracts incurred significant loss of potency at all dilutions with storage. Short ragweed was stable at all dilutions. Potency of extracts of timothy grass, Bermuda grass, Russian thistle, white oak, box elder, and cat were all reduced by combination with one or more extracts potentially containing proteases. Only short ragweed and D. farinae, which was in a final concentration of 25% glycerin, were resistant. Alternaria extract was most frequently responsible for loss of potency, followed by cockroach and Cladosporium extracts. Combination with extracts of Penicillium and a house dust mite mix did not reduce the potency of any extract.

REVIEW:
Nelson HS
The use of standardized extracts in allergen immunotherapy.
J Allergy Clin Immunol. 2000; 106: 41-5.
This article is a survey of immunotherapy doses used by allergists in the US. It is also an excellent review of the potency of the standardized extracts used in allergy vaccines. The authors also review the evidence base for recommended maintenance doses for selected pollens, cat, and house dust mite immunotherapy.

RESEARCH FRONTIER:
Creticos PS, Chen Y-H, Schroeder JT
New approaches in immunotherapy: allergen vaccination with immunostimulatory DNA.
Immunol Allergy Clin North Am NOV-2004; 24: 569-81
This article addresses a specific adjuvant approach to immunotherapy in which highly active immunostimulatory phosphorothioate oligodeoxyribonucleotide (ISS-ODN) moieties are linked to the principal allergenic moiety of a relevant aeroallergen. The immune mechanisms by which the adjuvant effect is mediated are reviewed and contrated to conventional IT. Phase I and phase II clinical studies of patients with ragweed-induced allergic rhinitis are also reviewed. The initial phase I and phase II clinical trials demonstrated the improved immunogenicity and therapeutic potential of the construct and suggested that AIC may be a superior therapeutic agent, when compared with conventional immunotherapy.

Recombinant allergens for immunotherapy.
Valenta R
J Allergy Clin Immunol 2007; 119(4): 826-30

Allergen immunotherapy: what can and cannot be mixed?
Esch RE
J Allergy Clin Immunol - 01-SEP-2008; 122(3): 659-60
This article is a nice little clinical pearl with a handy table indicating compatible and incompatible extracts based on protease content.

Immunomodulatory nanoparticles as adjuvants and allergen-delivery system to human dendritic cells: Implications for specific immunotherapy.
Broos S
Vaccine 2010; 28: 5075-85
This study demonstrates that poly(gamma-glutamic acid) (gamma-PGA) nanoparticles (NPs) are activators of human monocyte-derived dendritic cells (MoDCs). Gamma-PGA NPs strongly stimulate production of chemokines and inflammatory cytokines as well as up-regulation of co-stimulatory molecules and immunomodulatory mediators involved in efficient T cell priming. Furthermore, MoDCs from allergic subjects stimulated in vitro with a mixture of gamma-PGA NPs and extract of grass pollen allergens Phleum pratense (Phl p) augment allergen-specific IL-10 production and proliferation of autologous CD4(+) memory T cells. Thus, gamma-PGA NPs are promising as sophisticated adjuvants and allergen-delivery systems in allergen-specific immunotherapy.

Therapeutic vaccines against IgE-mediated allergies.
Hellman L
Expert Rev Vaccines 2008; 7(2): 193-208.
This review focuses on the progress in the development of vaccines against IgE-mediated allergies and new methods to enhance the immunogenicity of the vaccines. Targets under investigation are the IgE molecule itself and several Th2 cytokines, that is, IL-4, -5, -13, -33, -18 and thymic stromal lymphopoietin.

From allergen genes to allergy vaccines.
Valenta R
Annu Rev Immunol - 2010; 28: 211-41.
Comprehensive review. The structures of the most common allergens have been revealed through molecular cloning technology in the past two decades. Allergy vaccines have been constructed that are able to selectively target the aberrant immune responses in allergic patients via different pathways of the immune system. This is a review of various types of allergy vaccines that have been developed based on allergen structures, results from their clinical application in allergic patients, and future strategies for allergen-specific immunotherapy and allergy prophylaxis.

IV. Research Principles

A. Research ethics

REVIEW:
Brody B, McCullough LB, Sharp RR
Consensus and Controversy in Clinical Research Ethics
JAMA. 2005;294:1411-1414.
An international consensus for protecting the rights and interests of research subjects has emerged in a process that began with the Declaration of Helsinki and continues in the development of official guidelines as well as a growing scholarly literature. Despite this consensus, legitimate ethical controversies persist. This article discusses points of consensus and controversy in clinical research ethics, focusing on substantive, rather than procedural, concerns.

LANDMARK DOCUMENT:
Declaration of Helsinki: ethical principles for medical research involving human subjects. Available at: http://www.wma.net/e/policy/b3.htm.

NOTE:
There are several websites at the National Institutes of health that may be helpful in designing learning activities for fellows in training that are related to research ethics including…
http://ohsr.od.nih.gov/guidelines/graybook.html#app3
Guidelines for the conduct of research involving human subjects at the National Institutes of Health

http://ohsr.od.nih.gov/guidelines/belmont.html
The Belmont Report: Ethical Principles and Guidelines for the protection of human subjects of research

B. Experimental design

REVIEW Descriptive Studies:
Grimes DA, Schulz KF
Descriptive studies: what they can and cannot do.
Lancet. 2002 Jan 12;359:145-9.
Descriptive studies often represent the first scientific toe in the water in new areas of inquiry. A fundamental element of descriptive reporting is a clear, specific, and measurable definition of the disease or condition in question. Like newspapers, good descriptive reporting answers the five basic W questions: who, what, why, when, where. and a sixth: so what? Case reports, case-series reports, cross-sectional studies, and surveillance studies deal with individuals, whereas ecological correlational studies examine populations. The case report is the least-publishable unit in medical literature. Case-series reports aggregate individual cases in one publication. Clustering of unusual cases in a short period often heralds a new epidemic, as happened with AIDS. Cross-sectional (prevalence) studies describe the health of populations. Surveillance can be thought of as watchfulness over a community; feedback to those who need to know is an integral component of surveillance. Ecological correlational studies look for associations between exposures and outcomes in populations-eg, per capita cigarette sales and rates of coronary artery disease-rather than in individuals. Three important uses of descriptive studies include trend analysis, health-care planning, and hypothesis generation. A frequent error in reports of descriptive studies is overstepping the data: studies without a comparison group allow no inferences to be drawn about associations, causal or otherwise. Hypotheses about causation from descriptive studies are often tested in rigorous analytical studies.

REVIEW Case Control Studies:
Grimes DA, Schutz KF
Case-control studies: research in reverse.
Lancet. 2002 Feb 2;359:431-4.
Epidemiologists benefit greatly from having case-control study designs in their research armamentarium. Case-control studies can yield important scientific findings with relatively little time, money, and effort compared with other study designs. This seemingly quick road to research results entices many newly trained epidemiologists. Indeed, investigators implement

case-control studies more frequently than any other analytical epidemiological study. Unfortunately, case-control designs also tend to be more susceptible to biases than other comparative studies. Although easier to do, they are also easier to do wrong. Five main notions guide investigators who do, or readers who assess, case-control studies. First, investigators must explicitly define the criteria for diagnosis of a case and any eligibility criteria used for selection. Second, controls should come from the same population as the cases, and their selection should be independent of the exposures of interest. Third, investigators should blind the data gatherers to the case or control status of participants or, if impossible, at least blind them to the main hypothesis of the study. Fourth, data gatherers need to be thoroughly trained to elicit exposure in a similar manner from cases and controls; they should use memory aids to facilitate and balance recall between cases and controls. Finally, investigators should address confounding in casecontrol studies, either in the design stage or with analytical techniques. Devotion of meticulous attention to these points enhances the validity of the results and bolsters the reader's confidence in the findings.

REVIEW Cohort Studies:
Grimes DA, Schulz KF
Cohort studies: marching towards outcomes.
Lancet. 2002 Jan 26;359:341-5.

A cohort study tracks two or more groups forward from exposure to outcome. This type of study can be done by going ahead in time from the present (prospective cohort study) or, alternatively, by going back in time to comprise the cohorts and following them up to the present (retrospective cohort study). A cohort study is the best way to identify incidence and natural history of a disease, and can be used to examine multiple outcomes after a single exposure. However, this type of study is less useful for examination of rare events or those that take a long time to develop. A cohort study should provide specific definitions of exposures and outcomes: determination of both should be as objective as possible. The control group (unexposed) should be similar in all important respects to the exposed, with the exception of not having the exposure. Observational studies, however, rarely achieve such a degree of similarity, so investigators need to measure and control for confounding factors. Reduction of loss to follow-up over time is a challenge, since differential losses to follow-up introduce bias. Variations on the cohort theme include the before-after study and nested case-control study (within a cohort study). Strengths of a cohort study include the ability to calculate incidence rates, relative risks, and 95% CIs. This format is the preferred way of presenting study results, rather that with p values.

NOTE Randomized Controlled Trials:

Randomized Controlled Trials form the basis of modern evidence based medical practice. The “Lancet Series” of reviews by Schulz and Grimes on aspects RCTs are an excellent resource for teaching about designing these important interventional studies.

Schulz KF, Grimes DA

- Generation of allocation sequences in randomised trials: chance, not choice. Lancet, 2002;359:515-519
- Allocation concealment in randomised trials: defending against deciphering. Lancet 2002;359:614-618
- Blinding in randomised trials: hiding who got what. Lancet 2002;359:696-700

- Sample size slippages in randomised trials: exclusions and the lost and wayward. Lancet 2002;359:781-785
- Unequal group sizes in randomised trials: guarding against guessing. Lancet 2002;359:966-970
- Sample size calculations in randomised trials: mandatory and mystical. Lancet 2005;365:1348-1353

C. Data analysis, biostatistics and use of computer database, spreadsheet and statistical analysis applications

REVIEW:
Donna M. Windish, MD, MPH,1 Marie Diener-West,
A Clinician-Educator's Roadmap to Choosing and Interpreting Statistical Tests
J Gen Int Med 2006;21:656-660
As educators seek confirmation of successful trainee achievement, medical education must move toward a more evidence-based approach to teaching and evaluation. Although medical training often provides physicians with a general background in biostatistics, many are not prepared to apply these skills. This can hinder clinician educators as they wish to develop, analyze and disseminate their scholarly work. This paper is intended to be a concise educational tool and guide for choosing and interpreting statistical tests aimed toward medical education assessment. It includes guidelines and examples that clinicianeducators can use when analyzing and interpreting studies and whenwriting methods and results sections of reports.

REVIEW:
Katz MH
Multivariable analysis: a primer for readers of medical research.
Ann Intern Med. 2003 Apr 15;138(8):644-50
Many clinical readers, especially those uncomfortable with mathematics, treat published multivariable models as a black box, accepting the author's explanation of the results. However, multivariable analysis can be understood without undue concern for the underlying mathematics. This paper reviews the basics of multivariable analysis, including what multivariable models are, why they are used, what types exist, what assumptions underlie them, how they should be interpreted, and how they can be evaluated. A deeper understanding of multivariable models enables readers to decide for themselves how much weight to give to the results of published analyses

REVIEW:
Grimes DA, Schultz KF
Uses and abuses of screening tests.
Lancet. 2002 Mar 9;359(9309):881-4
Screening tests are ubiquitous in contemporary practice, yet the principles of screening are widely misunderstood. Screening is the testing of apparently well people to find those at increased risk of having a disease or disorder. Although an earlier diagnosis generally has intuitive appeal, earlier might not always be better, or worth the cost. Four terms describe the validity of a screening test: sensitivity, specificity, and predictive value of positive and negative results. For tests with continuous variables--eg, blood glucose--sensitivity and specificity are inversely related; where the cutoff for abnormal is placed should indicate the clinical effect of wrong results. The prevalence of disease in a population affects screening test performance: in

low-prevalence settings, even very good tests have poor predictive value positives. Hence, knowledge of the approximate prevalence of disease is a prerequisite to interpreting screening test results. Tests are often done in sequence, as is true for syphilis and HIV-1 infection. Leadtime and length biases distort the apparent value of screening programmes; randomised controlled trials are the only way to avoid these biases. Screening can improve health; strong indirect evidence links cervical cytology programmes to declines in cervical cancer mortality. However, inappropriate application or interpretation of screening tests can rob people of their perceived health, initiate harmful diagnostic testing, and squander health-care resources.

REVIEW:
Grimes DA, Schutz KF
Bias and causal associations in observational research.
Lancet. 2002 Jan 19;359:248-52.
Readers of medical literature need to consider two types of validity, internal and external. Internal validity means that the study measured what it set out to; external validity is the ability to generalise from the study to the reader's patients. With respect to internal validity, selection bias, information bias, and confounding are present to some degree in all observational research. Selection bias stems from an absence of comparability between groups being studied. Information bias results from incorrect determination of exposure, outcome, or both. The effect of information bias depends on its type. If information is gathered differently for one group than for another, bias results. By contrast, non-differential misclassification tends to obscure real differences. Confounding is a mixing or blurring of effects: a researcher attempts to relate an exposure to an outcome but actually measures the effect of a third factor (the confounding variable). Confounding can be controlled in several ways: restriction, matching, stratification, and more sophisticated multivariate techniques. If a reader cannot explain away study results on the basis of selection, information, or confounding bias, then chance might be another explanation. Chance should be examined last, however, since these biases can account for highly significant, though bogus results. Differentiation between spurious, indirect, and causal associations can be difficult. Criteria such as temporal sequence, strength and consistency of an association, and evidence of a dose-response effect lend support to a causal link.

REVIEW:
Schulz KF, Grimes DA
Multiplicity in randomised trials I: endpoints and treatments
The Lancet 2005;365:1591-1595
Multiplicity problems emerge from investigators looking at many additional endpoints and treatment group comparisons. Thousands of potential comparisons can emanate from one trial. Investigators might only report the significant comparisons, an unscientific practice if unwitting, and fraudulent if intentional. Researchers must report all the endpoints analysed and treatments compared. Some statisticians propose statistical adjustments to account for multiplicity. Simply defined, they test for no effects in all the primary endpoints undertaken versus an effect in one or more of those endpoints. In general, statistical adjustments for multiplicity provide crude answers to an irrelevant question. However, investigators should use adjustments when the clinical decision-making argument rests solely on one or more of the primary endpoints being significant. In these cases, adjustments somewhat rescue scattershot analyses. Readers need to be aware of the potential for under-reporting of analyses.

REVIEW:
Schulz KF, Grimes DA
Multiplicity in randomised trials II: subgroup and interim analyses
The Lancet 2005;365:1657-1661.
Subgroup analyses can pose serious multiplicity concerns. By testing enough subgroups, a falsepositive result will probably emerge by chance alone. Investigators might undertake many analyses but only report the significant effects, distorting the medical literature. In general, we discourage subgroup analyses. However, if they are necessary, researchers should do statistical tests of interaction, rather than analyse every separate subgroup. Investigators cannot avoid interim analyses when data monitoring is indicated. However, repeatedly testing at every interim raises multiplicity concerns, and not accounting for multiplicity escalates the false-positive error. Statistical stopping methods must be used. The O'Brien-Fleming and Peto group sequential stopping methods are easily implemented and preserve the intended alpha level and power. Both adopt stringent criteria (low nominal p values) during the interim analyses. Implementing a trial under these stopping rules resembles a conventional trial, with the exception that it can be terminated early should a treatment prove greatly superior. Investigators and readers, however, need to grasp that the estimated treatment effects are prone to exaggeration, a random high, with early stopping.

D. Epidemiology (Also see IV.B for experimental designs)

REVIEW:
Grimes DA, Schultz KF
Compared to what? Finding controls for case-control studies.
Lancet 2005;365:1429-1433
Use of control (comparison) groups is a powerful research tool. In case-control studies, controls estimate the frequency of an exposure in the population under study. Controls can be taken from known or unknown study populations. A known group consists of a defined population observed over a period, such as passengers on a cruise ship. When the study group is known, a sample of the population can be used as controls. If no population roster exists, then techniques such as random-digit dialling can be used. Sometimes, however, the study group is unknown, for example, motor-vehicle crash victims brought to an emergency department, who may come from far away. In this situation, hospital controls, neighbourhood controls, and friend, associate, or relative controls can be used. In general, one well-selected control group is better than two or more. When the number of cases is small, the ratio of controls to cases can be raised to improve the ability to find important differences. Although no ideal control group exists, readers need to think carefully about how representative the controls are. Poor choice of controls can lead to both wrong results and possible medical harm. Use of control (comparison) groups is a powerful research tool. In case-control studies, controls estimate the frequency of an exposure in the population under study. Controls can be taken from known or unknown study populations. A known group consists of a defined population observed over a period, such as passengers on a cruise ship. When the study group is known, a sample of the population can be used as controls. If no population roster exists, then techniques such as random-digit dialling can be used. Sometimes, however, the study group is unknown, for example, motor-vehicle crash victims brought to an emergency department, who may come from far away. In this situation, hospital controls, neighbourhood controls, and friend, associate, or relative controls can be used. In

general, one well-selected control group is better than two or more. When the number of cases is small, the ratio of controls to cases can be raised to improve the ability to find important differences. Although no ideal control group exists, readers need to think carefully about how representative the controls are. Poor choice of controls can lead to both wrong results and possible medical harm.

REVIEW:
Grimes DA, Schultz KF
An overview of clinical research: the lay of the land
Lancet 2002;359:57-61
Many clinicians report that they cannot read the medical literature critically. To address this difficulty, we provide a primer of clinical research for clinicians and researchers alike. Clinical research falls into two general categories: experimental and observational, based on whether the investigator assigns the exposures or not. Experimental trials can also be subdivided into two: randomised and non-randomised. Observational studies can be either analytical or descriptive. Analytical studies feature a comparison (control) group, whereas descriptive studies do not. Within analytical studies, cohort studies track people forward in time from exposure to outcome. By contrast, case-control studies work in reverse, tracing back from outcome to exposure. Crosssectional studies are like a snapshot, which measures both exposure and outcome at one time point. Descriptive studies, such as case-series reports, do not have a comparison group. Thus, in this type of study, investigators cannot examine associations, a fact often forgotten or ignored. Measures of association, such as relative risk or odds ratio, are the preferred way of expressing results of dichotomous outcomes-eg, sick versus healthy. Confidence intervals around these measures indicate the precision of these results. Measures of association with confidence intervals reveal the strength, direction, and a plausible range of an effect as well as the likelihood of chance occurrence. By contrast, p values address only chance. Testing null hypotheses at a p value of 0.05 has no basis in medicine and should be discouraged.

NOTE:
There are several websites that contain educational materials and additional links that can be useful resources in designing learning activities for fellows-in-training. Two such sites are…
www.epidemiolog.net
This site contains epidemiology learning materials, including a free online "evolving" textbook.
www.epibiostat.ucsf.edu/epidem/epidem.html
The WWW VL Epidemiology site is part of the Virtual Library created by the World Wide Web Consortium at MIT and is a non-commercial listing of Web resources in epidemiology. The page is widely indexed and provides a comprehensive up-to-date resource listing. It is maintained as a public service by the Dept. of Epidemiology and Biostatistics, University of California San Francisco.

E. Informed Consent

REVIEW:
Wendler D
Can we ensure that all research subjects give valid consent?
Arch Intern Med. 2004;164:2201-4
To ensure that research subjects provide valid consent, most commentators direct clinical

investigators to formally assess potential subjects who are at increased risk for lacking the capacity to consent. Current data reveal, however, that subjects with no known cognitive impairments often fail to give valid consent. These data imply that the prevailing focus on individuals' capacity to consent is too narrow. To protect subjects, as well as the integrity of clinical research, the actual consent of all subjects should be formally assessed. Recent development of several preliminary consent assessment tools suggests that, in addition to being ethically preferable, with additional research this approach may be practically feasible. Future research should focus on developing a postdecision questionnaire that can be adapted to individual studies and used to assess the voluntariness and understanding of all research subjects.

F. Adverse Event Reporting

REVIEW:

Morse MA, Califf RM, Sugarman J.

Monitoring and ensuring safety during clinical research

JAMA 2001;285:1201-5

Increased numbers of clinical trials, many of which are large, multicenter, and sometimes international, and the marked shift of funding for clinical trials to industry have made apparent the inadequacy of mechanisms for protecting human subjects that were developed when clinical research was generally carried out on a small scale at single institutions. To address concerns regarding the protection of human subjects, a group of professionals with expertise in various aspects of clinical trials was assembled in May 2000. Participants described and evaluated the mechanisms by which clinical trials are monitored, focusing on adverse event reporting and the processes by which various parties with oversight responsibilities interact in the course of these trials. In this article, we describe the manner in which adverse event reporting might function to enhance safety and the role of data monitoring committees in using aggregate data from these reports, outline the problems that now exist for institutional review boards as they are faced with multiple adverse event reports from clinical trials while conducting continuing review, and offer recommendations for improving the current approach.

G. Grant Writing

REVIEW:

Inouye SK, Fiellin DA.

An evidence-based guide to writing grant proposals for clinical research

Ann Intern Med. 2005;142:274-82

The competition for funds to conduct clinical research is intense, and only a minority of grant proposals receive funding. In particular, funding for patient-oriented research lags behind that allocated for basic science research. Grant writing is a skill of fundamental importance to the clinical researcher, and conducting high-quality clinical research requires funds received through successful grant proposals. This article provides recommendations for the grant-writing process for clinical researchers. On the basis of observations from a National Institutes of Health study section, we describe types and sources of grant funds, provide key recommendations regarding the process of grant writing, and highlight the sections of grants that are frequently scrutinized and critiqued. We also provide specific recommendations to help grant writers improve the quality of areas commonly cited as deficient. Application of this systematic approach will make the task more manageable for anyone who writes grants.

V. Clinical Sciences

The subspecialty of allergy and immunology encompasses three major clinical areas: allergic diseases and asthma, immunoregulatory disorders, and immunodeficiency diseases. It is the intention of allergy and immunology training programs to train residents as expert consultants and accomplished practitioners in these areas. Moreover, the scholastic approaches to maintain understanding of recent advances and current concepts of the specialty over a professional lifetime must be in instilled during the training program. The following is an outline of the diseases about which allergy and immunology fellows must be knowledgeable. Training programs may vary their emphasis on the basis of mission, expertise, and resources. It is expected that all residents be trained in the physiology, pathology, differential diagnosis, and treatment of such diseases with understanding of the use therapeutic modalities including mechanisms of action, dosing, adverse effects, and costs of therapy. Explicit instruction should also be given on the importance of behavioral studies and bioethics in regard to clinical trials and appropriate use of diagnostic and therapeutic techniques.

A. Allergic Diseases and Related Disorders

1. Upper airway disease

a. Rhinitis, sinusitis, nasal polyposis, otitis (bacterial and serous), and laryngeal disorders

i. Allergic and Nonallergic Rhinitis

REVIEW:
Sarin S
The role of the nervous system in rhinitis
J Allergy Clin Immunol. 2006 Nov;118(5):999-1016

The nose provides defensive and homeostatic functions requiring rapid responses to physical and chemical stimuli. As a result, it is armed with a complex nervous system that includes sensory, parasympathetic, and sympathetic nerves. Sensory nerves transmit signals from the mucosa, generating sensations, such as pruritus; motor reflexes, such as sneezing; and parasympathetic and sympathetic reflexes that affect the glandular and vascular nasal apparatuses. Reflexes directed to the nose are also generated by inputs from other body regions. Hence all symptoms that constitute the nosologic entity of rhinitis can be triggered through neural pathways. In addition, neural signals generated in the nose can influence distal physiology, such as that of the bronchial tree and the cardiovascular system. Neural function can be chronically upregulated in the presence of mucosal inflammation, acutely with an allergic reaction, or even in the absence of inflammation, as in cases of nonallergic rhinitis. Upregulation of the nasal nervous system can occur at various levels of the reflex pathways, resulting in exaggerated responses (neural hyperresponsiveness), as well as in increased capacity for generation of neurogenic inflammation, a phenomenon that depends on the release of neuropeptides on antidromic stimulation of nociceptive sensory nerves. The molecular mechanisms of hyperresponsiveness are not understood, but several inflammatory products appear to be playing a role. Neurotrophins, such as the nerve growth factor, are prime

candidates as mediators of neural hyperresponsiveness. The many interactions between the nervous and immune systems contribute to nasal physiology but also to nasal disease.

REVIEW:
Saleh HA.
Perennial rhinitis.
BMJ.2007;335:502-7
Perennial rhinitis can be defined clinically as an inflammatory condition of the nose characterised by nasal obstruction, sneezing, itching, or rhinorrhoea, occurring for an hour or more on most days throughout the year. Rhinitis is commonly managed by both primary and secondary care physicians. Although most cases can be diagnosed and treated in primary care, referral to secondary care is often necessary when patients do not respond to treatment or other diagnoses are suspected.

REVIEW:
Berger WE
Nonallergic rhinitis in children
Curr Allergy Asthma Rep 2007;7:112-6
Nonallergic rhinitis in children is a medical condition that has not been well defined and the true incidence is unknown. Current treatment recommendations are based on data obtained from adult studies. The mechanisms of pediatric nonallergic rhinitis are also unclear. The concept that laryngopharyngeal reflux (LPR) events may play a critical role in the pathogenesis of upper airway disease is presently under investigation. Although LPR is being better delineated and appropriate methods of diagnosis and treatment are being studied, substantial evidence links LPR with several disease states including rhinitis, sinus disease, and middle ear disease. Due to the lack of information concerning the etiology of nonallergic rhinitis in children, LPR should be considered in the differential diagnosis of a child with negative skin tests and chronic rhinitis symptoms. The clinician should especially give attention to this diagnosis when a child presents with recurrent co-morbid conditions such as chronic sinusitis or persistent middle ear disease.

REVIEW:
Schubert MS
Allergic Fungal Sinusitis
Clin Rev in Allergy Immunol 2006 ;30:205-16
Many common chronic inflammatory rhinosinusitis conditions (hypertrophic sinus disease [HSD]) have the histopathological profile of allergic or asthmatic inflammation. Allergic fungal sinusitis (AFS) is both a type of noninvasive fungal rhinosinusitis and a type of HSD. AFS has clinicopathological features that make it similar, but not identical, to allergic bronchopulmonary aspergillosis (ABPA). Allergic mucin is a defined pathological entity occurring in ABPA, AFS, and in the HSD "eosinophilic mucin rhinosinusitis (EMRS)." Diagnosis of AFS requires a careful review of surgical reports, histopathology, and culture results. Treatment includes surgery and aggressive postoperative medical management of allergic inflammatory disease. Prognosis is good with integrated medical-surgical follow-up, but recurrence remains problematic. The association of ABPA, AFS, and HSD with class II genes of the major histocompatibility complex places the initiation of these inflammatory diseases within the context of antigen presentation and the acquired immune response. Pathological immunomanipulation of this response by local microbial

superantigens may be a common mechanism for disease pathogenesis. Future research into the molecular biology of these related conditions may offer insight into the pathogenesis of other chronic inflammatory diseases.

REVIEW:
Prenner BM
Allergic rhinitis: treatment based on patient profiles.
Am J Med 2006;119:230-7
Allergic rhinitis is a common medical condition characterized by nasal, throat, and ocular itching; rhinorrhea; sneezing; nasal congestion; and, less frequently, cough. The treatment of allergic rhinitis should control these symptoms without adversely affecting daily activities or cognitive performance and should prevent sequelae such as asthma exacerbation or sinusitis. This review describes a stepwise approach to treatment of allergic rhinitis derived from a synthesis of clinical trial results, patient preferences, and real-world tolerability data. Key clinical considerations include frequency and intensity of symptoms, patient age, comorbidities, compliance with treatment regimens (influenced by formulation, route and frequency of administration), and effects on quality of life. Oral second-generation antihistamines, versus first-generation agents and inhaled corticosteroids, should be considered first-line treatment because they provide rapid relief of most allergic rhinitis symptoms without safety and tolerability issues. Additional therapeutic agents can then be added or substituted based on individual symptom response.

REVIEW:
Passalacqua G
Rhinitis, rhinosinusitis and quality of life in children.
Pediatr Allergy Immunol. 2007;18:40-5.
Quality of life (QoL) or, rather, health-related QoL, is currently regarded as a crucial aspect of the general well-being of patients and, in consequence, of the effects of a disease and its treatment. This is particularly true for respiratory allergy (asthma and rhinitis), which are chronic diseases and also for sinusitis (rhinosinusitis). A number of questionnaires (instruments), either generic or specific, have been developed and validated to assess the QoL in adults and children, for asthma and rhinitis, whereas there are few specific instruments for chronic rhinosinusitis. The literature provides strong evidence of the effects of allergic rhinitis, asthma and their treatments on QoL in paediatric patients, as well as in adults, whereas the number of experimental data on rhinosinusitis is limited, especially in children. Clinical trials evidenced some controversial points, mainly the weak correlation existing between QoL and traditional objective parameters. It has become clear that the QoL questionnaires measure the aspects of the disease that partially differ from the routinely evaluated parameters and that QoL should integrate, not replace, the objective measurements.

REVIEW:
Nathan RA.
The burden of allergic rhinitis.
Allergy Asthma Proceed 2007; 28:3-9
Although formerly regarded as a nuisance disease, allergic rhinitis (AR) has a considerable effect on quality of life and can have significant consequences if left untreated. The total burden of this disease lies not only in impaired physical and social functioning but also in a financial burden

made greater when considering evidence that AR is a possible causal factor in comorbid diseases such as asthma or sinusitis. Compared with matched controls, patients with AR have an approximate twofold increase in medication costs and 1.8-fold the number of visits to health practitioners. Hidden direct costs include the treatment of comorbid asthma, chronic sinusitis, otitis media, upper respiratory infection, and nasal polyposis. Nasal congestion, the most prominent symptom in AR, is associated with sleep-disordered breathing, a condition that can have a profound effect on mental health, including increased psychiatric disorders, depression, anxiety, and alcohol abuse. Furthermore, sleep-disordered breathing in childhood and adolescence is associated with increased disorders of learning performance, behavior, and attention. In the United States, AR results in 3.5 million lost workdays and 2 million lost schooldays annually. Patients struggle to alleviate their misery, frequently self-adjusting their treatment regimen of over-the-counter and prescription medications because of lack of efficacy, deterioration of efficacy, lack of 24-hour relief, and bothersome side effects. Ironically, health care providers overestimate patient satisfaction with therapy. Therefore, improvement in patient-practitioner communication may enhance patient adherence with prescribed regimens.

REVIEW:
Greiner AN
Pharmacologic rationale for treating allergic and nonallergic rhinits
J Allergy Clin Immunol 2006;118:185-96
Allergic rhinitis (AR) and perennial nonallergic rhinitis (PNAR) represent conditions affecting millions of individuals across the world. Although the diagnosis of AR might be presumptively based on the types of symptoms and the history of allergen triggers, confirmation requires documentation of specific IgE reactivity. In contrast, PNAR is a condition with similar symptomatology but in which the patient has no identifiable specific allergic sensitivities. This review presents the diverse options of currently available pharmacologic agents for the treatment of AR and PNAR, including intranasal corticosteroids, H1-antihistamines, decongestants, cromolyn sodium, antileukotrienes, anticholinergics, capsaicin, anti-IgE, and intranasal saline. Furthermore, appropriate stepped-up, stepped-down pharmacotherapeutic algorithms are described for the various forms of rhinitis.

REVIEW:
Nelson H.
Advances in upper airway diseases and allergen immunotherapy.
J Allergy Clin Immunol. 2007;119:872-80
The purpose of this review is to highlight important articles on upper airway diseases and immunotherapy that appeared during 2006. Studies from Europe continue to examine the usefulness of the Allergic Rhinitis and its Impact on Asthma classification of allergic rhinitis as intermittent or persistent and its levels of severity as mild or moderate/severe. A number of physical agents were shown to effect nasal inflammation: sudden temperature changes in patients with allergic rhinitis increased eosinophilic inflammation; in children with allergic asthma, the personal exposure to particles <2.5 microm air pollution correlated with percent of nasal eosinophils and levels of markers of nasal exudation; and in patients who developed rhinorrhea on exposure to cold and windy weather, nasal challenge with cold dry air caused sloughing of nasal epithelial cells. A 3-month double-blind, placebo-controlled study of nasal washes with amphoteracin B showed no benefit in patients with chronic rhinosinusitis. Studies of

immunotherapy with grass and dog dander extracts confirmed the need for doses containing 15 to 20 microg of the major allergen for optimal effectiveness. The protective effect of immunotherapy on the development of asthma in children with allergic rhinitis was shown to still be present 2 years after completion of a 3-year course of treatment. Injection immunotherapy with a moderate dose of house dust mite extract in house dust-sensitive adults with atopic dermatitis reduced symptoms and use of corticosteroids and antihistamines compared with treatment with about 1/1000 of that dose of the same extract. Pretreatment for 9 weeks with the monoclonal anti-IgE antibody omalizumab reduced systemic reactions during rush immunotherapy 5-fold and allowed further build-up at weekly intervals without systemic reactions. A review of sublingual immunotherapy confirmed both efficacy and safety, but evidence for appropriate dosing and for the effectiveness of sublingual immunotherapy employing multiple allergen mixes was still lacking. Two studies with a sublingual grass pollen extract tablet showed a clear dose response and the ability to initiate sublingual immunotherapy without an up-dosing phase. A pilot study with cytosine phosphorothionate quanosine DNA conjugated to the major allergen of ragweed reported impressive improvement in symptoms the first pollen season that persisted during the second pollen season without any further administration of the conjugate. In conclusion, studies on rhinitis and sinusitis explored the pathophysiology of the disease more than offering new therapeutic approaches. Studies on immunotherapy addressed optimal dosing, but also a variety of safer and more convenient approaches such as reduction of IgE with omalizumab, conjugating allergen to immunostimulatory DNA sequences, or administration by the sublingual route.

REVIEW:
Akdis M
Mechanisms of allergen-specific immunotherapy
J Allergy Clin Immunol 2007;119:780-791
Allergen-specific immunotherapy (SIT) has been used for almost a century as a desensitizing therapy for allergic diseases and represents the only curative and specific method of treatment. Administration of appropriate concentrations of allergen extracts has been shown to be reproducibly effective when patients are carefully selected. The mechanisms by which allergen-SIT has its effects include the modulation of T-cell and B-cell responses and related antibody isotypes as well as effector cells of allergic inflammation, such as eosinophils, basophils, and mast cells. The balance between allergen-specific T-regulatory (Treg) and TH2 cells appears to be decisive in the development of allergic and healthy immune responses against allergens. Treg cells consistently represent the dominant subset specific for common environmental allergens in sensitized healthy individuals. In contrast, there is a high frequency of allergen-specific TH2 cells in patients with allergy. The induction of a tolerant state in peripheral T cells represents an essential step in allergen-SIT. Peripheral T-cell tolerance is characterized mainly by generation of allergen-specific Treg cells leading to suppressed T-cell proliferation and TH1 and TH2 cytokine responses against the allergen. This is accompanied by a significant increase in allergen-specific IgG4, and also IgG1 and IgA, and a decrease in IgE in the late stage of the disease. In addition, decreased tissue infiltration of mast cells and eosinophils and their mediator release including circulating basophils takes place. Current understanding of mechanisms of allergen-SIT, particularly the role of Treg cells in peripheral tolerance, may enable novel treatment strategies.

RESEARCH FRONTIER:
Creticos PS

Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis.
N Engl J Med. 2006; 5;355(:1445-55

BACKGROUND: Conjugating immunostimulatory sequences of DNA to specific allergens offers a new approach to allergen immunotherapy that reduces acute allergic responses. METHODS: We conducted a randomized, double-blind, placebo-controlled phase 2 trial of a vaccine consisting of Amb a 1, a ragweed-pollen antigen, conjugated to a phosphorothioate oligodeoxyribonucleotide immunostimulatory sequence of DNA (AIC) in 25 adults who were allergic to ragweed. Patients received six weekly injections of the AIC or placebo vaccine before the first ragweed season and were monitored during the next two ragweed seasons. RESULTS: There was no pattern of vaccine-associated systemic reactions or clinically significant laboratory abnormalities. AIC did not alter the primary end point, the vascular permeability response (measured by the albumin level in nasal-lavage fluid) to nasal provocation. During the first ragweed season, the AIC group had better peak-season rhinitis scores on the visual-analogue scale (P=0.006), peak-season daily nasal symptom diary scores (P=0.02), and midseason overall quality-of-life scores (P=0.05) than the placebo group. AIC induced a transient increase in Amb a 1-specific IgG antibody but suppressed the seasonal increase in Amb a 1-specific IgE antibody. A reduction in the number of interleukin-4-positive basophils in AIC-treated patients correlated with lower rhinitis visual-analogue scores (r=0.49, P=0.03). Clinical benefits of AIC were again observed in the subsequent ragweed season, with improvements over placebo in peak-season rhinitis visual-analogue scores (P=0.02) and peak-season daily nasal symptom diary scores (P=0.02). The seasonal specific IgE antibody response was again suppressed, with no significant change in IgE antibody titer during the ragweed season (P=0.19). CONCLUSIONS: In this pilot study, a 6-week regimen of the AIC vaccine appeared to offer long-term clinical efficacy in the treatment of ragweed allergic rhinitis.

REVIEW:
Nelson H
Allergen Immunotherapy: Where is it now?
J Allergy Clin Immunol 2007;119:769-79

The scientific basis and the proof of clinical effectiveness of allergen immunotherapy administered by subcutaneous injection (SCIT) are well established. It is effective treatment for sensitivity to Hymenoptera venom and for allergic rhinitis and allergic asthma. SCIT administered in the proper setting reduces the development of new sensitivities and progression from rhinitis to asthma. Further, the beneficial effects persist long after completion of a course of treatment. Although many people enjoy the benefits of SCIT, extension of its use to the many others who might be candidates for this treatment is limited by its drawbacks of safety concerns and the inconvenience of repeated clinic visits over several years to receive the injections. There are many attempts underway to improve on the safety and convenience while still retaining the benefits of SCIT. These include approaches using current allergen extracts, especially by administering them sublingually. Alternatively, through recombinant technology, extracts are being modified to reduce their allergenicity without reducing their immunogenicity. They are being linked to immunostimulatory DNA sequences that will modify their in vivo processing resulting in an enhanced nonallergic response or they are being incorporated into fusion proteins with inhibitory properties for mast cells and basophils.

REVIEW:
Cox LS.

Sublingual immunotherapy: a comprehensive review.
J Allergy Clin Immunol 2006;117:1021-35
Sublingual immunotherapy (SLIT) has been used with increasing frequency in Europe and is viewed with increasing interest by allergists in the United States. To address this interest, a Joint Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology's Immunotherapy and Allergy Diagnostic Committees reviewed the available literature on SLIT and prepared this report. The task force concluded that despite clear evidence that SLIT is an effective treatment, many questions remained unanswered, including effective dose, treatment schedules, and overall duration of treatment. Until these have been determined, an assessment of the cost/benefit ratio of the treatment cannot be made. SLIT does appear to be associated with few serious side effects, but it has not been administered in high-risk asthmatic patients, nor in the studies reviewed has it been administered as a mixture of non-cross-reacting allergens. Furthermore, there is currently no allergy extract approved for this use in the United States, nor is there a Current Procedural Terminology code for billing purposes. All of these factors should be given careful consideration by anyone contemplating initiating SLIT treatment for their allergic patients.

PRACTICE PARAMETER / GUIDELINE:
Allergen immunotherapy: a practice parameter second update
Joint Task Force on Practice Parameters;
J Allergy Clin Immunol. 2007;120:S25-85.
The objective of "Allergen immunotherapy: a practice parameter" is to improve the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. This parameter is intended to increase the appropriate use of allergen immunotherapy; reduce the underuse, overuse, and misuse of allergen immunotherapy; and establish guidelines for the safe and effective use of allergen immunotherapy, while reducing unwanted and unneeded variation in immunotherapy practice

ii. Sinusitis and Rhinosinusitis

REVIEW:
Brooke I
Acute and chronic bacterial sinusitis.
Infect Dis Clin North Am. 2007;21:427-48
Sinusitis is one of the most common complaints resulting in physician visits in the United States. An antecedent viral infection of the upper respiratory tract is the most common presentation. Despite its prevalence, most cases resolve spontaneously. Only a small proportion develops a secondary bacterial infection that will benefit from antimicrobial therapy. This article discusses the microbiology and pathogenesis of acute and chronic bacterial sinusitis. The role anaerobic bacterial in chronic and recurrent sinusitis is emphasized, and appropriate antimicrobial regimens are discussed.

REVIEW:
Steele RW
Chronic sinusitis in children
Clin Pediatr 2005;44:465-71

Clinical practice guidelines for the management of acute sinusitis in children have been published by the American Academy of Pediatrics. Of note is that in this document, a brief discussion of chronic disease concluded that the pathogenesis and management are essentially unknown. Although there are insufficient data in the literature to develop evidence-based clinical guidelines, a careful review of the literature and clinical experience of experts who manage pediatric chronic sinusitis is presented in an effort to develop specific recommendations and to offer practical treatment options. Factors associated with chronic sinusitis should be addressed individually and include recurrent viral upper respiratory infections, allergic and nonallergic rhinitis, ciliary dyskinesia, cystic fibrosis, immunodeficiency, and anatomic abnormalities. Bacteriology includes the 3 pathogens associated with acute disease i.e., Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis but with chronic sinusitis also includes Staphylococcus aureus, anaerobic bacteria, and fungi. Medical interventions discussed include endoscopic sinus surgery, saline nasal irrigation, intranasal decongestant therapy, intranasal steroids, and oral antibiotics. Clinical ranking without regard to side effects and cost suggests that endoscopic sinus surgery and antral irrigation have the highest probability of substantial symptom improvement. Other issues discussed include identification and management of gastroesophageal reflux disease (GERD), allergy, and immune deficiency.

REVIEW:
Piccirillo, JF
Acute bacterial sinusitis,
N Engl J Med; 2004;351, 902-10
OUTLINE: The Clinical Problem - Acute bacterial sinusitis; Strategies and Evidence; Diagnosis and Therapy; Uncomplicated Sinusitis; Complicated or Severe Sinusitis; Patients with Allergic Rhinitis; Areas of Uncertainty; Guidelines; Conclusions and Recommendations

REVIEW:
Bhattacharyya N.
Progress in surgical management of chronic rhinosinusitis and nasal polyposis.
Curr Allergy Asthma Rep. 2007;7:216-20.
Endoscopic sinus surgery (ESS) remains the treatment of choice for medically refractory chronic rhinosinusitis (CRS) with or without nasal polyposis (NP). ESS has undergone review, reassessment, and substantial refinement. Several advances (eg, powered instrumentation, image guidance, adjunctive intraoperative procedures) have expanded the scope of cases amenable to ESS, decreased operative time and intraoperative blood loss, and improved safety. Procoagulant nasal/sinus packing and refinements of technique have decreased the need for postoperative removal of packing, thus decreasing morbidity. Methods to reduce synechia formation (ie, mitomycin-c) have been explored, with mixed results. Novel methods of sinusotomy (eg, balloon catheter dilatation of the sinus ostia) have had limited but interesting short-term results. We can expect further advances in ESS with better patient outcomes. However, continued elucidation of the underlying pathophysiology of CRS and NP are essential to long-term improvement.

REVIEW:
Small CB
Judicious antibiotic use and intranasal corticosteroids in acute rhinosinusitis.
Am J Med. 2007;120:289-94.

Most patients with symptoms of acute rhinosinusitis are treated with antibiotics. However, many cases of rhinosinusitis are secondary to viral infections and unlikely to benefit from antibiotic therapy. Inappropriate use of antibiotics in patients with acute nonbacterial rhinosinusitis contributes to the increase in bacterial antibiotic resistance. Consequently, safe and effective alternatives to antibiotics are needed in the treatment of acute rhinosinusitis caused by viral infections. Recent results from controlled trials have shown that intranasal corticosteroids, used in combination with antibiotics or as monotherapy in selected cases, provide significant symptom relief and resolution of acute rhinosinusitis. The use of intranasal corticosteroids in acute rhinosinusitis therefore might reduce the inappropriate use of antimicrobial therapy in acute rhinosinusitis.

KEY CLINICAL PUBLICATION:
Williamson IG
Antibiotics and Topical Nasal Steroid for Treatment of Acute Maxillary Sinusitis: A Randomized Controlled Trial
JAMA. 2007;298(21):2487-2496
CONTEXT: Acute sinusitis is a common clinical problem that usually results in a prescription for antibiotics but the role of antibiotics is debated. Anti-inflammatory drugs such as topical steroids may be beneficial but are underresearched. OBJECTIVE: To determine the effectiveness of amoxicillin and topical budesonide in acute maxillary sinusitis. DESIGIN, SETTING AND PATIENTS: A double-blind, randomized, placebo-controlled factorial trial of 240 adults (aged ≥ 16 years) with acute nonrecurrent sinusitis (had ≥2 diagnostic criteria: purulent rhinorrhea with unilateral predominance, local pain with unilateral predominance, purulent rhinorrhea bilateral, presence of pus in the nasal cavity) at 58 family practices (74 family physicians) between November 2001 and November 2005. Patients were randomized to 1 of 4 treatment groups: antibiotic and nasal steroid; placebo antibiotic and nasal steroid; antibiotic and placebo nasal steroid; placebo antibiotic and placebo nasal steroid. INTERVENTION: A dose of 500 mg of amoxicillin 3 times per day for 7 days and 200 µg of budesonide in each nostril once per day for 10 days. MAIN OUTCOME MEASURES: Proportion clinically cured at day 10 using patient symptom diaries and the duration and severity of symptoms. RESULTS: The proportions of patients with symptoms lasting 10 or more days were 29 of 100 (29%) for amoxicillin vs 36 of 107 (33.6%) for no amoxicillin (adjusted odds ratio, 0.99; 95% confidence interval, 0.57-1.73). The proportions of patients with symptoms lasting 10 or more days were 32 of 102 (31.4%) for topical budesonide vs 33 of 105 (31.4%) for no budesonide (adjusted odds ratio, 0.93; 95% confidence interval, 0.54-1.62). Secondary analysis suggested that nasal steroids were significantly more effective in patients with less severe symptoms at baseline. CONCLUSION: Neither an antibiotic nor a topical steroid alone or in combination was effective as a treatment for acute sinusitis in the primary care setting.

REVIEW:
Harvey R
Nasal saline irrigations for the symptoms of chronic rhinosinusitis.
Cochrane Database Syst Rev. 2007 Jul 18;(3):CD006394
BACKGROUND: The use of nasal irrigation for the treatment of nose and sinus complaints has its foundations in yogic and homeopathic traditions. There has been increasing use of saline irrigation, douches, sprays and rinsing as an adjunct to the medical management of chronic

rhinosinusitis. Treatment strategies often include the use of topical saline from once to more than four times a day. Considerable patient effort is often involved. Any additional benefit has been difficult to discern from other treatments. OBJECTIVES: To evaluate the effectiveness and safety of topical saline in the management of chronic rhinosinusitis. SEARCH STRATEGY: Our search included the Cochrane Ear, Nose and Throat Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4 2006), MEDLINE (1950 to 2006) and EMBASE (1974 to 2006). The date of the last search was November 2006. SELECTION CRITERIA: Randomised controlled trials in which saline was evaluated in comparison with either no treatment, a placebo, as an adjunct to other treatments or against treatments. The comparison of hypertonic versus isotonic solutions was also compared. DATA COLLECTION AND ANALYSIS: Trials were graded for methodological quality using the Cochrane approach (modification of Chalmers 1990). Only symptom scores from saline versus no treatment and symptom and radiological scores from the hypertonic versus isotonic group could be pooled for statistical analysis. A narrative overview of the remaining results is presented. MAIN RESULTS: Eight trials were identified that satisfied the inclusion criteria. Three studies compared topical saline against no treatment, one against placebo, one as an adjunct to and one against an intranasal steroid spray. Two studies compared different hypertonic solutions against isotonic saline.There is evidence that saline is beneficial in the treatment of the symptoms of chronic rhinosinusitis when used as the sole modality of treatment. Evidence also exists in favour of saline as a treatment adjunct. No superiority was seen when saline was compared against a reflexology 'placebo'. Saline is not as effective as an intranasal steroid. Some evidence suggests that hypertonic solutions improve objective measures but the impact on symptoms is less clear. AUTHORS' CONCLUSIONS: Saline irrigations are well tolerated. Although minor side effects are common, the beneficial effect of saline appears to outweigh these drawbacks for the majority of patients. The use of topical saline could be included as a treatment adjunct for the symptoms of chronic rhinosinusitis.

PRACTICE PARAMETERS GUIDELINE:
Slavin RG, Spector SL, Bernstein I et al
The diagnosis and management of sinusitis: A practice parameter
J Allergy Clin Immunol 2005;116:S13-S47
The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing “The diagnosis and management of sinusitis: a practice parameter update.” This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. These parameters are not designed for pharmaceutical companies in drug promotion.

iii. Nasal Polyposis

REVIEW:
Fokkens W

European position paper on rhinosinusitis and nasal polyps 2007
Rhinology – Supplement 2007;20:1-136
Rhinosinusitis is a significant and increasing health problem which results in a large financial burden on society. This evidence based position paper describes what is known about rhinosinusitis and nasal polyps, offers evidence based recommendations on diagnosis and treatment, and considers how we can make progress with research in this area. Rhinitis and sinusitis usually coexist and are concurrent in most individuals; thus, the correct terminology is now rhinosinusitis. Rhinosinusitis (including nasal polyps) is defined as inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), +/- facial pain/pressure, +/- reduction or loss of smell; and either endoscopic signs of polyps and/or mucopurulent discharge primarily from middle meatus and/or; oedema/mucosal obstruction primarily in middle meatus, and/or CT changes showing mucosal changes within the ostiomeatal complex and/or sinuses. The paper gives different definitions for epidemiology, first line and second line treatment and for research. Furthermore the paper describes the anatomy and (patho)physiology, epidemiology and predisposing factors, inflammatory mechanisms, evidence based diagnosis, medical and surgical treatment in acute and chronic rhinosinusitis and nasal polyposis in adults and children. Evidence based schemes for diagnosis and treatment are given for the first and second line clinicians. Moreover attention is given to complications and socio-economic cost of chronic rhinosinusitis and nasal polyps. Last but not least the relation to the lower airways is discussed.

REVIEW:
Rinnia AB
Nasal polyposis: a cellular-based approach to answering questions.
Allergy 2007; 62:348-58
This review aims at discussing some of the difficulties and pitfalls in NP research, and to identify the important cellular players and interactions in the pathophysiology of NP. We would also like to suggest potential relevant future directions for research. Understanding the pathogenesis of NP may lead to new treatment options for this incapacitating disease.

REVIEW:
Pawliczak R.
Pathogenesis of nasal polyps: an update.
Curr Allergy Asthma Rep. 2005;5:463-71
The cause of nasal polyp formation is still unknown. Genetic predisposition has been suggested, but there are scanty data to support such theories. Activated epithelial cells may be the major source of mediators inducing influx of inflammatory cells (mostly eosinophils) and proliferation and activation of fibroblasts leading to nasal polyp formation. Infectious agents (including viruses, bacteria, or fungi) may be potential primary factors activating nasal epithelial cells. Proinflammatory cytokines and growth factors play important roles in the persistence of mucosal inflammation associated with nasal polyps. Arachidonic acid metabolites seem to be particularly important in the pathogenesis of nasal polyps in patients with aspirin hypersensitivity rhinosinusitis/asthma syndrome.

REVIEW:

Stenvenson DD
Selection of patients for ASA desensitization
J Allergy Clin Immunol 2006; 801-4
Aspirin-exacerbated respiratory disease (AERD) is an acquired disease that consists of chronic hyperplastic eosinophilic sinusitis and nasal polyposis, asthma, and aspirin hypersensitivity. There are very few patients with AERD who only have AERD and no other provoking factors. For example, in our series of 300 patients with AERD, two thirds had positive wheal-and-flare skin test responses that were frequently present since childhood.1 Almost all patients with AERD have complications of infectious rhinitis and sinusitis (viral, bacterial, and fungal). Furthermore, all of the other myriad provoking factors for asthma, such as gastroesophageal reflux disease (GERD), irritant inhalation, and exercise, continue to be active provocateurs. Therefore clinicians need to identify other provoking factors and aggressively treat these non-AERD–provoking factors and mechanisms.

REVIEW:
Bhattacharyya N.
Progress in surgical management of chronic rhinosinusitis and nasal polyposis.
Curr Allergy Asthma Rep. 2007 7:216-20
Endoscopic sinus surgery (ESS) remains the treatment of choice for medically refractory chronic rhinosinusitis (CRS) with or without nasal polyposis (NP). ESS has undergone review, reassessment, and substantial refinement. Several advances (eg, powered instrumentation, image guidance, adjunctive intraoperative procedures) have expanded the scope of cases amenable to ESS, decreased operative time and intraoperative blood loss, and improved safety. Procoagulant nasal/sinus packing and refinements of technique have decreased the need for postoperative removal of packing, thus decreasing morbidity. Methods to reduce synechia formation (ie, mitomycin-c) have been explored, with mixed results. Novel methods of sinusotomy (eg, balloon catheter dilatation of the sinus ostia) have had limited but interesting short-term results. We can expect further advances in ESS with better patient outcomes. However, continued elucidation of the underlying pathophysiology of CRS and NP are essential to long-term improvement.

RESEARCH FRONTIER:
Wang J
Involvement of Toll-like receptors in the immune response of nasal polyp epithelial cells.
Clin Immunol 2007;124:345-52
Recognition systems employed by airway epithelial cells to respond to microbial exposure include the action of Toll-like receptors (TLRs). We investigated the presence and function of TLR2, 3, and 4 in primary cultures of human nasal polyp epithelial cells. dsRNA stimulation significantly enhanced the expression and secretion of RANTES, IP-10, IL-8, and GM-CSF. LPS also exhibited stimulatory action, but it was much weaker than dsRNA. Peptidoglycan had no significant stimulatory action on the genes. Flow cytometry showed that the nasal polyp epithelial cell mainly expressed TLR3 in an intracellular compartment, but expression of TLR2 and TLR4 was very low on both the cell surface and in the cell. The immune response of primary nasal polyp epithelial cells induced by TLR3 could not be blocked by anti-TLR3 antibody. Among the TLR ligands evaluated, dsRNA, the ligand for TLR3, mediated the strongest pro-inflammatory effects in primary nasal polyp epithelial cells.

RESEARCH FRONTIER:
Ediger D
Airway inflammation in nasal polyposis: immunopathological aspects of relation to asthma
Clin Exp Allergy. 2005 Mar;35:319-26

BACKGROUND: Nasal polyposis (NP) is a chronic inflammatory disorder of the upper respiratory tract, which is often coexist with asthma. However, the pathogenesis of especially in patients with NP is still a matter of debate. OBJECTIVE: To better understand the immunopathologic mechanism involved in this relationship, we investigated the inflammatory cell profiles in bronchial and nasal tissues of patients with NP alone and with concomitant asthma. METHODS: Seventeen patients with NP (six male, 11 female, age range: 19-63, mean age: 38.29+/-13.27 years) were selected for the study. Subjects were divided into two groups based on the presence of asthma or bronchial hyper-responsiveness (BHR). NP without BHR (Group 1) (n=8), NP and asthma or BHR (Group 2) (n=9). All patients underwent atopy evaluation including detailed history, skin prick test (SPT), total and specific IgE determination in sera. None of the subjects had taken inhaled, nasal or oral corticosteroids for at least 1 month before the study. Respiratory symptoms of asthmatic patients were controlled with only short acting beta(2)-agonist inhaler drugs as needed. NP tissue, nasal and bronchial mucosa biopsies were taken from all patients using fiberoptic endoscopy. CD3, CD8, CD16, CD68, AA1 (mast cell tryptase), human leucocyte antigen-DR (HLA-DR) and eosinophil peroxidase (EPO) expressing cells in specimens were determined by immunohistochemical methods. Positively staining inflammatory cell types were counted. Subepithelial lamina propria and periglandular areas were separately evaluated. RESULTS: No significant difference was found in polyp tissue, nasal and bronchial CD3(+), CD8(+), CD16(+), CD68(+), AA1(+), HLA-DR(+) and EPO(+) positive cells between groups. There were significantly higher numbers of CD8(+), CD16(+), HLA-DR(+), EPO(+) cells in the polyp tissue and nasal mucosa vs. the bronchial mucosa in all groups ($P<0.05$). However, CD8(+) cells were significantly increased in the polyp tissue and bronchial mucosa of patients with NP alone when compared with the patients with both asthma and NP ($P<0.05$). CD3(+), CD68(+) and CD16(+) cell counts were tended to be higher within the nasal polyp tissue of patients with isolated NP compared with counts within nasal and bronchial mucosa of patients with NP and asthma. Also, patients with isolated NP showed more HLA-DR(+) cells in the nasal polyp tissue and nasal mucosa than those of patients with NP and asthma. Immunoreactivity for EPO(+) eosinophils within the nasal and bronchial mucosa was more prominent in patients with NP and asthma compared with patients with NP alone. The number of EPO(+) eosinophils within the polyp tissue, nasal and bronchial mucosa was higher in the skin prick test negative (SPT -ve) group than the SPT positive (SPT +ve) ones. CONCLUSIONS: Our results demonstrate that infiltration of inflammatory cells in the nasal and the lower airways do not remarkably differ between patients with NP alone who has no evidence of BHR and asthmatic patients with NP. However, patients with SPT-ve NP reveal more intense eosinophilic inflammation in the entire respiratory mucosa.

iv. Otitis

REVIEW:
Pelton SI.
Otitis media: re-evaluation of diagnosis and treatment in the era of antimicrobial resistance, pneumococcal conjugate vaccine, and evolving morbidity
Pediatr Clin NA 2005; 52:711-28

The changing susceptibility of bacterial otopathogens is only one aspect of the evolving concepts regarding pathogenesis, immunoprophylaxis, pharmacodynamics, and sequelae of acute otitis media that mandates new insights for achieving a successful outcome. 2004 guidelines by the American Academy of Pediatrics for the treatment of acute otitis media provide one perspective that proposes a rethinking of the routine use of antimicrobial therapy with the hope of preventing further increases in bacterial resistance among otopathogens. The goals of this article are to incorporate the advances in diagnosis, treatment, prevention, and management of sequelae into strategies that optimize the outcome of acute otitis media and limit further emergence of resistant otopathogens.

RESEARCH FRONTIER:
Samuel EA
Cytokine regulation of mucin secretion in a human middle ear epithelial model
Cytokine 2007 (December 4 e publication ahead of print)
Objectives: Middle ear mucins are associated with otitis media (OM), contribute to hearing loss and are regulated by cytokines. This work investigates the regulation of mucin secretion from human middle ear epithelial cells (HMEEC) by inflammatory cytokines interleukin-1beta (IL-1beta), tumor necrosis factor-alpha (TNF-alpha) and cytokine inhibitors interleukin-1 receptor antagonist (IL-1ra) and anti-tumor necrosis factor-alpha antibody (TNFab). Methods: HMEEC were exposed to IL-1beta and TNF-alpha in a dose- and time-dependent manner. Cytokine stimulated HMEEC were also exposed to IL-1ra and TNFab in a dose-dependent manner. Mucin secretion was characterized by exclusion chromatography and liquid scintillation. Results: HMEEC exposed to IL-1beta and TNF-alpha demonstrated significant upregulation of mucin secretion in a dose-dependent fashion. Cultures exposed to IL-1beta at 100ng/ml and TNF-alpha at 200ng/ml showed increased mucin secretion in time-dependent experiments at 16h (P=0.00008) for TNF-alpha and 8 (P=0.028) and 16h (P=0.00001) for IL-1beta. IL-1ra and TNFab inhibited the effects of increased mucin secretion by IL-1beta and TNF-alpha. Conclusions: IL-1beta and TNF-alpha upregulate mucin secretion from HMEEC in a dose- and time-dependant manner and these effects can be inhibited by cytokine blockade. Improved understanding of these mechanisms has the potential to alter the approach and management of OM and lead to novel therapeutic interventions.

v. Laryngeal disorders

REVIEW:
Ford CN
Evaluation and management of laryngoesophageal reflux
JAMA. 2005;294:1534-40.
CONTEXT: Laryngopharyngeal reflux (LPR) is a major cause of laryngeal inflammation and presents with a constellation of symptoms different from classic gastroesophageal reflux disease. OBJECTIVE: To provide a practical approach to evaluating and managing cases of LPR. EVIDENCE ACQUISITION: The PubMed database and the Ovid Database of Systematic reviews were systematically searched for laryngopharyngeal reflux, laryngopharyngeal reflux fundoplication, laryngopharyngeal reflux PPI treatment, and gastroesophageal reflux AND laryngitis. Pertinent subject matter journals and reference lists of key research articles were also hand-searched for articles relevant to the analysis. EVIDENCE SYNTHESIS: Reflux of gastric contents is a major cause of laryngeal pathology. The pathophysiology and symptom complex of

LPR differs from gastroesophageal reflux disease. Laryngeal pathology results from small amounts of refluxate--typically occurring while upright during the daytime--causing damage to laryngeal tissues and producing localized symptoms. Unlike classic gastroesophageal reflux, LPR is not usually associated with esophagitis, heartburn, or complaints of regurgitation. There is no pathognomonic symptom or finding, but characteristic symptoms and laryngoscopic findings provide the basis for validated assessment instruments (the Reflux Symptom Index and Reflux Finding Score) useful in initial diagnosis. There are 3 approaches to confirming the diagnosis of LPR: (1) response of symptoms to behavioral and empirical medical treatment, (2) endoscopic observation of mucosal injury, and (3) demonstration of reflux events by impedance and pH-monitoring studies and barium swallow esophagram. While pH monitoring remains the standard for confirming the diagnosis of gastroesophageal reflux, the addition of multichannel intraluminal impedance technology improves diagnostic accuracy for describing LPR events. Ambulatory multichannel intraluminal impedance assessment allows for identification of gaseous as well as liquid refluxate and detection of nonacid reflux events that are likely significant in confirming LPR. Although some patients respond to conservative behavioral and medical management, as is the case with gastroesophageal reflux, most require more aggressive and prolonged treatment to achieve regression of symptoms and laryngeal tissue changes. Surgical intervention such as laparoscopic fundoplication is useful in selected recalcitrant cases with laxity of the gastroesophageal sphincter. CONCLUSIONS: Laryngopharyngeal reflux should be suspected when the history and laryngoscopy findings are suggestive of the diagnosis. Failure to respond to a 3-month trial of behavioral change and gastric acid suppression by adequate doses of proton pump inhibitor medication dictates need for confirmatory studies. Multichannel intraluminal impedance and pH-monitoring studies are most useful in confirming LPR and assessing the magnitude of the problem.

REVIEW:
Ibrahim WH
Paradoxical vocal cord motion disorder: past, present and future.
Postgrad Med J 2007;83:164-72
Paradoxical vocal cord motion disorder (PVCM), also called vocal cord dysfunction, is an important differential diagnosis for asthma. The disorder is often misdiagnosed as asthma leading to unnecessary drug use, very high medical utilisation and occasionally tracheal intubation or tracheostomy. Laryngoscopy is the gold standard for diagnosis of PVCM. Speech therapy and psychotherapy are considered the cornerstone of management of this disorder. The aim of this article is to increase the awareness of PVCM among doctors, highlighting the main characteristics that distinguish it from asthma and discuss the recent medical achievements and the possible future perspectives related to this disorder.

CUTTING EDGE ARTICLE:
Cukier-Blaj S, Bewley A, Aviv JE, Murry T.
Paradoxical Vocal Fold Motion: A Sensory-Motor Laryngeal Disorder
Laryngoscope. 2007 Nov 8 [Epub ahead of print]
OBJECTIVES:: The purpose of this study is to determine the laryngeal sensitivity (LS) thresholds and the ratings of laryngopharyngeal reflux symptoms in patients with paradoxical vocal fold motion (PVFM). METHODS:: This is a chart review following Institutional Review Board approval of 75 patients from January 2006 to June 2007. The patients were diagnosed with PVFM

following case history, transnasal flexible laryngoscopy and spirometric testing. The data analyzed consisted of the reflux symptom index (RSI) and laryngopharyngeal sensitivity (LS). Laryngeal sensitivity and RSI were graded according to mild, moderate, or severe. RESULTS:: There were 12 (16%) patients with normal RSI scores, 37 patients (49.3%) with moderate RSI (RSI 11-22), and 26 patients (34.7%) with severe RSI (RSI >22). The right LS was normal in 11 patients (14.7%), moderately impaired in 16 patients (21.3%), and severely impaired in 48 (64%) patients. The left LS showed normal sensation in 11 patients (14.7%), moderately impaired LS in 13 patients (17.3%), and severe impairment in 51 patients (68%). Only one patient had both normal sensation and normal RSI, and 70.4% of patients had abnormal RSI and sensation thresholds. CONCLUSIONS:: Patients diagnosed with PVFM had a high prevalence of symptoms related to LPR and markedly reduced LS. These findings suggest that PVFM may be triggered by reduced peripheral sensation or laryngeal inflammation.

b. Clinical skills and interpretive strategies for diagnosis of upper airway diseases: skin testing (epicutaneous and intracutaneous); cytology of nasal secretions; understanding of indications for and methodology of nasal challenges; rhinoscopy; nasal and ear examination; gross assessment of upper airway imaging studies.

i. skin testing

REVIEW:
Oppenheimer J
Skin testing.
Ann Allergy Asthma Immunol. 2006; 96:S6-12
OBJECTIVE: To provide the reader with a relevant review of the literature regarding skin testing in the allergist's office. DATA SOURCES: A PubMed search for the years 1970 through 2005 was performed using the following keywords: allergy skin testing, skin prick testing, and intradermal skin testing. STUDY SELECTION: Articles that highlighted aspects of sentinel to clinical allergists' use of skin testing in the office, such as methods of skin testing, intradermal vs skin prick testing, skin test devices, and methods of expressing skin test results, were selected for further review. RESULTS: Skin testing remains the central test to confirm an allergic response. It is minimally invasive and when performed correctly has good reproducibility. Results are easily quantifiable and correlate well with end organ challenge. It is imperative however that technicians who perform the skin tests and the clinicians who order or interpret these tests understand the characteristics of the specific tests they are administering. It is also important that the clinician express skin test results in a manner that allows easy interpretation by another physician. CONCLUSIONS: Allergists must consider controllable variables that affect skin test results and their interpretation. When not considered, they may be responsible for some of the inaccuracies associated with allergy skin testing.

REVIEW:
Portnoy J
Evidence-based allergy diagnostic tests
Current Allergy & Asthma Reports 2006;6:455-61

Effective management of allergic diseases relies on the ability to make an accurate diagnosis. Although clinicians rely on experience obtained over many years of practice, such experience is anecdotal and unique to the individual using it. The result is a tendency for patients with similar clinical presentations to receive different diagnoses and treatment, depending on which provider they happened to see. The probability that a patient has a particular diagnosis can be determined using a combination of diagnostic tests. To make the best use of tests, it is important to understand their performance characteristics in terms of reproducibility and likelihood ratios. A test that is reproducible but that does not predict the presence of a disease is not helpful, nor is an accurate test that is not reproducible. To improve the reproducibility of diagnostic tests, it is important that proficiency testing be instituted for both skin and in vitro tests so that the coefficient of variance can be determined. This has already been done for the latter and needs to be done for skin tests as well. With use of a combination of history and appropriate diagnostic tests, the probability that a particular diagnosis is present can be increased or decreased sufficiently either to confirm it or to rule it out. As proficiency testing of allergy tests becomes more common and the use of tests becomes more consistent, we believe that patients with allergic diseases will benefit.

LANDMARK ARTICLE:
Malling HJ
Proposed guidelines for quantitative skin prick test procedure to determine the biological activity of allergenic extracts using parallel line assay,
Allergy; 1987;42, 391-4
Guidelines are proposed for determining the potency of allergenic extracts in relation to a referenceextract using parallel line bio-assay. The practical performance, limitations, and advantages of skinprick test are discussed.

ii. cytology of nasal secretions

DIAGNOSTIC METHODS RESEARCH
Ventura MT
Validity and reproducibility of morphologic analysis of nasal secretions obtained using ultrasonic nebulization of hypertonic solution.
Ann Allergy Asthma Immunol. 2007;99:232-5.
BACKGROUND: Collection of nasal secretions is important for the evaluation of upper airways inflammation in many nasal disorders. OBJECTIVE: To study the validity and reproducibility of nasal secretion cellularity induced by nebulization of hypertonic solution in patients with allergic rhinitis (AR), patients with nonallergic rhinitis with eosinophilia syndrome (NARES), and control subjects. METHODS: Sixty-eight individuals (29 with AR [mean +/- SD age, 33.3 +/- 16.9 years], 23 with NARES [mean +/- SD age, 46.4 +/- 16.6 years], and 16 controls [mean +/- SD age, 42.1 +/- 15.1 years]) underwent ultrasonic nebulization of hypertonic (4.5%) saline solution on 2 different occasions to study the validity and reproducibility of total and differential cell counts of nasal secretions. RESULTS: The mean +/- SD percentage of eosinophils was significantly higher in samples from patients with AR (20.8% +/- 23.1%) and NARES (18.7% +/- 22.8%) than in samples from controls (0.6% +/- 0.6%; $P < .001$ for both). There was a significant correlation between 2 samples of nasal secretions obtained on 2 different occasions for percentages of macrophages, neutrophils, eosinophils, and epithelial cells. CONCLUSIONS: The analysis of nasal secretions obtained using ultrasonic nebulization of hypertonic solution can distinguish patients with AR and NARES from controls. The reproducibility of this technique is good for

macrophages, neutrophils, eosinophils, and epithelial cells. This method could be used to detect nasal airway inflammation in clinical settings.

ii. nasal challenges

REVIEW:

Litvyakova LI

Human nasal allergen provocation for determination of true allergic rhinitis: methods for clinicians

Curr Allergy Asthma Rep.2002 2:194-202.

The nasal provocation test (NPT) could be more extensively used in the diagnosis of allergic rhinitis by practicing physicians. However, the procedure has not been standardized, and has mainly been utilized for scientific purposes in the US. This review illustrates a wide variety of techniques and approaches to dosing and concentration of allergen extracts, and delivery systems. It also outlines the lack of a unified outcomes-evaluation system, including clinical symptom scores and nasal patency measurements, in different countries. NPT is a safe, simple, and useful method when conducted with the consideration of indications and contraindications. Standardized NPT has the potential to become a more frequently used additional clinical test in the diagnosis of allergic rhinitis.

iv. Rhinoscopy

REVIEW:

Tichenor WS

Nasal and sinus endoscopy for medical management of resistant rhinosinusitis, including postsurgical patients.

J Allergy Clin Immunol. 2007 Nov 2 e-publication ahead of print

Nasal endoscopy has been practiced by allergists since the early 1980s; however, allergists in general have not embraced endoscopic evaluation of patients with sinus disease, either before or after surgery. Allergists are in a unique position to render medical (as opposed to surgical) care of patients with sinusitis. There has been a growing realization that endoscopy is a valuable procedure for the evaluation and medical treatment of patients with difficult sinusitis. This has resulted in the need for a resource to allow allergists to understand the nature of endoscopic findings in patients with sinusitis, either preoperatively or postoperatively. This article introduces the findings at endoscopy that are common in patients with sinusitis, including those that may be seen after surgery. The findings include perforation of the septum, retained secretions, small surgical ostium caused by postoperative ostial stenosis, previous Caldwell Luc procedure, recirculation of mucus, hyperplastic nasal disease, synechiae, recurrent disease in previously unaffected sinuses, empty nose syndrome, frontal sinus disease, dental disease, and other, more complicated entities.

v. nasal and ear examination

REVIEW:

Onusko E

Tympanometry

Am Fam Physician. 2004 Nov 1;70(9):1713-20

Tympanometry provides useful quantitative information about the presence of fluid in the middle ear, mobility of the middle ear system, and ear canal volume. Its use has been recommended in

conjunction with more qualitative information (e.g., history, appearance, and mobility of the tympanic membrane) in the evaluation of otitis media with effusion and to a lesser extent in acute otitis media. It also can provide useful information about the patency of tympanostomy tubes. Tympanometry is not reliable in infants younger than seven months because of the highly compliant ear canals of infants. Tympanogram tracings are classified as type A (normal), type B (flat, clearly abnormal), and type C (indicating a significantly negative pressure in the middle ear, possibly indicative of pathology). According to the Agency for Healthcare Research and Quality guidelines on otitis media with effusion, the positive predictive value of an abnormal (flat, type B) tympanogram is between 49 and 99 percent. A type C curve may be useful when correlated with other findings, but by itself it is an imprecise estimate of middle ear pressure and does not have high sensitivity or specificity for middle ear disorders.

REVIEW:
Nathan RA.
Objective monitoring of nasal patency and nasal physiology in rhinitis.
J Allergy Clin Immunol.2005; 115:S442-59
Nasal obstruction can be monitored objectively by measurement of nasal airflow, as evaluated by nasal peak flow, or as airways resistance/conductance as evaluated by rhinomanometry. Peak flow can be measured during inspiration or expiration. Of these measurements, nasal inspiratory peak flow is the best validated technique for home monitoring in clinical trials. The equipment is portable, relatively inexpensive, and simple to use. One disadvantage, however, is that nasal inspiratory peak flow is influenced by lower airway as well as upper airway function. Rhinomanometry is a more sensitive technique that is specific for nasal measurements. The equipment, however, requires an operator, is more expensive, and is not portable. Thus, it is applicable only for clinic visit measures in clinical trials. Measures of nasal responsiveness are at present largely confined to research studies investigating disease mechanisms in allergic and nonallergic rhinitis. The techniques are insufficiently standardized to be applied to multicenter clinical trials but could be used in limited-center studies to gain insight into the regulatory effects of different therapeutic modalities.

REVIEW:
Howarth PH.
Objective monitoring of nasal airway inflammation in rhinitis.
J Allergy Clin Immunol.2005; 115:S414-41
Allergic rhinitis is an inflammatory nasal disorder in which a range of different cells participates. A variety of approaches has been used to monitor nasal inflammation objectively to investigate disease processes and to evaluate the effect of therapeutic intervention. These approaches include nasal lavage, nasal cytology, and nasal biopsy, together with the more recently established measurement of nasal nitric oxide (NO) concentration. Although all provide information about nasal mucosal inflammation, the extent of information that can be obtained by each approach, the ease of sampling, and the complexity of sample handling differ. Such considerations influence the choice of approach when measurement of nasal inflammation is to be an objective outcome parameter in a clinical trial.

REVIEW:
Uzzaman A

Acoustic rhinometry in the practice of allergy.
Ann Allerg Asthma Immunol 2006; 97:745-51
OBJECTIVE: To provide a comprehensive practical overview of the use of acoustic rhinometry in the practice of allergy. DATA SOURCES: An all-inclusive PubMed search was conducted for articles on acoustic rhinometry that were published in peer-reviewed journals, between 1989 and 2006, using the keywords acoustic rhinometry, allergic rhinitis, and nasal provocation testing. STUDY SELECTION: The expert opinion of the authors was used to select studies for inclusion in this review. RESULTS: Acoustic rhinometry is a sound-based technique used to measure nasal cavity area and volume. It has been validated by comparison to measurements with computed tomography and magnetic resonance imaging. Acoustic rhinometry requires minimal patient cooperation and may be used in adults, children, and infants. It is used by medical practitioners to diagnose and evaluate therapeutic responses in conditions such as rhinitis and to measure nasal dimensions during allergen provocation testing. Acoustic rhinometry also provides a visual reflection of the nasal response to therapy, which may be useful in increasing compliance to prescribed medications. CONCLUSIONS: Acoustic rhinometry is a safe, noninvasive, objective, and validated measure of nasal obstruction that appears to be of practical use in the diagnosis and management of inflammatory diseases of the upper airways.

vi. upper airway imaging studies

REVIEW:
Mafee MF
Imaging of rhinosinusitis and its complications: plain film, CT, and MRI
Clin Rev Allergy Immunol 2006;30:165-86
Conventional plain-film radiography may be used as a screening method for various pathological conditions of the sinonasal cavities. However, CT scanning remains the study of choice for the imaging evaluation of acute and chronic inflammatory diseases of sinonasal cavities. MRI is superior to CT in differentiating inflammatory conditions from neoplastic processes. The most common complications of rhinosinusitis in children occur in the orbit. The information obtained from the CT scan and MRI, together with clinical findings, may be the best guidelines for clinical management and the mode of treatment. Although intracranial complications of sinusitis are relatively rare, prompt recognition of these disease states is important to prevent permanent neurological deficit or fatality. It is prudent to obtain MRI of the sinuses, orbits, and brain whenever extensive or multiple complications of sinusitis are suspected, in addition to CT scanning. Chronic rhinosinusitis is a clinical diagnosis, confirmed and staged with the CT scan of sinonasal cavities. Chronic inflammatory disease is often associated with mucosal thickening and sclerosis of the bone, particularly within the sinuses. Chronic extramucosal fungal sinusitis develops as a saprophytic growth in retained secretions in a sinus cavity. The imaging manifestations of chronic mycotic rhinosinusitis may be nonspecific or highly suggestive of the presence of fungal infection. The presence of diffuse increased attenuation within the paranasal sinuses and nasal cavity should be considered as chronic allergic hypersensitivity aspergillosis (chronic noninvasive aspergillosis) or chronic hyperplastic sinusitis and polyposis associated with desiccated, retained mucosal secretions. The MRI characteristics of fungal sinusitis depend on the stage of the disease.

REVIEW:
Bhattacharyya, Jones, Hill and Shapiro,

The diagnostic accuracy of computed tomography in pediatric chronic rhinosinusitis, Arch Otolaryngol Head Neck Surg; 2004;130:1029-32,

OBJECTIVE: To determine the accuracy of computed tomography (CT) in the diagnosis of pediatric chronic rhinosinusitis (CRS). SETTING: Multi-institutional prospective dual cohort study. METHODS: Two cohorts of children undergoing CT of the paranasal sinuses were prospectively evaluated. The first cohort consisted of children undergoing CT in preparation for endoscopic sinus surgery (diseased group). The second cohort consisted of children undergoing CT for nonsinusitis reasons (nondiseased control group). Sinus CT scans were scored according to the Lund-MacKay system. Diagnostic accuracy was quantified with the receiver operating characteristic curve. Sensitivity, specificity, and predictive value analyses were conducted. RESULTS: A total of 66 pediatric patients (mean age, 8 years) were studied in the diseased group and exhibited a mean Lund score of 10.4 (95% confidence interval, 9.2-11.5); 192 control patients (mean age, 9 years) exhibited a mean Lund score of 2.8 (95% confidence interval, 2.4-3.2). The area under the curve for the receiver operating characteristic was 0.923 (P<.001), indicating excellent diagnostic accuracy. Adopting a Lund score cutoff of 5 to represent true disease, the CT scan demonstrated a sensitivity and specificity of 86% and 85%, respectively. Lund scores of 2 or less have an excellent negative predictive value, whereas Lund scores of 5 or greater have an excellent positive predictive value (ie, strongly indicate true disease). CONCLUSIONS: The sinus CT scan demonstrates excellent diagnostic accuracy for the diagnosis of pediatric CRS, with excellent sensitivity and specificity. However, its predictive value depends substantially on the baserate prevalence of CRS in the population being evaluation.

vii. Environmental assessment and control

REVIEW:

Simpson A

The role of allergen avoidance in the secondary prevention of atopic disorders

Curr Opin Allergy Clin Immunol. 2005;5:223-7

PURPOSE OF REVIEW: Allergen avoidance is recommended as part of the treatment programme of many patients with allergic diseases in Europe and the USA. However, clinical trials of allergen avoidance tend to be small and the findings inconsistent. Several larger studies have recently been published, making a review of the new literature timely. RECENT FINDINGS: There have been two large double-blind, placebo-controlled studies on the use of encasings (mattress, pillow and duvet) as a single intervention in adults with asthma. In both studies, participants in the active and the control group showed an improvement in peak flow, but there was no difference between groups over a 12-month period. A further smaller study of encasings reported an improvement in peak flow from 1 week in the active group; this study, however, was only of 9 weeks' duration. In children, the use of encasings was associated with a reduction in asthma medication usage, but not until 6 months into the study. A multifaceted intervention study, with the intervention tailored to the child's sensitization status and home environment (including environmental tobacco smoke), resulted in significant reductions in emergency room visits and symptoms in the active group. SUMMARY: The evidence suggests that interventions in children (either single or multifaceted) are associated with a meaningful and sustained improvement in asthma control. However, for adults, allergen proof encasings as a single intervention cannot be recommended. There is a need for a large-scale multifaceted intervention study in adults with asthma.

REVIEW:

Eggleston P
Improving indoor environments: reducing allergen exposures.
J Allergy Clin Immunol 2005 ;116:122-6
Homes cannot be made allergen free, but exposure to the major indoor allergens can be reduced. All reduction recommendations are based on the principle of reducing or isolating the source, and certain recommendations can be made on the basis of published evidence. House dust mite avoidance measures include fitting allergen-proof mattress and pillow encasings, washing bedding regularly, and reducing humidity. Furred pet avoidance requires removal of the pet form the home, followed by thorough and repeated cleaning; room air cleaners, washing the pet, and isolating the pet from a bedroom are ineffective alternatives. Cockroach allergen avoidance begins with effective pest control, followed by thorough and repeated cleaning; 1 to 2 months are required to eliminate roaches, and an additional 4 to 6 months are required to remove residual allergen. Once allergen levels have been reduced, continued efforts are necessary to maintain the home free of allergen sources.

KEY RESEARCH PUBLICATION:
Morgan WJ
Results of a home-based environmental intervention among urban children with asthma
N Engl J Med 2004; 351:1068-80.
BACKGROUND: Children with asthma who live in the inner city are exposed to multiple indoor allergens and environmental tobacco smoke in their homes. Reductions in these triggers of asthma have been difficult to achieve and have seldom been associated with decreased morbidity from asthma. The objective of this study was to determine whether an environmental intervention tailored to each child's allergic sensitization and environmental risk factors could improve asthma-related outcomes. METHODS: We enrolled 937 children with atopic asthma (age, 5 to 11 years) in seven major U.S. cities in a randomized, controlled trial of an environmental intervention that lasted one year (intervention year) and included education and remediation for exposure to both allergens and environmental tobacco smoke. Home environmental exposures were assessed every six months, and asthma-related complications were assessed every two months during the intervention and for one year after the intervention. RESULTS: For every 2-week period, the intervention group had fewer days with symptoms than did the control group both during the intervention year (3.39 vs. 4.20 days, $P<0.001$) and the year afterward (2.62 vs. 3.21 days, $P<0.001$), as well as greater declines in the levels of allergens at home, such as Dermatophagoides farinae (Der f1) allergen in the bed ($P<0.001$) and on the bedroom floor ($P=0.004$), D. pteronyssinus in the bed ($P=0.007$), and cockroach allergen on the bedroom floor ($P<0.001$). Reductions in the levels of cockroach allergen and dust-mite allergen (Der f1) on the bedroom floor were significantly correlated with reduced complications of asthma ($P<0.001$). CONCLUSIONS: Among inner-city children with atopic asthma, an individualized, home-based, comprehensive environmental intervention decreases exposure to indoor allergens, including cockroach and dust-mite allergens, resulting in reduced asthma-associated morbidity.

RESEARCH FRONTIER:
Sercombe JK
Evaluation of home allergen sampling devices.
Allergy. 2005;60:515-20

BACKGROUND: Simple, inexpensive methods of sampling from allergen reservoirs are necessary for large-scale studies or low-cost householder-operated allergen measurement. METHODS: We tested two commercial devices: the Indoor Biotechnologies Mitest Dust Collector and the Drager Bio-Check Allergen Control; two devices of our own design: the Electrostatic Cloth Sampler (ECS) and the Press Tape Sampler (PTS); and a Vacuum Sampler as used in many allergen studies (our Reference Method). Devices were used to collect dust mite allergen samples from 16 domestic carpets. Results were examined for correlations between the sampling methods. RESULTS: With mite allergen concentration expressed as microg/g, the Mitest, the ECS and the PTS correlated with the Reference Method but not with each other. When mite allergen concentration was expressed as microg/m2 the Mitest and the ECS correlated with the Reference Method but the PTS did not. In the high allergen conditions of this study, the Drager Bio-Check did not relate to any methods. CONCLUSIONS: The Mitest Dust Collector, the ECS and the PTS show performance consistent with the Reference Method. Many techniques can be used to collect dust mite allergen samples. More investigation is needed to prove any method as superior for estimating allergen exposure.

REVIEW Guideline:
Asher I
World Allergy Organization guidelines for prevention of allergy and allergic asthma
www.worldallergy.org/wad2007/article.pdf

2. Eye Disease

a. Allergic and vernal conjunctivitis, iritis, iridocyclitis

REVIEW:
Bielory L
Differential diagnoses of conjunctivitis for clinical allergist-immunologists.
Ann Allergy Asthma Immunol 2007;98:105-14
OBJECTIVE: To provide a clinical overview of the types of conjunctivitis that are encountered by practicing clinical allergist-immunologists. DATA SOURCES: Published literature in peer reviewed journals found in the National Library of Medicine (PubMed) database using the keywords ocular allergy and/or allergic conjunctivitis. STUDY SELECTION: Studies related to ocular allergy and/or allergic conjunctivitis were selected for inclusion in this review. RESULTS: Four clinical scenarios are presented that mimic frequently encountered inflammatory disorders that present as red eyes. CONCLUSIONS: The signs and symptoms associated with the various inflammatory conditions affecting the conjunctiva often overlap and need to be differentiated to maximize care for patients with conjunctivitis.

REVIEW:
Ono SJ
Allergic conjunctivitis: update on pathophysiology and prospects for future treatment
J Allergy Clin Immunol 2005;115:118-22
Allergic conjunctivitis is in actuality a group of diseases affecting the ocular surface and is usually associated with type 1 hypersensitivity reactions. Two acute disorders, seasonal allergic conjunctivitis and perennial allergic conjunctivitis, exist, as do 3 chronic diseases, vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis. The ocular

surface inflammation (usually mast cell driven) results in itching, tearing, lid and conjunctival edema-redness, and photophobia during the acute phase and can lead to a classic late-phase response (with associated eosinophilia and neutrophilia) in a subset of individuals. As is the case in other allergic diseases, a chronic disease can also develop, accompanied by remodeling of the ocular surface tissues. In severe cases the patient experiences extreme discomfort and sustains damage to the ocular surface. For such cases, there is no highly effective and safe treatment regimen. Topical administration of corticosteroids is used in severe cases but is associated with an increased risk for the development of cataracts and glaucoma. Thus there is a worldwide search for new biotargets for the treatment of these diseases. Here we provide a brief update of the clinical symptoms associated with these diseases, the rationale for disease classification, recent advances in our understanding of the pathogenesis of the diseases, and an update on both preclinical and clinical advances toward refined therapies for these diseases.

REVIEW:
Manzouri B
Pharmacotherapy of allergic eye disease.
Expert Opin Pharmacother. 2006 Jun;7(9):1191-200.
Allergic eye disease is a term that refers to a number of disease processes that affect about one-fifth of the world's population. Although the more advanced forms of the disease can be sight threatening, the most disabling effects are due to the clinical manifestations, and hence quality of life, with some patients having seasonal exacerbations of their symptoms, whereas others have symptoms that are present throughout the year. Recent increased understanding of the cellular and mediator mechanisms that are involved in the various disease manifestations has greatly facilitated the development of more effective treatment options. Newer topical medications are being used that have multiple actions, such as an antihistaminic effect coupled with mast-cell stabilisation, and which require reduced daily dosing due to their longer duration of action. With greater research into newer therapies and more effective modes of delivery, improved healthcare outcomes with a lower economic burden will be achieved for patients with allergic eye disease

REVIEW:
Schultz BL
Pharmacology of ocular allergy.
Curr Opin Allergy Clinl Immunol 2006;6:383-9
PURPOSE OF REVIEW: To evaluate the pharmacology of current drug development directed towards ocular allergy. Increased worldwide prevalence of ocular allergy has stimulated expansion of management strategies towards physiologic and immunologic drug targets. RECENT FINDINGS: Present drug targets are located in the conjunctival mucosal surface at the initial site of allergen exposure. Pharmacologic intervention attends to early and late phase reactions. Targets generating a response include mast cells, IgE, released preformed mediator histamine, and newly formed mediators, such as prostaglandins, leukotrienes and cytokines. Methods to simulate allergy and measure efficacy of drugs are the conjunctival allergen challenge and the conjunctival provocation test. Pharmacologic outcome is measured via cytologic biomarkers and clinical signs/symptoms of redness, itching, lid swelling and chemosis. Endpoint instruments such as the Ocular Allergy Index and Eye Allergy Patient Impact Questionnaire have emerged from the field of pharmacoeconomics. SUMMARY: Important pharmacologic properties of targets have been revealed. First, histamine is more specifically antagonized by second generation antihistamines.

Second, newly formed mediators and downstream responders (prostaglandins, leukotrienes, interleukins, intercellular adhesion molecule 1, tumor necrosis factor, vascular cell adhesion molecule, eosinophils and neutrophils) are more selectively antagonized by dual/multiple-action agents.

REVIEW:
McCluskey P
The eye in systemic inflammatory diseases
Lancet 2004;364:2125-33
Systemic inflammatory diseases commonly affect the sclera, cornea, retina, and orbit, and can pose a serious threat to sight. They encompass both primary and secondary vasculitic disorders and specific granulomatous inflammatory conditions. As well as direct eye involvement from the systemic inflammatory process, there can be signs of ocular ischaemia due to carotid or ophthalmic arteritis, hypertensive retinopathy, and ocular complications such as chloroquine maculopathy related to anti-inflammatory drug treatment. Additionally, systemic infection relating to the eye, either as the result of primary infective disease processes or infection secondary to immunosuppression, might be mistaken as endogenous intraocular inflammation. Infection can closely mimic the ocular signs of endogenous inflammation, and in selected patients (such as those who have been immunosuppressed to treat vasculitis and who additionally have had invasive surgery, indwelling intravenous catheters, or systemic sepsis), it might be necessary to specifically exclude infection by the sampling and culturing of intraocular fluids and tissue.

b. Clinical skills: eye examination

REVIEW:
Roy FH
The Red Eye
Ann Ophthal 2006;38:35-8
A red eye is a cardinal sign of ocular inflammation. Most cases are benign and can be managed by the primary care provider. The key is recognizing cases requiring ophthalmological consultation by differentiating between ciliary and conjunctival injection. Ciliary injection indicates inflammation of the cornea, iris, or ciliary body, whereas conjunctival injection mainly affects the posterior conjunctival blood vessels.

REVIEW:
Weinstock FJ
Common eye disorders: six patients to refer
Postgrad Med.1996;99:107-116
Thorough ocular history taking and physical examination are essential to establish a diagnosis in patients presenting with eye conditions. Some conditions require ophthalmologic referral to avoid serious complications and even vision loss. These include corneal ulcers, retinal detachment, iritis, glaucoma, retinal artery occlusion, and endophthalmitis. Because primary open-angle glaucoma can have an insidious onset and cause irreversible damage, funduscopic examination should be a part of every complete physical examination.

3. Dermatologic disease

a. Overview

REVIEW:
Blauvelt A, Hwang ST, Udey MC.
Allergic and immunologic diseases of the skin.
J Allergy Clin Immunol 2003;111:S560-70.
Many skin diseases have an inflammatory or immune component, and anti-inflammatory drugs comprise a major portion of a dermatologist's therapeutic armamentarium. Although causes of most of these diseases remain obscure, mechanisms of lesion formation and explanations for symptoms are increasingly well documented. These developments, coupled with the expected availability of novel selective immunomodulatory agents, herald a new era for immunodermatology. Patients with psoriasis, allergic contact dermatitis, atopic dermatitis, urticaria, and autoantibodymediated blistering diseases are among those who are likely to benefit from advances in the understanding of disease pathogenesis and the emergence of immunotherapeutics.

RESEARCH FRONTIER:
Sauder DN.
Mechanism of action and emerging role of immune response modifier therapy in dermatologic conditions.
J Cutan Med Surg. 2004;8 Suppl 3:3-12.
Immune response modifiers (IRMs) are agents that target the body's immune system (i.e., cytokines, receptors, and inflammatory cells) to combat disease. Topical IRM therapies, which encompass both proinflammatory and immunosuppressive therapeutics, have been used to successfully treat a number of dermatologic conditions. Proinflammatory treatments include Toll-like receptor agonists (e.g., imiquimod 5% cream) and interferon (e.g., interferon-alpha) therapies, which have been used in the treatment of external genital warts, basal cell carcinoma, and other dermatologic diseases. Immunosuppressive therapies include topical and intralesional corticosteroids, anti-tumor necrosis factor agents (e.g., infliximab and etanercept), and anti-CD4+ T-cell agents, including calcineurin inhibitors and mycophenolate. These agents have been used to treat a number of conditions, including atopic and seborrheic dermatitis and psoriasis. This article reviews the mechanism of action of IRMs and the application of IRMs in several dermatologic diseases.

REVIEW:
Allergy &Immunology, Medical Knowledge and Self-Assessment Program.
3rd Ed. Pp145-66
This is a nice review for most of the immune mediated dermatological disorders and will be helpful for fellows taking their ABAI exam.

b. Etiology, Pathophysiology and Mechanisms of Immune Mediated Dermatological Disorders. (Atopic Dermatitis, contact dermatitis, Urticaria & angioedema, blistering dermatological disorders, Stevens Johnson syndrome & toxic epidermal necrolysis

i. Atopic Dermatitis

REVIEW:
Ong PY
Immune dysregulation in atopic dermatitis.
Curr Allergy Asthma Rep. 2006;6:384-9.
Atopic dermatitis is a chronic inflammatory skin disease that causes significant morbidity in affected individuals. It is characterized by dysregulated immune responses that consist of an increased systemic Th2 response and a combination of Th2 and Th1 responses in the skin lesions. In this article, we review factors that contribute to these abnormal responses, including key effector cells of the immune system, chemokines, defective skin barrier, genetic predisposition, and environmental triggers. Understanding these pathomechanisms may improve our current therapies for atopic dermatitis.

REVIEW:
Cork MJ
New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions.
J Allergy Clin Immunol. 2006;118:3-21; quiz 22-3.
Atopic dermatitis (AD) is a multifactorial, chronic inflammatory skin disorder in which genetic mutations and cutaneous hyper reactivity to environmental stimuli play a causative role. Genetic mutations alone might not be enough to cause clinical manifestations of AD, and this review will propose a new perspective on the importance of epidermal barrier dysfunction in genetically predisposed individuals, predisposing them to the harmful effects of environmental agents. The skin barrier is known to be damaged in patients with AD, both in acute eczematous lesions and also in clinically unaffected skin. Skin barrier function can be impaired first by a genetic predisposition to produce increased levels of stratum corneum chymotryptic enzyme. This protease enzyme causes premature breakdown of corneodesmosomes, leading to impairment of the epidermal barrier. The addition of environmental interactions, such as washing with soap and detergents, or long-term application of topical corticosteroids can further increase production of stratum corneum chymotryptic enzyme and impair epidermal barrier function. The epidermal barrier can also be damaged by exogenous proteases from house dust mites and Staphylococcus aureus. One or more of these factors in combination might lead to a defective barrier, thereby increasing the risk of allergen penetration and succeeding inflammatory reaction, thus contributing to exacerbations of this disease

REVIEW:
Lebwohl M,
Impaired skin barrier function in dermatologic disease and repair with moisturization.
Cutis. 2005 Dec;76(6 Suppl):7-12
There is a substantial body of data demonstrating that atopic dermatitis and various other skin diseases are associated with disturbances of skin barrier function as evidenced by an increase in

transepidermal water loss (TEWL), a decrease in water-binding properties, and a reduction in skin surface lipids, specifically levels of ceramides. The results of clinical studies suggest that these deficits can be addressed through the judicious use of appropriate moisturizers, which have been shown to improve skin hydration, reduce susceptibility to irritation, and restore the integrity of the stratum corneum. Some emollients also supply the compromised stratum corneum with vital lipids and accelerate barrier recovery. Moisturizers serve as an important first-line therapeutic option for patients with atopic dermatitis and other chronic skin diseases and can be highly beneficial in improving the clinical signs and symptoms of these challenging dermatologic conditions.

ii. Contact Dermatitis

REVIEW:

Krob HA, Fleischer AB, D'Agostino R, Haverstock CL, Feldman S

Prevalence and relevance of contact dermatitis allergens: a meta-analysis of 15 years of published T.R.U.E. test data.

J Am Acad Dermatol. 2004 Sep; 51: 349-53

BACKGROUND: The patch test procedure is frequently employed to help determine or confirm the cause of allergic contact dermatitis (ACD). The T.R.U.E. Test has become a global standard and is the commercially available patch test system currently used within the United States. Although many studies report T.R.U.E. Test data, none has measured the overall prevalence and relevance of reactions to the allergens tested by the T.R.U.E. Test. Our objective is to describe the prevalence and relevance of contact dermatitis allergens as tested by the T.R.U.E. Test. METHODS: We conducted a search of the MEDLINE database from 1966 to June 2000 for all publications on the use of the T.R.U.E. Test in the clinical evaluation of ACD in human subjects. Inclusion and exclusion criteria were applied. For each study, we identified and recorded the number of subjects tested, the number of patients with positive reactions, and the number with relevant reactions. Data were analyzed using the SAS system (Cary, NC). RESULTS: Ours is the first study to compile the entire corpus of published T.R.U.E. Test data and to examine these data using meta-analytic techniques. The meta-analysis shows that nickel (14.7% of tested patients), thimerosal (5.0%), cobalt (4.8%), fragrance mix (3.4%), and balsam of Peru (3.0%) are the most prevalent allergens. The 5 least prevalent allergens are paraben mix (0.5%), black rubber mix (0.6%), quaternium-15 (0.6%), quinoline mix (0.7%), and caine mix (0.7%). By contrast, North American Contact Dermatitis Data Group (NACDG) data show that the 5 most prevalent allergens are nickel (14.3%), fragrance mix (14%), neomycin (11.6%), balsam of Peru (10.4%), and thimerosal (10.4%). NACDG data indicate that the prevalence of allergy to cobalt is 9.2%. In order to assess the clinical importance of T.R.U.E. Test allergens, we employ the Significance-Prevalence Index Number (SPIN). Based on SPIN, the most clinically important allergens tested by the T.R.U.E. Test are nickel (SPIN=894), cobalt (266), fragrance mix (158), colophony (141), and thiuram mix (138). CONCLUSIONS: Our results identify the prevalence of common contact dermatitis allergens as tested by the T.R.U.E. Test and are in general agreement with previously published reports using other patch test methods. Over 3700 allergens have been identified as causing ACD, of which the T.R.U.E. Test tests only 23. Thus, the T.R.U.E. Test is a screening test at best. Comparison with NACDG data suggests that clinically important allergens may be missed by the T.R.U.E. Test.

iii. Urticaria & Angioedema

REVIEW:

Kaplan AP.
Chronic urticaria: Pathogenesis and treatment.
J Allergy Clin Immunol 2004;114:465-74.
Patients previously designated as having chronic idiopathic urticaria are now divided into 2 groups: 40% to 50% with chronic autoimmune urticaria, and the remainder with chronic idiopathic urticaria. Patients in both groups may have concomitant angioedema (approximately 40%). The autoimmune subgroup has an association with antithyroid antibodies and is caused by IgG antibody to the alpha subunit of the IgE receptor (35% to 40%), usually reactive with unoccupied IgE receptors, or IgG antibody to IgE (5% to 10%). Complement activation augments histamine secretion by release of C5a. The IgG subclasses that appear to be pathogenic are IgG(1), IgG(3), and, to a lesser degree, IgG(4), but not IgG(2). Histology of chronic urticaria (both subtypes) reveals a perivascular non-necrotizing infiltrate of CD4(+) lymphocytes consisting of a mixture of T (H) 1 and T (H) 2 subtypes, plus monocytes, neutrophils, eosinophils, and basophils. These cells are recruited as a result of interactions with C5a, cell priming cytokines, chemokines, and adhesion molecules. Suggested therapy for patients with severe disease involves the use of high-dose hydroxyzine or diphenhydramine when nonsedating antihistamines are ineffective, supplemented by H-2 antagonists and leukotriene antagonists. The most severe patient may require protracted treatment with low-dose alternate-day steroid or cyclosporine. Cyclosporine can be steroid-sparing when side effects are encountered or when use of steroids is relatively contraindicated. Careful monitoring of blood pressure, BUN, creatinine, and urinalysis is required.

REVIEW:
Sheikh J.
Autoantibodies to the high-affinity IgE receptor in chronic urticaria: how important are they?
Curr Opin Allergy Clin Immunol. 2005 Oct;5:403-7
PURPOSE OF REVIEW: Eighty to 90% of patients with chronic urticaria have no specific external cause for their disease, which is therefore labeled 'chronic idiopathic urticaria'. We now know, however, that as many as 30-50% of patients have evidence of an autoantibody to the high-affinity receptor for IgE (FcepsilonRI), which may be pathogenic. The exact prevalence and role of these autoantibodies is still under investigation. RECENT FINDINGS: The frequency of autoantibodies to FcepsilonRI in chronic urticaria has been estimated at 30-50%, but extensive epidemiological studies have not been done. Recent work has confirmed that autoantibodies to FcepsilonRI can be functional, meaning that they can cause histamine release from basophils in vitro. Evidence increasingly suggests that such autoantibodies are also functional in vivo, but conclusive evidence is still lacking. Approximately 50% of cases of urticaria still have no known cause, but recent studies have demonstrated that some of these patients may have intrinsic abnormalities of basophils or mast cells. SUMMARY: The recent evidence that is discussed in this review helps to clarify the role of autoantibodies in some cases of urticaria, but also points towards other non-autoimmune mechanisms that might be pathogenic. Further investigation in these areas will help us to understand the cause of urticaria in cases that are still classified as 'idiopathic'.

REVIEW:
Weldon D.
Differential diagnosis of angioedema.
Immunol Allergy Clin North Am. 2006 Nov;26:603-13

There are many conditions that may present with swelling that mimics angioedema. When swelling persists for greater than a few days or is unresponsive to treatment for urticaria/angioedema, other etiologies should be considered. In most instances, a thorough history and physical examination will define other etiologies. However, for more persistent conditions, further laboratory evaluation and a biopsy may be required to define the diagnosis. Rarely is a more aggressive approach required to make the diagnosis. Clinicians should remember that if the swelling does not act like angioedema, it more than likely is not angioedema

iv. Blistering dermatological disorders

REVIEW:
Stanley JR
Mechanisms of Disease: Pemphigus, Bullous Impetigo, and the Staphylococcal Scalded-Skin Syndrome
N Engl J Med 2006;355:1800-1810
Pemphigus, which is caused by autoantibodies, and bullous impetigo (including its generalized form, the staphylococcal scalded-skin syndrome), which is caused by *Staphylococcus aureus,* are seemingly unrelated diseases. However, 200 years ago, astute clinicians realized that these diseases had enough clinical similarities to call bullous impetigo and the scalded-skin syndrome in infants "pemphigus neonatorum." In this review we explain how a common mechanism accounts for the clinical overlap of these blistering diseases of the skin, and how the unraveling of the molecular pathophysiology of pemphigus provided the clues that were necessary to determine the mechanism of the formation of blisters in bullous impetigo and the staphylococcal scalded-skin syndrome. We also discuss how this new understanding of the pathophysiology of pemphigus could improve the diagnosis and treatment of this potentially life-threatening disease.

REVIEW:
Yeh SW, Ahmed B, Sami N, Ahmed AR.
Blistering disorders: diagnosis and treatment.
Dermatologic Therapy 2003;16:214-223.
Blistering diseases are a heterogeneous group of disorders that can affect either skin and mucous membrane, or both, varying in presentation, clinical course, pathohistology, immunopathology and treatment. Not infrequently the diagnosis is delayed. This can result in severe, and sometimes fatal consequences. Although these diseases are rare, it is very important to make an accurate diagnosis based on a combination of clinical profile and laboratory observations. A brief review is presented of the following bullous diseases: pemphigus, paraneoplastic pemphigus, bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita, dermatitis herpetiformis, linear IgA bullous disease, porphyria cutanea tarda, and subcorneal pustular dermatitis. Their clinical, pathohistologic and immunopathologic features and recommendations for therapy are discussed.

v. Stevens Johnson syndrome and toxic epidermal necrolysis

REVIEW:
Khalili B
Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis.
Ann Allergy Asthma Immunol 2006;97:272-80;

OBJECTIVE: To review the current pathophysiologic mechanisms and recent therapeutic trends in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). DATA SOURCES: A MEDLINE search for SJS and TEN in combination with Fas, Fas ligand (FasL), cytotoxic T cells, intravenous immunoglobulin, and cyclosporine for articles published in English during 1966 to 2006. STUDY SELECTION: Information was derived from original research articles and reviews published in peer-reviewed journals. RESULTS: The hallmark of SJS and TEN is epidermal cell apoptosis, which may be mediated through keratinocyte Fas-FasL interaction or through cytotoxic T-cell release of perforin and granzyme B. Whereas systemic corticosteroid therapy showed contradictory results, intravenous immunoglobulin (IVIG) and cyclosporine have shown promising outcomes. IVIG contains anti-Fas antibodies that can abrogate apoptosis when preincubated with keratinocytes. Most studies on IVIG in SJS and TEN reported improvement in arresting disease progression and reduction in time to skin healing. Because of variations among studies, the findings cannot be optimally compared. In general, mortality varied from 0% to 12% in studies that supported the use of IVIG and 25% to 41.7% in those that did not demonstrate a beneficial effect. Cyclosporine inhibits CD8 activation and thus may reduce epidermal destruction. Relatively few case reports and 1 case series have been published regarding the use of cyclosporine in SJS and TEN. In general, cyclosporine was associated with a significant improvement in time to disease arrest and to complete reepithelization, with no reported fatalities. CONCLUSIONS: Both IVIG and cyclosporine have been associated with enhanced healing and better survival through inhibition of apoptosis. Multicenter, randomized, placebo-controlled trials using a standardized design are needed to validate these findings.

REVIEW:
Parrillo S
Stevens-Johnson syndrome and toxic epidermal necrolysis.
Curr Allergy Asthma Rep 2007;7:243-7
Since their first descriptions in 1922 and 1948, respectively, Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) have become recognized as manifestations--with different severity--of the same disease process along a spectrum of illness. Even today, decades after their description, there is still disagreement about when a particular bullous disease evolves from erythema multiforme to SJS/TEN. There is no disagreement, however, about the potentially life-threatening nature of the disease. Many cases are misdiagnosed, especially in their early stages. In this paper we address our current understanding of this disease spectrum and discuss both accepted and more controversial modes of therapy.

c. Clinical skills, diagnostic methods and practical management of immune mediated dermatologic disorders.

i. Clinical Skills and diagnostic methods

REVIEW:
Knowles SR
Recognition and management of severe cutaneous drug reactions.
Dermatol Clin. 2007;25:245-53
Cutaneous drug reactions are among the most common types of adverse drug reactions. This article focuses on the recognition and management of severe cutaneous drug eruptions, including the drug-hypersensitivity syndrome, serum sickness-like reaction, acute generalized

exanthematous pustulosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Cutaneous reactions are considered severe when they can result in serious skin damage or involve multiple organs. Some of these reactions can cause significant morbidity or death. Each may be confounded by diagnostic difficulties, confusion in ascertaining causality, and treatment challenges.

REVIEW:
Kumar V
Immunofluorescence and enzyme immunomicroscopy methods.
J Immunoassay. 2000 May-Aug;21(2-3):235-53
Immunohistochemistry is a very versatile immunopathological tool for the study of distribution and differentiation of antigens and of the presence of in vivo-bound immune complexes. In addition, these methods are invaluable for detection of circulating antibodies to the various antigens. Such methods may be the only ones of choice in certain situations. For the detection and quantitation of these antigens, it is very essential that the immunohistochemical methods for detecting them are properly standardized, with the inclusion of appropriate controls.

REVIEW:
Collins B
Immunofluorescenc Methods in the Diagnosis of Renal and Skin Diseases
Manual of Molecular and Clinical Laboratory Immunology. 7th edition pp 414-423.
This chapter emphasize the common immunofluorescence techniques used for diagnosis and interpretation with skin diseases

REVIEW:
Brockow K,
General considerations for skin test procedures in the diagnosis of drug hypersensitivity.
J Immunoassay. 2000;21:235-53
Article reviews the techniques and indications of skin testing in drug hyprsensitivity review.

REVIEW:
Mowad CM
Patch testing: pitfalls and performance
Curr Opin Allergy Clin Immunol. 2006;6:340-4
PURPOSE OF REVIEW: Contact dermatitis is a common disease process that includes allergic and irritant contact dermatitis. The gold standard for diagnosing allergic contact dermatitis, a type IV delayed hypersensitivity reaction, is patch testing. Patch testing is not a difficult procedure, however, there are several critical components that determine the success of the test: having an appropriate level of suspicion for the diagnosis of allergic contact dermatitis, an adequate threshold for patch testing, the necessary experience to properly interpret the results and to determine their relevance, and the ability to thoroughly educate the patient about the condition. RECENT FINDINGS: Research shows that patch testing practices differ among individuals and specialties. The level of patch testing education, interest in, and experience with, the procedure can affect the results of the test. Some of these practice differences and how they affect the outcome of patch testing are highlighted. SUMMARY: Physicians' knowledge and experience with patch testing, their level of interest and access to allergens will determine the performance of this test, the reliability of the results and the benefits gained from this procedure.

ii. Practical Management of Atopic Dermatitis

REVIEW PRACTICE GUIDELINE :

Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report

J Allergy Clin Immunol 2006;118:152-169

There are remarkable differences in the diagnostic and therapeutic management of atopic dermatitis practiced by dermatologists and pediatricians in different countries. Therefore, the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology nominated expert teams who were given the task of finding a consensus to serve as a guideline for clinical practice in Europe as well as in North America. The consensus report is part of the PRACTALL initiative, which is endorsed by both academies.

iii. Practical Management of Contact Dermatitis

REVIEW PRACTICE GUIDELINE Contact Dermatitis:

Beltrani VS, Bernstein IL, Cohen DE, et al

Contact Dermatitis: A Practice Parameter

Ann Allergy Asthma Immunol 2006;97:S1-S38

The major goal of these guidelines is to ensure that CD patients benefit from the best available diagnostic and therapeutic applications by consultant allergists/clinical immunologists. In achieving this balance, allergists/clinical immunologists may choose to develop a collegial working relationship with a CD-oriented dermatologist subspecialist for assistance with diagnosis, differential diagnosis, and management of unusual clinical presentations or refractory CD. The general principles in this Practice Parameter should alsohelp to develop improved understanding of CD among otherhealth care professionals, students, residents, and fellows.

iv. Practical Management of Urticaria and Angioedema

PRACTICE PARAMETER GUIDELINE – Urticaria:

Joint Task Force on Practice Parameters

Diagnosis and Management of Urticaria/Angioedema

Ann Allergy Asthma Immunol 2000;85:S521-544

This practice parameter consists of two parts: (1) a section on acute urticaria and (2) a section on chronic urticaria. Each part has its own diagnostic and management algorithm with referenced narrative annotations. These are designed to assist clinical decision making for both diagnosis and management. Clinical decision points are clearly shown and each of these proceeds stepwise to logical implementation strategies. Supplemental information in the form of commentaries and a list of references is provided for each part. This parameter includes pertinent considerations about etiology, histopathology, differential diagnosis, and associated conditions. Special emphasis is placed on current principles of management.

PRACTICE PARAMETER GUIDELINE Hereditary Angioedema:

Bowen T

2003 International Consensus Algorithm For the Diagnosis, Therapy, and Management of Hereditary Angioedema.

J Allergy Clin Immunol. 2004;114:629-37

C1 inhibitor deficiency (hereditary angioedema [HAE]) is a rare disorder for which there is a lack of consensus concerning diagnosis, therapy, and management, particularly in Canada. European initiatives have driven the approach to managing HAE with 3 C1-INH Deficiency Workshops held every 2 years in Hungary starting in 1999, with the third Workshop having recently been held in May 2003. The European Contact Board has established a European HAE Registry that will hopefully advance our knowledge of this disorder. The Canadian Hereditary Angioedema Society/Société d'Angioédème Héréditaire du Canada organized a Canadian International Consensus Conference held in Toronto, Ontario, Canada, on October 24 to 26, 2003, to foster consensus between major European and North American HAE treatment centers. Papers were presented by investigators from Europe and North America, and this consensus algorithm approach was discussed. There is a paucity of double-blind placebo-controlled trials in the treatment of HAE, making levels of evidence to support the algorithm less than optimal. Enclosed is the consensus algorithm approach recommended for the diagnosis, therapy, and management of HAE and agreed to by the authors of this article. This document is only a consensus algorithm approach and requires validation. As such, participants agreed to make this a living 2003 algorithm (ie, a work in progress) and agreed to review its content at future international HAE meetings. The consensus, however, has strength in that it was arrived at by the meeting of patient-care providers along with patient group representatives and individual patients reviewing information available to date and reaching agreement on how to approach the diagnosis, therapy, and management of HAE circa 2003. Hopefully evidence to support approaches to the management of HAE will approach the level of meta-analysis of randomized controlled trials in the near future.

v. Practical Management of Blistering Dermatologic Disorders

REVIEW:

Mutasim DF

Management of Autoimmune Bullous Disease:Pharmacology and Therapeutics.

J Am Acad Derm: 2004;51;859-877

Bullous diseases are associated with high morbidity and mortality. They result from autoimmune response to one or more components of the basement membrane or desmosomes. Management consists of treating the immunologic basis of the disease, treating the inflammatory process involved in lesion formation, and providing supportive care both locally and systemically. Therapeutic agents are chosen based on their known pharmacologic properties and evidence of effectiveness derived from observations and studies.Learning objectives At the completion of this learning activity, participants should be able to understand the pharmacology of drugs used in the treatment of bullous diseases, the principles of therapy for various such diseases, and a practical approach to the management of these diseases.

vi. Practical Management of Stevens Johnson syndrome / TEN

REVIEW:

Chia FL

Severe cutaneous adverse reactions to drugs.

Curr Opin Allergy Clin Immunol. 2007;7:304-9

PURPOSE OF REVIEW: This paper updates the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis supported by relevant views about the pathogenesis. RECENT FINDINGS: Building on the thesis that Stevens-Johnson syndrome and toxic epidermal necrolysis are due to dermal cell apoptosis, molecular pathways that may lead to this have been proposed.

Intravenous immunoglobulin is postulated to block apoptosis via the Fas pathway. Most series on the use of intravenous immunoglobulin in toxic epidermal necrolysis have been favourable. Tumour necrosis factor is also thought to be an important mediator of cell death in toxic epidermal necrolysis. There was impressive control of the progression of toxic epidermal necrolysis with intravenous anti-tumour necrosis factor antibody infliximab in two cases. Strong associations between human leukocyte antigen subtypes and severe cutaneous reactions due to allopurinol and carbamazepine have been described. SUMMARY: To date, there is no established treatment of Stevens-Johnson syndrome/toxic epidermal necrolysis. With advancing knowledge of the pathogenesis, it is hoped that better forms of treatment may result.

4. Lower respiratory tract disease

a. Asthma and related disorders (exercise-induce, allergic bronchopulmonary aspergillosis, and aspirin exacerbated respiratory disease); including assessment of severity and control; hypersensitivity pneumonitis; chronic obstructive pulmonary disease; bronchitis, croup & RSV; cystic fibrosis, immotile cilia syndrome, sarcoid, occupational lung disease, chronic cough

i. Pediatric Asthma

REVIEW UPDATE:
Szefler SJ.
Advances in pediatric asthma 2006.
J Allergy Clin Immunol;119:558-62, 2007

Because the outcomes experienced in adult asthma often result from pathophysiology that begins in early childhood, this year's summary focuses on recent advances in pediatric asthma. This past year, we have learned that early intervention with inhaled corticosteroids in childhood asthma reduces morbidity but does not alter the natural history of asthma. Theme issues over the last year focused attention on severe asthma and black box warnings. Both of these themes significantly affect the management of childhood asthma. Responsiveness to asthma treatment is heterogeneous even among patients with asthma of similar severity. This heterogeneity calls attention to the importance of assessing control and adjusting treatment accordingly. We are now moving toward an individualized approach to asthma therapy and searching for biomarkers and genetics as a resource to guide treatment. To improve asthma control, we must continue to obtain information on early asthma, severe asthma, asthma exacerbations, and methods to improve asthma control. Evaluation and management of severe asthma in children include verification of the diagnosis, assessment for coexisting illnesses, and identification of effective treatment strategies directed to adherence, medication delivery, and combination therapy. Application of biomarkers and genetics could be useful tools in individualizing our approach to the management of childhood asthma.

KEY CLINICAL RESEARCH:
Sorkness C
Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial.
J Allergy Clin Immunol. 2007;119:64-72

BACKGROUND: More evidence is needed on which to base recommendations for treatment of mild-moderate persistent asthma in school-aged children. OBJECTIVE: The Pediatric Asthma Controller Trial (PACT) compared the effectiveness of 3 regimens in achieving asthma control. METHODS: A total of 285 children (ages 6-14 years) with mild-moderate persistent asthma on the basis of symptoms, and with FEV(1) >or= 80% predicted and methacholine FEV(1) PC(20) <or= 12.5 mg/mL, were randomized to 1 of 3 double-blind 48-week treatments: fluticasone 100 microg twice daily (fluticasone monotherapy), fluticasone 100 microg/salmeterol 50 microg in the morning and salmeterol 50 mug in the evening (PACT combination), and montelukast 5 mg in the evening. Outcomes included asthma control days (primary outcome), exacerbations, humanistic measurements, and pulmonary function measurements. RESULTS: Fluticasone monotherapy and PACT combination were comparable in many patient-measured outcomes, including percent of asthma control days, but fluticasone monotherapy was superior for clinic-measured FEV(1)/forced vital capacity (P = .015), maximum bronchodilator response (P = .009), exhaled nitric oxide (P < .001), and PC(20) (P < .001). Fluticasone monotherapy was superior to montelukast for asthma control days (64.2% vs 52.5%; P = .004) and for all other control outcomes. Growth over 48 weeks was not statistically different (fluticasone, 5.3 cm; PACT combination, 5.3 cm; montelukast, 5.7 cm). CONCLUSION: Both fluticasone monotherapy and PACT combination achieved greater improvements in asthma control days than montelukast. However, fluticasone monotherapy was superior to PACT combination in achieving other dimensions of asthma control. Growth was similar in all groups. CLINICAL IMPLICATIONS: Therefore, of the regimens tested, the PACT study findings favor fluticasone monotherapy in treating children with mild-moderate persistent asthma with FEV(1) >or= 80% predicted, confirming current guideline recommendations.

ii. Adult Asthma

REVIEW UPDATE:

Apter A

Advances in adult asthma 2006: its risk factors, course, and management

J Allergy Clin Immunol;119:563-6, 2007

This Advances article updates our understanding of risk factors for asthma and its course and management. Studies relevant to clinical practice are discussed, with special attention to their clinical research methods.

REVIEW:

Chanez P

Severe asthma in adults: what are the important questions?

J Allergy Clin Immunol.2007;119:1337-48

The term severe refractory asthma (SRA) in adults applies to patients who remain difficult to control despite extensive re-evaluation of diagnosis and management following an observational period of at least 6 months by a specialist. Factors that influence asthma control should be recognized and adequately addressed prior to confirming the diagnosis of SRA. This report presents statements according to the literature defining SRA in order address the important questions. Phenotyping SRA will improve our understanding of mechanisms, natural history, and prognosis. Female gender, obesity, and smoking are associated with SRA. Atopy is less frequent in SRA, but occupational sensitizers are common inducers of new-onset SRA. Viruses contribute to severe exacerbations and can persist in the airways for long periods. Inflammatory cells are in the airways of the majority of patients with SRA and persist despite steroid therapy. The T(H)2

immune process alone is inadequate to explain SRA. Reduced responsiveness to corticosteroids is common, and epithelial cell and smooth muscle abnormalities are found, contributing to airway narrowing. Large and small airway wall thickening is observed, but parenchymal abnormalities may influence airway limitation. Inhaled corticosteroids and bronchodilators are the mainstay of treatment, but patients with SRA remain uncontrolled, indicating a need for new therapies.

iii. Pathogenesis

REVIEW UPDATE:
Boyce J
Asthma 2005-2006: bench to bedside
J Allergy Clin Immunol; 2006 118(3):582-6
Asthma is a prevalent and complex syndrome with several phenotypic variants. The central features are bronchial inflammation and airway hyperresponsiveness. Many aspects of asthma, such as control of airway hyperresponsiveness, causative factors, and variable responses to treatment, remain poorly understood. This review highlights some of the latest insights into the pathogenesis of asthma that might ultimately bear on the development or choice of treatment modalities.

REVIEW UPDATE:
Moore WC
Update in asthma 2006.
Am J Respir Crit Care Med. 2007;175:649-54
Asthma-related investigations reported in 2006 ranged from the characterization of clinical asthma and airway obstruction, to human biologic studies and the use of animal models to better understand pathobiologic mechanisms at a cellular and molecular level. The concept of "risk" has been featured prominently, with articles identifying factors that increase the risk of developing asthma as well as those aimed at identifying risk factors for asthma exacerbations and adverse outcomes. Studies have continued to explore the utility of noninvasive biomarkers (exhaled nitric oxide, exhaled breath condensate) to identify, modify , and treat disease while increasing understanding of pathophysiologic mechanisms in asthma. Clinical trials have sought to optimize treatment with established asthma drugs and to evaluate novel modalities to fill voids in our current armory of asthma medications. Overall, this year has been an interesting journey, particularly in clinical asthma research, challenging accepted concepts in asthma therapy, and urging clinicians to expand their assessment of patients to identify and modify patient risk in addition to traditional measures of asthma control.

iv. Exercise Induced Asthma

REVIEW:
Anderson SD
How does exercise cause asthma attacks?.
Curr Opin Allergy Clinical Immunol 2006;6:37-42
PURPOSE OF REVIEW: To remind readers that evaporative water loss from the airway surface is the stimulus for exercise-induced bronchoconstriction. To emphasize that recruitment of the peripheral airways determines severity of exercise-induced bronchoconstriction. To draw attention to the potential for injury of the epithelium and for plasma exudation to contribute to the pathogenesis of exercise-induced bronchoconstriction in athletes. To emphasize that many

inflammatory mediators are involved in exercise-induced bronchoconstriction and that some are found in both asthmatic and healthy subjects. RECENT FINDINGS: That inflammatory mediators are released into the airways in response to exercise and can be measured by inducing sputum (histamine, cysteinyl leukotrienes) or collecting condensate from exhaled air (cysteinyl leukotrienes and adenosine). The concentration of mediators was reduced in response to a combination of loratadine and montelukast. Exercise is a stimulus for upregulating the genes coding for the 5-lipoxygenase pathway in healthy subjects. SUMMARY: Dehydration of the airways results in release of mediators. The likely source of these mediators is the mast cell. Epithelial injury occurs in exercise-induced bronchoconstriction. The process of repair may contribute to the development of airway hyperresponsiveness in healthy subjects. Measuring the airway response to exercise, or a surrogate for exercise, as an indicator of airway hyperresponsiveness is warranted in patients with symptoms of asthma.

REVIEW:
Weiler JM
EXERCISE-INDUCED ASTHMA: Work Group Report: American Academy of Allergy, Asthma & Immunology Work Group Report: Exercise-induced asthma
J Allergy Clinical Immunol 2007;119:1349-1358.
A complete review of exercise-induced asthma. Including epidemiology and pathogenesis. An overview of the evaluation and work-up is provided as well as differential diagnosis and current therapeutic options

v. Aspirin Exacerbated Respiratory Disease

REVIEW:
Stevenson DD
Clinical and pathologic perspectives on aspirin sensitivity and asthma.
J Allergy Clin Immunol 2006;118:773-86
Aspirin and other nonsteroidal anti-inflammatory drugs that inhibit COX-1 induce unique nonallergic reactions, consisting of attacks of rhinitis and asthma. These hypersensitivity reactions occur in a subset of asthmatic subjects, thus identifying them as having this exclusive clinical presentation. We refer to these patients as having aspirin-exacerbated respiratory disease, a disease process that produces devastating eosinophilic inflammation of both the upper and lower respiratory tracts. This review focuses on a description of patients with aspirin-exacerbated respiratory disease, methods available to diagnose their condition, the unique ability of all nonsteroidal anti-inflammatory drugs that inhibit COX-1 to cross-react with aspirin, an update on pathogenesis, and current thoughts about treatment.

vi. Emerging Asthma Therapy

REVIEW:
O'Byrne PM.
Cytokines or their antagonists for the treatment of asthma.
Chest. 130:244-50, 2006
T helper (Th) type 2 cytokines, particularly interleukin (IL)-4, IL-5, and IL-13, may be important in the development of allergic asthma. Humanized monoclonal antibodies (MoAbs) against IL-5 and a recombinant human soluble IL-4 receptor (sIL-4R) have been developed as possible treatments. These approaches have not yet proven to be successful in patients with persistent

asthma. This may suggest that neither IL-4 nor IL-5 is important in asthma pathogenesis. There is, however, insufficient information about the efficacy of sIL-4R and the anti-IL-5 MoAbs in asthma to draw any firm conclusions about the importance of these Th2 cytokines. Also, the administration of the potentially antiinflammatory cytokines IL-12 and interferon-gamma has not shown benefit in asthmatic patients. By contrast, the treatment of severe oral steroid-dependent asthma with soluble tumor necrosis factor-alpha receptor has demonstrated very promising results, suggesting that this cytokine plays an important role in the persistence of severe asthma.

vii. ABPA

REVIEW:

Virnig C

Allergic bronchopulmonary aspergillosis: a US perspective

Curr Opin Pulm Med 2007;13:67-71

PURPOSE OF REVIEW: The present article is an update of allergic bronchopulmonary aspergillosis. Although a rare condition, allergic bronchopulmonary aspergillosis does affect a number of patients with asthma and cystic fibrosis. Prompt recognition and treatment of the disease is critical to improving patient outcomes. RECENT FINDINGS: There is currently much active research being performed in the area of allergic bronchopulmonary aspergillosis. Fascinating insights are being made into the pathophysiology and genetics of the disease. Additionally, research is ongoing on the use of recombinant Aspergillus allergens as an aid to the diagnosis of allergic bronchopulmonary aspergillosis. SUMMARY: These new insights into the genetics and pathophysiology of allergic bronchopulmonary aspergillosis and the development of these new diagnostic techniques could ultimately lead to improved patient treatment. These areas form an important basis for further research

viii. Asthma Assessment

REVIEW:

Lundback B

Assessment of asthma control and its impact on optimal treatment strategy.

Allergy 2007;62:611-9

Achieving and maintaining optimal asthma control is a major asthma management goal advocated by the Global Initiative for Asthma (GINA). Recent evidence suggests that while asthma control is clearly achievable in most asthmatics, not all asthmatics attain optimal asthma control. The difficulty is compounded further because patients, physicians and regulatory bodies have different perceptions of what is meant by asthma control. The challenge therefore remains as to how best to assess asthma control and define management strategies to ensure that this control is achieved and maintained. Despite the availability of several patient-based tools for assessing asthma control, these are mostly employed in a research setting or in selected specialist clinics. A symptom-based treatment approach also may have its limitations because patients can be poor judges of disease symptoms and severity and under-estimation may lead to inadequate treatment of airway inflammation and airway hyperresponsiveness (AHR) when treatment is administered as on-demand reliever therapy, since the effect of treatment on these underlying features occurs over a longer time course. The clinical benefits of sustained maintenance treatment for at least 3 months has been documented in recent studies of salmeterol/fluticasone propionate combination, which have demonstrated correlations between reduction in airway inflammation/AHR and reduction in exacerbation rates. In view of the putative limitations of a purely symptom-based asthma

management plan, we suggest that treatment should be focussed on management of all aspects of the disease rather than management of symptoms alone, with a practical approach being treatment for a minimum of 3 months with an optimal dose to ensure maximal effects are seen on asthma control, airway inflammation, lung function, and remodelling.

WORKSHOP ON ASTHMA SCREENING IN CHILDREN
Gerald LB
An Official ATS Workshop Report: Issues in Screening for Asthma in Children
Proc Am Thorac Soc 2007;133-141

ix. Hypersensitivity Pneumonitis

REVIEW:
Ismail T
Extrinsic allergic alveolitis
Respirology. 11:262-8, 2006
Extrinsic allergic alveolitis (also known as hypersensitivity pneumonitis) is caused by repeated inhalation of mainly organic antigens by sensitized subjects. This induces a hypersensitivity response in the distal bronchioles and alveoli and subjects may present clinically with a variety of symptoms. The aims of this review are to describe the current concepts of the immunological response, the diverse clinical presentation of this disease, the relevant investigations and management, and areas for future studies.

REVIEW:
Mohr LC.
Hypersensitivity pneumonitis
Cur Opin Pulm Med. 2004;10:401-11.
PURPOSE OF REVIEW: Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a granulomatous, inflammatory disease of the lungs caused by the inhalation of antigenic organic particles or fumes. The disease may present as an acute, subacute, or chronic illness. Episodes of acute and subacute HP usually resolve following cessation of antigen exposure. Chronic HP may be progressive, irreversible, and result in debilitating fibrotic lung disease. This review discusses current concepts regarding the diagnosis, pathogenesis, and treatment of HP. RECENT FINDINGS: The pathogenesis of HP involves both type III and type IV hypersensitivity reactions that are mediated by immune complexes and Th1 T cells, respectively. Proinflammatory cytokines and chemokines activate alveolar macrophages, cause an influx of CD8+ lymphocytes into the lungs, facilitate granuloma formation, and promote the development of pulmonary fibrosis. IFN-gamma is essential for the development of HP and IL-10 appears to modulate the severity of disease. TNF-alpha and TGF-beta have been implicated in development of the pulmonary fibrosis that is seen in chronic HP. It has been shown that pigeon fanciers with HP have an increase in the frequency of HLA-DRB1*1305 and HLA-DQB1*0501 alleles, a decrease in the frequency of the HLA-BRB1*0802 allele, and an increased frequency of the TNF-2 (-308) polymorphism of the TNF-alpha promoter gene. SUMMARY: A careful environmental and occupational history and establishment of exposure to a known inciting antigen are key factors in making the diagnosis of HP. Serum precipitating antibodies, bronchoalveolar lavage, and lung biopsy may be helpful in making the diagnosis. Avoidance of organic antigen exposure is the

most important factor in the management of HP. Corticosteroids are indicated for the treatment of severe acute and subacute HP and for chronic HP that is severe or progressive. Long-term corticosteroid therapy for the treatment of chronic HP should be considered only if objective improvement in clinical signs, pulmonary function, or radiographic abnormalities is documented.

x. COPD / Bronchitis

GUIDELINE REVIEW:
Rabe KF
Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.
Am of Respir & Crit Care Med 2006;176(6):532-55

Chronic obstructive pulmonary disease (COPD) remains a major public health problem. It is the fourth leading cause of chronic morbidity and mortality in the United States, and is projected to rank fifth in 2020 in burden of disease worldwide, according to a study published by the World Bank/World Health Organization. Yet, COPD remains relatively unknown or ignored by the public as well as public health and government officials. In 1998, in an effort to bring more attention to COPD, its management, and its prevention, a committed group of scientists encouraged the U.S. National Heart, Lung, and Blood Institute and the World Health Organization to form the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Among the important objectives of GOLD are to increase awareness of COPD and to help the millions of people who suffer from this disease and die prematurely of it or its complications. The first step in the GOLD program was to prepare a consensus report, Global Strategy for the Diagnosis, Management, and Prevention of COPD, published in 2001. The present, newly revised document follows the same format as the original consensus report, but has been updated to reflect the many publications on COPD that have appeared. GOLD national leaders, a network of international experts, have initiated investigations of the causes and prevalence of COPD in their countries, and developed innovative approaches for the dissemination and implementation of COPD management guidelines. We appreciate the enormous amount of work the GOLD national leaders have done on behalf of their patients with COPD. Despite the achievements in the 5 years since the GOLD report was originally published, considerable additional work is ahead of us if we are to control this major public health problem. The GOLD initiative will continue to bring COPD to the attention of governments, public health officials, health care workers, and the general public, but a concerted effort by all involved in health care will be necessary.

xi. Cystic Fibrosis

REVIEW Adult:
Gershman AJ
Cystic fibrosis in adults: an overview for the internist.
Cleve Clin J Med. 2006;73:1065-74

The care of patients with cystic fibrosis (CF) has improved over the past 30 years, and most patients now survive well into adulthood. As a result, clinicians other than pediatricians are more likely than in the past to see CF patients and manage their respiratory, gastrointestinal, pancreatic, and reproductive complications.

Ratjen F. Doring G
Cystic fibrosis

Lancet 2003;361:681-9.
Cystic fibrosis is the most common autosomal recessive disorder in white people, with a frequency of about 1 in 2500 livebirths. Discovery of the mutated gene encoding a defective chloride channel in epithelial cells--named cystic fibrosis transmembrane conductance regulator (CFTR)--has improved our understanding of the disorder's pathophysiology and has aided diagnosis, but has shown the disease's complexity. Gene replacement therapy is still far from being used in patients with cystic fibrosis, mostly because of difficulties of targeting the appropriate cells. Life expectancy of patients with the disorder has been greatly increased over past decades because of better notions of symptomatic treatment strategies. Here, we summarise advances in understanding and treatment of cystic fibrosis, focusing on pulmonary disease, which accounts for most morbidity and deaths.

xii. Sarcoidosis

REVIEW:
Lynch JP
Pulmonary Sarcoidosis
Semin Respir Crit Care Med. 2007 Feb;28(1):53-74
Sarcoidosis, a granulomatous disorder of unknown etiology, characteristically involves multiple organs. However, pulmonary manifestations typically dominate. Chest radiographs are abnormal in 85 to 95% of patients. Abnormalities in pulmonary function tests are common and may be associated with cough, dyspnea, and exercise limitation. However, one third or more of patients are asymptomatic, with incidental abnormalities on chest radiographs. The clinical course and expression of pulmonary sarcoidosis are variable. Spontaneous remissions occur in nearly two thirds of patients. The course is chronic in up to 30% of patients. Chronic pulmonary sarcoidosis may result in progressive (sometimes life-threatening) loss of lung function. Fatalities ascribed to sarcoidosis occur in 1 to 4% of patients. Although the impact of treatment is controversial, corticosteroids may be highly effective in some patients. Immunosuppressive, cytotoxic, or immunomodulatory agents are reserved for patients failing or experiencing adverse effects from corticosteroids. Lung transplantation is a viable option for patients with life-threatening disease failing medical therapy.

REVIEW:
Cox CE.
Sarcoidosis
Med Clin North Am 2005;89:817-28.
Sarcoidosis is a disease found in most populations worldwide, although it has a proclivity for relatively young African-American women in the United States. Although the pathogenesis is unknown, there likely are social, environmental, and genetic factors that are involved. Sarcoidosis seems to be different between whites and African Americans, with the latter population experiencing more severe and chronic disease. Improving access to care and addressing other disparities in health care may help to bridge the gap in health outcomes observed between patients.

xiii. Occupational Asthma

REVIEW:
Mapp C
Occupational Asthma

Am J Respir Crit Care Med. 2005;172:280-305
Substantial epidemiologic and clinical evidence indicates that agents inhaled at work can induce asthma. In industrialized countries, occupational factors have been implicated in 9 to 15% of all cases of adult asthma. Work-related asthma includes (1) immunologic occupational asthma (OA), characterized by a latency period before the onset of symptoms; (2) nonimmunologic OA, which occurs after single or multiple exposures to high concentrations of irritant materials; (3) work-aggravated asthma, which is preexisting or concurrent asthma exacerbated by workplace exposures; and (4) variant syndromes. Assessment of the work environment has improved, making it possible to measure concentrations of several high- and low-molecular-weight agents in the workplace. The identification of host factors, polymorphisms, and candidate genes associated with OA is in progress and may improve our understanding of mechanisms involved in OA. A reliable diagnosis of OA should be confirmed by objective testing early after its onset. Removal of the worker from exposure to the causal agent and treatment with inhaled glucocorticoids lead to a better outcome. Finally, strategies for preventing OA should be implemented and their cost-effectiveness examined.

xiv. Chronic Cough

REVIEW:
Taming Chronic Cough
Rank MA,
Ann Allergy Asthma Immunol. 2007;98:305-313
OBJECTIVE: To review the available evidence on treating chronic cough to relay a thoughtful, evidence-based approach for the diagnosis and treatment of chronic cough. RESULTS: Few randomized controlled trials have addressed the diagnosis and treatment of chronic cough. There are several prospective noncontrolled trials for adults with chronic cough that found a high percentage of cough resolution when using an approach that focused on the diagnosis and treatment of the most common causes: asthma, gastroesophageal reflux disease, and upper airway cough syndrome. Preliminary studies in children support an approach that distinguishes between a wet and dry cough, as well as an in-depth investigation of any specific symptoms that point to an underlying chronic illness. CONCLUSION: Allergists, as experts in treating upper airway and lower airway disorders, are uniquely poised to diagnose and treat chronic cough.

b. Specific skills and practical management : chest exam, interpretation of pulmonary function testing, bronchial challenges, sputum and exhaled breath analysis, and gross interpretation of imaging studies.

i. Pulmonary Function Testing

REVIEW:
Pellegrino R, Viegi G, Brusasco V, Crapo RO et al.
Interpretative strategies for lung function tests
Eur Respir J. 2005;26:948-68.
This section is written to provide guidance in interpreting pulmonary function tests (PFTs) to medical directors of hospital-bansed laboratories that perform PFTs, and physicians who are responsible for interpreting the results of PFTs most commonly ordered for clinical purposes. Specifically, this section addresses the interpretation of spirometry, bronchodilator response, carbon monoxide diffusing capacity (DL,CO) and lung volumes.

ii. Bronchial Challenge

PRACTICE PARAMETER / GUIDELINE - (METHACHOLINE &EXERCISE CHALLENGE):
Official Statement of the American Thoracic Society
Guidelines for Methacholine and Exercise Challenge Testing
Am J Respir Crit Care Med 2000;161:309-329.

REVIEW AIRWAY HYPERRESPONSIVENESS:
Cockcroft DW
Mechanisms of airway hyperresponsiveness
J Allergy Clin Immunol 2006;118:551-9.
Airway hyperresponsiveness (AHR) to direct (histamine and methacholine) and indirect (exercise, cold air, hyperventilation, AMP) challenges is a universal and defining feature of asthma. One component of AHR is transient or inducible and occurs after allergen exposure, for example, and improves occasionally rapidly after inhaled corticosteroids or environmental control. This transient airway hyperresponsiveness is more marked to the indirect stimuli. There are convincing data linking this component of AHR to airway inflammation; however, the precise mechanisms linking airway inflammation and hyperresponsiveness of the airway smooth muscle are not clear. The other component of AHR is more persistent and is relatively refractory to environmental control and inhaled corticosteroids. This is likely secondary to structural airway changes, which are collectively referred to as airway remodeling, and which are a result of the chronic (rather than the acute) effects of airway inflammation. This persistent AHR is best reflected by airway hyperresponsiveness to direct stimuli such as methacholine. The mechanisms are also uncertain, but reduced airway caliber, increased airway wall thickness, increased airway smooth muscle mass, and perhaps contractility likely all play a role

iii. Sputum /Exhaled Breath Analysis

REVIEW:
Hunt J
Exhaled breath condensate: an overview.
Immunol Allergy Clin North Am. 2007;27:587-96
Exhaled breath condensate (EBC) is a promising source of biomarkers of lung disease. EBC is not a biomarker, but rather a matrix in which biomarkers may be identified, in that way equivalent to blood, sweat, tears, urine, and saliva. EBC may be thought of either as a body fluid or as a condensate of exhaled gas. The field of EBC research has advanced gradually, with the debates surrounding an emerging field helping to pose questions and gradually leading to answers. Conscientous assay technique will likely find in EBC any substance of substantially high enough concentration in the airway lining fluid.

REVIEW:
Spahn J
Exhaled breath condensate: an overview.
Immunol Allergy Clin North Am. 2007;27:607-622
Several inflammatory cells are thought to contribute to the pathogenesis of asthma. Among these, the eosinophil appears to be a major effector cell. This review focuses primarily on the clinical

utility of sputum eosinophil counts in asthma. Several studies have shown sputum eosinophils to be associated with both asthma severity and level of asthma control. In addition, the presence of sputum eosinophilia is strongly predictive of a favorable response to glucocorticoid therapy. Conversely, the absence of sputum eosinophilia is predictive of a poor response to glucocorticoid therapy. Sputum eosinophilia also predicts asthma relapse in subjects who have their inhaled glucocorticoid reduced or withdrawn. Lastly, inhaled glucocorticoid therapy can be titrated to keep the sputum eosinophil count at or below 2%.

REVIEW:
Stewart L
Exhaled Nitric Oxide.
Immunol Allergy Clin North Am. 2007;27:571-86
Exhaled nitric oxide (FENO) is a noninvasive easily measurable biomarker that is proving to be an excellent surrogate for eosinophilic inflammation in the lungs of patients who have asthma. Although large-scale normative data are still awaited, preliminary studies have shown FENO to be helpful in diagnosing and assessing severity and control for asthma. FENO levels have also proven helpful in diagnosing and managing several other inflammatory lung diseases.

iv. Chest Imaging

Silva CI
Hypersensitivity pneumonitis: spectrum of high-resolution CT and pathologic findings.
AJR Am J of Roentgenol 2007;188:334-44
OBJECTIVE: The purpose of this article is to illustrate the spectrum of pathologic and high-resolution CT features of hypersensitivity pneumonitis (HP). CONCLUSION: High-resolution CT plays an important role in the diagnosis of HP. A confident diagnosis of subacute HP is based on the presence of ground-glass opacities, poorly defined centrilobular nodules, and mosaic attenuation on inspiratory images and of air trapping on expiratory CT images. Chronic HP is characterized on high-resolution CT by the presence of reticulation due to fibrosis superimposed on findings of subacute HP. Histologically, subacute HP is characterized by the presence of cellular bronchiolitis, noncaseating granulomas, and bronchiolocentric lymphocytic interstitial pneumonitis. Areas of organizing pneumonia also may be seen. The high-resolution CT and pathologic features of chronic HP frequently overlap with those of nonspecific interstitial pneumonia and usual interstitial pneumonia. Awareness of the various manifestations of HP is important for early diagnosis and management.

v. Practical Management Asthma

PRACTICE PARAMETER GUIDELINE (ASTHMA UPDATE):
NAEPP expert panel report 3
Guidelines for the Diagnosis and Management of Asthma
www.nhlbi.nih.gov/guidelines/asthma/index.htm

SUMMARY DOCUMENT:
J Allergy Clin Immunol 2007;120: S94-S138
Highlights of the National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma–Full Report 2007 are presented in this EPR-3 summary report.

PRACTICE PARAMETER GLOBAL INITIATVE FOR ASTHMA (GINA):
Guidelines for the Diagnosis and Treatment of Asthma
Updated December 2006
www.ginasthma.com/Guidelineitem.asp?l1=2&l2=1&intId=60

PRACTICE PARAMETER / GUIDELINE (PEDIATRIC ASTHMA):
AAAAI / NAEPP Inititative
Pediatric Asthma: Promoting Best Practices
Web Publication at
www.aaaai.org/members/resources/initiatives/pediatricasthmaguidelines/default.stm

PRACTICE PARAMETER / GUIDELINE (ASTHMA IN PREGNANCY):
NAEPP expert panel report.
Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update.
NIH Publication 05-5236 March 2005
www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm

REVIEW:
Strunk R
Omalizumab for Asthma
N Engl J Med 2006; 354:2689-2695
This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.

REVIEW:
Sorkness C
Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial.
J Allergy Clin Immunol. 2007;119:64-72
BACKGROUND: More evidence is needed on which to base recommendations for treatment of mild-moderate persistent asthma in school-aged children. OBJECTIVE: The Pediatric Asthma Controller Trial (PACT) compared the effectiveness of 3 regimens in achieving asthma control. METHODS: A total of 285 children (ages 6-14 years) with mild-moderate persistent asthma on the basis of symptoms, and with FEV(1) >or= 80% predicted and methacholine FEV(1) PC(20) <or= 12.5 mg/mL, were randomized to 1 of 3 double-blind 48-week treatments: fluticasone 100 microg twice daily (fluticasone monotherapy), fluticasone 100 microg/salmeterol 50 microg in the morning and salmeterol 50 mug in the evening (PACT combination), and montelukast 5 mg in the evening. Outcomes included asthma control days (primary outcome), exacerbations, humanistic measurements, and pulmonary function measurements. RESULTS: Fluticasone monotherapy and PACT combination were comparable in many patient-measured outcomes, including percent of asthma control days, but fluticasone monotherapy was superior for clinic-measured FEV(1)/forced

vital capacity (P = .015), maximum bronchodilator response (P = .009), exhaled nitric oxide (P < .001), and PC(20) (P < .001). Fluticasone monotherapy was superior to montelukast for asthma control days (64.2% vs 52.5%; P = .004) and for all other control outcomes. Growth over 48 weeks was not statistically different (fluticasone, 5.3 cm; PACT combination, 5.3 cm; montelukast, 5.7 cm). CONCLUSION: Both fluticasone monotherapy and PACT combination achieved greater improvements in asthma control days than montelukast. However, fluticasone monotherapy was superior to PACT combination in achieving other dimensions of asthma control. Growth was similar in all groups. CLINICAL IMPLICATIONS: Therefore, of the regimens tested, the PACT study findings favor fluticasone monotherapy in treating children with mild-moderate persistent asthma with FEV(1) >or= 80% predicted, confirming current guideline recommendations.

REVIEW:
Tamesis GP
Heterogeneity in response to asthma medications.
Curr Opin Allergy Clin Immunol. 2007;7:185-9
PURPOSE OF REVIEW: Evidence for the heterogeneity of response to asthma medications including inhaled corticosteroids and leukotriene receptor antagonists is mounting. beta2-Adrenoceptor gene polymorphisms may contribute to asthma responsiveness to short- and long-acting beta2-agonists. This review examines recent articles describing variability in response to inhaled corticosteroids, leukotriene receptor antagonists and short-acting beta2-agonists specifically in pediatric persistent asthmatics. RECENT FINDINGS: In the late 1990's, differences in the response to a leukotriene receptor antagonist and an inhaled corticosteroid in adults with moderate persistent asthma were first described. Subsequently, similar findings have recently been elucidated in children with mild to moderate persistent asthma. The variability in response to these two classes of control medicines now appears to encompass all ages with persistent asthma. In general, despite the variability in response to these medications, both resulted in improved clinical and physiologic control measures. SUMMARY: Childhood asthma is a complex disease with numerous clinical phenotypes that contribute to response variability to asthma medications.

vi. Practical Management –Key publications clarifying risks & benefits of asthma therapy

vii. Inhaled corticosteroids

KEY CLINICAL INVESTIGATION:
Guilbert TW
Long-term inhaled corticosteroids in preschool children at high risk for asthma.
N Engl J Med 2006; 354: 1985-97.
BACKGROUND: It is unknown whether inhaled corticosteroids can modify the subsequent development of asthma in preschool children at high risk for asthma. METHODS: We randomly assigned 285 participants two or three years of age with a positive asthma predictive index to treatment with fluticasone propionate (at a dose of 88 mug twice daily) or masked placebo for two years, followed by a one-year period without study medication. The primary outcome was the proportion of episode-free days during the observation year. RESULTS: During the observation year, no significant differences were seen between the two groups in the proportion of episode-free days, the number of exacerbations, or lung function. During the treatment period, as compared with placebo use, use of the inhaled corticosteroid was associated with a greater proportion of

episode-free days (P=0.006) and a lower rate of exacerbations (P<0.001) and of supplementary use of controller medication (P<0.001). In the inhaled-corticosteroid group, as compared with the placebo group, the mean increase in height was 1.1 cm less at 24 months (P<0.001), but by the end of the trial, the height increase was 0.7 cm less (P=0.008). During treatment, the inhaled corticosteroid reduced symptoms and exacerbations but slowed growth, albeit temporarily and not progressively. CONCLUSIONS: In preschool children at high risk for asthma, two years of inhaled-corticosteroid therapy did not change the development of asthma symptoms or lung function during a third, treatment-free year. These findings do not provide support for a subsequent disease-modifying effect of inhaled corticosteroids after the treatment is discontinued.

KEY CLINICAL INVESTIGATION:
Murray CS
Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy INfants (IFWIN): double-blind, randomised, controlled study.
Lancet. 2006 Aug 26;368(9537):754-62
BACKGROUND: Wheezing and asthma often begins in early childhood, but it is difficult to predict whether or not a wheezy infant will develop asthma. Some researchers suggest that treatment with inhaled corticosteroids at the first signs of wheezing in childhood could prevent the development of asthma later in life. However, other investigators have reported that although such treatment could help control symptoms, the benefits can disappear within months of stopping treatment. We tested our hypothesis that to prevent loss of lung function and worsening asthma later in childhood, anti-inflammatory treatment needs to be started early in life. METHODS: We did a randomised, double-blind, controlled study of inhaled fluticasone propionate 100 mug twice daily in young children who were followed prospectively and randomised after either one prolonged (>1 month) or two medically confirmed wheezy episodes. The dose of study drug was reduced every 3 months to the minimum needed. If the symptoms were not under control by 3 months, open-label fluticasone propionate 100 mug twice daily was added to the treatment. Children were followed-up to 5 years of age, at which point we gave their parents or guardians questionnaires, and measured the children's lung function (specific airways resistance [sR(aw)], forced expiratory volume in 1s [FEV1]) and airway reactivity (eucapnic voluntary hyperventilation [EVH] challenge). This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN86717853. FINDINGS: We followed 1073 children prospectively, of whom 333 were eligible, and 200 of these began treatment (130 male, median age 1.2 years [range 0.5-4.9]; 101 placebo, 99 treatment); 173 (85 treatment, 88 placebo) completed the follow-up at age five years. The groups did not differ significantly in the proportion of children with current wheeze, physician-diagnosed asthma or use of asthma medication, lung function, or airway reactivity (percentage change in FEV1, adjusted mean for placebo 5.5% [95% CI -2.5 to 13.4]) vs for treatment 5.0% [-2.2 to 12.2], p=0.87). There were no differences in the results after adjustment for open-label fluticasone propionate, nor between the two groups in the time before the open-label drug was added (estimated hazard ratio 1.12 [95% CI 0.73-1.73], p=0.60), or the proportion needing the open-label drug (43 [42.57%] placebo, 41 [41.41%] treatment). INTERPRETATION: The early use of inhaled fluticasone propionate for wheezing in preschool children had no effect on the natural history of asthma or wheeze later in childhood, and did not prevent lung function decline or reduce airway reactivity

KEY CLINICAL INVESTIGATION:

Bisgaard H
Intermittent inhaled corticosteroids in infants with episodic wheezing.
N Engl J Med 2006; 354:1998-2005
BACKGROUND: We hypothesized that asthma is preceded by a stage of recurrent episodes of wheezing during the first years of life and that inhaled corticosteroid therapy during symptomatic episodes in this early phase may delay progression to persistent wheezing. METHODS: We assigned one-month-old infants to treatment with two-week courses of inhaled budesonide (400 mug per day) or placebo, initiated after a three-day episode of wheezing, in this single-center, randomized, double-blind, prospective study of three years' duration. The primary outcome was the number of symptom-free days; key secondary outcomes were the time to discontinuation due to persistent wheezing and safety, as evaluated by height and bone mineral density at the end of the study. RESULTS: We enrolled 411 infants and randomly assigned 294 to receive budesonide at a first episode of wheezing. The proportion of symptom-free days was 83 percent in the budesonide group and 82 percent in the placebo group (absolute difference, 1 percent; 95 percent confidence interval, -4.8 to 6.9 percent). Twenty-four percent of children in the budesonide group had persistent wheezing, as compared with 21 percent in the placebo group (hazard ratio, 1.22; 95 percent confidence interval, 0.71 to 2.13)--a finding that was unaffected by the presence or absence of atopic dermatitis. The mean duration of the acute episodes was 10 days in both groups and was independent of respiratory viral status. Height and bone mineral density were not affected by treatment. CONCLUSIONS: Intermittent inhaled corticosteroid therapy had no effect on the progression from episodic to persistent wheezing and no short-term benefit during episodes of wheezing in the first three years of life.

KEY CLINICAL INVESTIGATION:
Jarjour N
Control of airway inflammation maintained at a lower steroid dose with 100/50 microg of fluticasone propionate/salmeterol.
J Allergy Clin Immunol. 2006;118:44-52.
BACKGROUND: Inhaled corticosteroids (ICSs) have been shown to reverse epithelial damage and decrease lamina reticularis thickness in patients with asthma. OBJECTIVE: This study investigated whether clinical asthma control and airway inflammation could be maintained after switching therapy from medium-dose fluticasone propionate (FP) to low-dose FP administered with the long-acting beta2-agonist (LABA) salmeterol. METHODS: Eighty-eight subjects (age, > or =18 years) who, during open-label screening, demonstrated improved asthma control after an increase from 100 microg of FP twice daily to 250 microg of FP twice daily were randomized to receive 100/50 microg of FP/salmeterol through a Diskus inhaler (GlaxoSmithKline, Research Triangle Park, NC) twice daily or continue 250 microg of FP twice daily through a Diskus inhaler for 24 weeks. Clinical outcomes were monitored, and bronchial biopsy specimens and bronchoalveolar lavage fluid were obtained before and after 24 weeks of treatment. RESULTS: There were no significant differences between treatments with respect to eosinophils in the bronchial mucosa and bronchoalveolar lavage fluid; mucosal mast cells, neutrophils, or CD3+, CD4+, CD8+, or CD25+ T lymphocytes; or concentration of mediators (GM-CSF, IL-8, and eosinophil cationic protein). The 2 treatments were not different with respect to lamina reticularis thickness. Consistent with the airway inflammatory measures, clinical and physiologic measures of asthma control were also similar. CONCLUSION: This study demonstrates that control of asthma and airway inflammation is maintained over the 24-week treatment period when patients requiring

a medium-dose ICS are switched to a lower-dose ICS with a LABA. CLINICAL IMPLICATIONS: A lower-dose ICS with a LABA is effective in controlling inflammation and providing clinical asthma control, confirming current guideline recommendations.

KEY CLINICAL INVESTIGATION:
Szefler S
Characterization of within-subject responses to fluticasone and montelukast in childhood asthma.
J Allergy Clin Immunol 2005;115:233-42
BACKGROUND: Responses to inhaled corticosteroids (ICSs) and leukotriene receptor antagonists (LTRAs) vary among asthmatic patients. OBJECTIVE: We sought to determine whether responses to ICSs and LTRAs are concordant for individuals or whether asthmatic patients who do not respond to one medication respond to the other. METHODS: Children 6 to 17 years of age with mild-to-moderate persistent asthma were randomized to one of 2 crossover sequences, including 8 weeks of an ICS, fluticasone propionate (100 microg twice daily), and 8 weeks of an LTRA, montelukast (5-10 mg nightly depending on age), in a multicenter, double-masked, 18-week trial. Response was assessed on the basis of improvement in FEV 1 and assessed for relationships to baseline asthma phenotype-associated biomarkers. RESULTS: Defining response as improvement in FEV 1 of 7.5% or greater, 17% of 126 participants responded to both medications, 23% responded to fluticasone alone, 5% responded to montelukast alone, and 55% responded to neither medication. Compared with those who responded to neither medication, favorable response to fluticasone alone was associated with higher levels of exhaled nitric oxide, total eosinophil counts, levels of serum IgE, and levels of serum eosinophil cationic protein and lower levels of methacholine PC(20) and pulmonary function; favorable response to montelukast alone was associated with younger age and shorter disease duration. Greater differential response to fluticasone over montelukast was associated with higher bronchodilator use, bronchodilator response, exhaled nitric oxide levels, and eosinophil cationic protein levels and lower methacholine PC(20) and pulmonary function values. CONCLUSIONS: Response to fluticasone and montelukast vary considerably. Children with low pulmonary function or high levels of markers associated with allergic inflammation should receive ICS therapy. Other children could receive either ICSs or LTRAs.

viii. LongActing Beta agonists

LANDMARK ARTICLE:
Nelson HS
The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol.
Chest. 2006;129:15-26
STUDY OBJECTIVE: To compare the safety of salmeterol xinafoate or placebo added to usual asthma care. DESIGN: A 28-week, randomized, double-blind, placebo-controlled, observational study. SETTING: Study subjects were seen once in the study physician's office for screening and were provided all blinded study medication for the entire study period. Follow-up by telephone was scheduled every 4 weeks. PARTICIPANTS: Subjects (> 12 years old) with asthma as judged by the study physician were eligible. Individuals with a history of long-acting beta2-agonist use were excluded. INTERVENTIONS: Salmeterol, 42 mug bid via metered-dose inhaler (MDI), and placebo bid via MDI. MEASUREMENTS AND RESULTS: Following an interim analysis in

26,355 subjects, the study was terminated due to findings in African Americans and difficulties in enrollment. The occurrence of the primary outcome, respiratory-related deaths, or life-threatening experiences was low and not significantly different for salmeterol vs placebo (50 vs 36; relative risk [RR] = 1.40; 95% confidence interval [CI], 0.91 to 2.14). There was a small, significant increase in respiratory-related deaths (24 vs 11; RR, 2.16; 95% CI, 1.06 to 4.41) and asthma-related deaths (13 vs 3; RR, 4.37; 95% CI, 1.25 to 15.34), and in combined asthma-related deaths or life-threatening experiences (37 vs 22; RR, 1.71; 95% CI, 1.01 to 2.89) in subjects receiving salmeterol vs placebo. The imbalance occurred largely in the African-American subpopulation: respiratory-related deaths or life-threatening experiences (20 vs 5; RR, 4.10; 95% CI, 1.54 to 10.90) and combined asthma-related deaths or life-threatening experiences (19 vs 4; RR, 4.92; 95% CI, 1.68 to 14.45) in subjects receiving salmeterol vs placebo. CONCLUSIONS: For the primary end point in the total population, there were no significant differences between treatments. There were small, but statistically significant increases in respiratory-related and asthma-related deaths and combined asthma-related deaths or life-threatening experiences in the total population receiving salmeterol. Subgroup analyses suggest the risk may be greater in African Americans compared with Caucasian subjects. Whether this risk is due to factors including but not limited to a physiologic treatment effect, genetic factors, or patient behaviors leading to poor outcomes remains unknown.

KEY CLINICAL INVESTIGATION:
Rabe KF
Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study.
Lancet 2006;368:744-753

BACKGROUND: The contributions of as-needed inhaled corticosteroids and long-acting beta2 agonists (LABA) to asthma control have not been fully established. We compared the efficacy and safety of three reliever strategies: a traditional short-acting beta2 agonist; a rapid-onset LABA (formoterol); and a combination of LABA and an inhaled corticosteroid (budesonide-formoterol) in symptomatic patients receiving budesonide-formoterol maintenance therapy. METHODS: We did a 12-month, double-blind, parallel-group study in 3394 patients (aged 12 years or older), in 289 centres in 20 countries, who were using inhaled corticosteroids at study entry and symptomatic on budesonide-formoterol (160 microg and 4.5 microg, respectively), one inhalation twice daily, during a 2-week run-in. After run-in, patients were randomly assigned budesonide-formoterol maintenance therapy plus one of three alternative as-needed medications-terbutaline (0.4 mg), formoterol (4.5 microg), or budesonide-formoterol (160 microg and 4.5 microg). The primary outcome was time to first severe exacerbation, defined as an event resulting in hospitalisation, emergency room treatment, or both, or the need for oral steroids for 3 days or more. FINDINGS: Time to first severe exacerbation was longer with as-needed budesonide-formoterol versus formoterol ($p=0.0048$; log-rank test) and with as-needed formoterol versus terbutaline ($p=0.0051$). The rate of severe exacerbations was 37, 29, and 19 per 100 patients per year with as-needed terbutaline, formoterol, and budesonide-formoterol, respectively (rate ratios budesonide-formoterol versus formoterol 0.67 [95% CI 0.56-0.80; $p<0.0001$]; budesonide-formoterol versus terbutaline 0.52 [0.44-0.62; $p<0.0001$]; formoterol versus terbutaline 0.78 [0.67-0.91; $p=0.0012$]). Asthma control days increased to a similar extent in all treatment groups. As-needed formoterol did not significantly improve symptoms compared with as-needed terbutaline. All treatments were well tolerated. INTERPRETATION: Both monocomponents of budesonide-

formoterol given as needed contribute to enhanced protection from severe exacerbations in patients receiving combination therapy for maintenance.

KEY CLINICAL INVESTIGATION:
Wechsler ME.
Adrenergic receptor polymorphisms and response to salmeterol.
Am J Respir Crit Care Med 2006;173:519-526.
RATIONALE: Several studies suggest that patients with asthma who are homozygous for arginine at the 16th position of the beta2-adrenergic receptor may not benefit from short-acting beta-agonists. OBJECTIVES: We investigated whether such genotype-specific effects occur when patients are treated with long-acting beta-agonists and whether such effects are modified by concurrent inhaled corticosteroid (ICS) use. METHODS: We compared salmeterol response in patients with asthma homozygous for arginine at B16 (B16Arg/Arg) with those homozygous for glycine at B16 (B16Gly/Gly) in two separate cohorts. In the first, subjects were randomized to regular therapy with salmeterol while simultaneously discontinuing ICS therapy. In the second, subjects were randomized to regular therapy with salmeterol while continuing concomitant ICS. RESULTS: In both trials, B16Arg/Arg subjects did not benefit compared with B16Gly/Gly subjects after salmeterol was initiated. In the first cohort, compared with placebo, the addition of salmeterol was associated with a 51.4 L/min lower A.M. peak expiratory flow (PEF; p = 0.005) in B16Arg/Arg subjects(salmeterol, n = 12; placebo, n = 5) as compared with B16Gly/Gly subjects (salmeterol, n = 13; placebo, n = 13). In the second cohort, B16Arg/Arg subjects treated with salmeterol and ICS concurrently (n = 8) had a lower A.M. PEF (36.8 L/min difference, p = 0.048) than B16Gly/Gly subjects (n = 22) treated with the same regimen. In addition, B16 Arg/Arg subjects in the second cohort had lower FEV1 (0.42 L, p = 0.003), increased symptom scores (0.2 units, p = 0.034), and increased albuterol rescue use (0.95 puffs/d, p = 0.004) compared with B16Gly/Gly subjects. CONCLUSIONS: Relative to B16Gly/Gly patients with asthma, B16Arg/Arg patients with asthma may have an impaired therapeutic response to salmeterol in either the absence or presence of concurrent ICS use. Investigation of alternate treatment strategies may benefit this group.

KEY CLINICAL INVESTIGATION:
Bleecker ER
Salmeterol response is not affected by b2-adrenergic receptor genotype in subjects with persistent asthma. J Allergy Clin Immunol 2006;118:809-816.
BACKGROUND: Recent studies suggest that there might be an association between albuterol use and worsening asthma in patients homozygous for arginine (Arg/Arg) at codon 16 of the beta-receptor. However, it is not known whether similar responses occur in Arg/Arg patients receiving long-acting beta2-agonists. OBJECTIVE: We sought to evaluate the effects of variation in the beta2-adrenergic receptor gene (ADRB2) on clinical response to salmeterol administered with fluticasone propionate. METHODS: Subjects (n = 183) currently receiving short-acting beta2-agonists were randomized to twice-daily therapy with salmeterol, 50 microg, administered with fluticasone propionate, 100 microg, in a single inhaler or daily therapy with montelukast for 12 weeks, followed by a 2- to 4-day run-out period. RESULTS: There was sustained and significant improvement (P < .001) over baseline in all measures of asthma control in subjects receiving salmeterol, regardless of Arg16Gly genotype. Morning peak expiratory flow in subjects with the Arg/Arg genotype showed 89.0 +/- 16.1 L/min improvement over baseline compared with 93.7 +/-

12.7 L/min for Gly/Gly subjects and 92.5 +/- 11.9 L/min for Arg/Gly subjects. Pairwise changes were similar for Arg/Arg compared with Gly/Gly or Arg/Gly genotypes (estimated differences, 4.7 L/min and 3.5 L/min, respectively). Responses did not appear to be modified by haplotype pairs. During the run-out period, all subjects had predictable and similar decreases in measures of asthma control, with no differences between genotypes. CONCLUSION: Response to salmeterol does not vary between ADRB2 genotypes after chronic dosing with an inhaled corticosteroid. CLINICAL IMPLICATIONS: Analyses from this study indicate that genetic polymorphisms leading to Arg16Gly sequence changes within the beta2-adrenergic receptor do not affect patients' responses to recommended asthma therapy with salmeterol and fluticasone propionate.

ix. Genetic polymorphisms and beta agonists

LANDMARK INVESTIGATION:

Martinez FD.

Association between genetic polymorphisms of the b2-adrenoceptor and response to albuterol in children with and without a history of wheezing.

J Clin Invest 1997;100:3184-3188.

The beta2-adrenergic receptor (beta2AR) agonists are the most widely used agents in the treatment of asthma, but the genetic determinants of responsiveness to these agents are unknown. Two polymorphic loci within the coding region of the beta2AR have been recently described at amino acids 16 and 27. It has been reported that glycine at codon 16 (Gly-16) is associated with increased agonist-promoted downregulation of the beta2AR as compared with arginine-16 (Arg-16). The form of the receptor with glutamic acid at codon 27 (Glu-27), on the other hand, has been shown to be resistant to downregulation when compared with glutamine-27 (Gln-27), but only when coexpressed with Arg-16. To assess if different genotypes of these two polymorphisms would show differential responses to inhaled beta2AR agonists, we genotyped 269 children who were participants in a longitudinal study of asthma. Spirometry was performed before and after administration of 180 microg of albuterol, and a positive response was considered an increase of >15.3% predicted FEV1. There was marked linkage disequilibrium between the two polymorphisms, with 97.8% of all chromosomes that carried Arg-16 also carrying Gln-27. When compared to homozygotes for Gly-16, homozygotes for Arg-16 were 5.3 times (95% confidence interval 1.6-17.7) and heterozygotes for beta2AR-16 were 2.3 times (1.3-4.2) more likely to respond to albuterol, respectively. Similar trends were observed for asthmatic and nonasthmatic children, and results were independent of baseline lung function, ethnic origin, and previous use of antiasthma medication. No association was found between the beta2AR-27 polymorphism and response to albuterol. These results may explain some of the variability in response to therapeutic doses of albuterol in children.

RESEARCH FRONTIER:

Israel E

Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomized, placebo-controlled cross-over trial.

Lancet 2004;364:1505-1512.

BACKGROUND: The issue of whether regular use of an inhaled beta2-adrenergic agonist worsens airflow and clinical outcomes in asthma is controversial. Retrospective studies have suggested that adverse effects occur in patients with a genetic polymorphism that results in homozygosity for arginine (Arg/Arg), rather than glycine (Gly/Gly), at aminoacid residue 16 of the beta2-adrenergic

receptor. However, the existence of any genotype-dependent difference has not been tested in a prospective clinical trial. METHODS: Patients with mild asthma, not using a controller medication, were enrolled in pairs matched for forced expiratory volume in 1 s (FEV1) according to whether they had the Arg/Arg (n=37; four of 41 matches withdrew before randomisation) or Gly/Gly (n=41) genotype. Regularly scheduled treatment with albuterol or placebo was given in a masked, cross-over design, for 16-week periods. During the study, as-needed albuterol use was discontinued and ipratropium bromide was used as needed. Morning peak expiratory flow rate (PEFR) was the primary outcome variable. The primary comparisons were between treatment period for each genotype; the secondary outcome was a treatment by genotype effect. Analyses were by intention to treat. FINDINGS: During the run-in period, when albuterol use was kept to a minimum, patients with the Arg/Arg genotype had an increase in morning PEFR of 23 L/min (p=0.0162); the change in patients with the Gly/Gly genotype was not significant (2 L/min; p=0.8399). During randomised treatment, patients with the Gly/Gly genotype had an increase in morning PEFR during treatment with regularly scheduled albuterol compared with placebo (14 L/min [95% CI 3 to 25]; p=0.0175). By contrast, patients with the Arg/Arg genotype had lower morning PEFR during treatment with albuterol than during the placebo period, when albuterol use was limited (-10 L/min [-19 to -2]; p=0.0209). The genotype-attributable treatment difference was therefore -24 L/min (-37 to -12; p=0.0003). There were similar genotype-specific effects in FEV1, symptoms, and use of supplementary reliever medication. INTERPRETATION: Genotype at the 16th aminoacid residue of the beta2-adrenergic receptor affects the long-term response to albuterol use. Bronchodilator treatments avoiding albuterol may be appropriate for patients with the Arg/Arg genotype.

x. Practical Management of Exercise Induced Asthma

REVIEW:
Weiler JM
EXERCISE-INDUCED ASTHMA: Work Group Report: American Academy of Allergy, Asthma & Immunology Work Group Report: Exercise-induced asthma
J Allergy Clinical Immunol 2007;119:1349-1358.
A complete review of exercise-induced asthma. Including epidemiology and pathogenesis. An overview of the evaluation and work-up is provided as well as differential diagnosis and current therapeutic options.

xi. Practical Management ABPA

REVIEW:
Tillie-Leblond I
Allergic bronchopulmonary aspergillosis
Allergy 2005;60:1004-1013
Allergic bronchopulomonary aspergillosis (ABPA) is associated with both asthma and cystic fibrosis. This article explores the pathophysiology of this disease including genetic factors that may play a role. The current diagnostic criteria are discussed including the clinical characteristics and stages of ABPA. The long term treatment options are discussed including the role of antifungals.

xii. Practical Management Hypersensitivity Pneumonitis

REVIEW:

Jacobs RL. Andrews CP. Coalson JJ.
Hypersensitivity pneumonitis: beyond classic occupational disease-changing concepts of diagnosis and management.
Ann Allergy Asthma Immunol 2005;95:115-28.
OBJECTIVE: To review inhaled antigens in home environments that cause hypersensitivity pneumonitis (HP) of varied clinical expressions and histopathologic patterns. DATA SOURCES: Computer-assisted MEDLINE and manual searches for articles concerning HP, interstitial lung disease (ILD), epidemiology of HP and ILD, challenge procedures of HP, and indoor fungi. STUDY SELECTION: Published articles concerning inhaled antigens in home environments and HP were selected. RESULTS: Current criteria for the diagnosis of HP are too restrictive, because most apply only to the classic acute presentation and are of limited value in the subacute and insidious forms. Clinical expressions vary across the gamut of respiratory tract signs and symptoms. Patterns on lung biopsy may include all histopathologic descriptions of idiopathic ILD. The home is the likely causative environment rather than the workplace. Exposures may be occult and require in-depth environmental histories and on-site investigations to detect antigens and sources. CONCLUSIONS: Natural or environmental challenges have become an important tool for diagnosing HP and determining effectiveness of remediation. Early diagnosis and effective remediation of the cause lead to a high survival rate, whereas diagnosis in advanced stages leads to disability and/or premature death.

xiii. Practical Management COPD / Bronchitis

PRACTICE PARAMETER / GUIDELINE (COPD):
Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. 2006 Update
available at www.goldcopd.com
Executive Summary
Am J Respir Crit Care Med 2007;176:532-55

xiv. Practical Management Chronic Cough

REVIEW:
Irwin RS
Diagnosis and Management of Cough Executive Summary: ACCP Evidence-Based Clinical Practice Guidelines
Chest. 2006;129:1S-23S
OBJECTIVE: review the literature to provide a comprehensive approach, including algorithms for the clinician to follow in evaluating and treating the patient with acute, subacute, and chronic cough. METHODS: We searched MEDLINE (through May 2004) for studies published in the English language since 1980 on human subjects using the medical subject heading terms "cough," "treatment of cough," and "empiric treatment of cough." We selected case series and prospective descriptive clinical trials. We also obtained any references from these studies that were pertinent to the topic. RESULTS: The relative frequency of the disorders (alone and in combination) that can cause cough as well as the sensitivity and specificity of many but not all diagnostic tests in predicting the cause of cough are known. An effective approach to successfully manage chronic cough is to sequentially evaluate and treat for the common causes of cough using a combination of selected diagnostic tests and empiric therapy. Sequential and additive therapy is often crucial

because more than one cause of cough is frequently present. CONCLUSION: Algorithms that provide a "road map" that the clinician can follow are useful and are presented for acute, subacute, and chronic cough.

REVIEW:
Pratter MR
An Empiric Integrative Approach to the Management of Cough: ACCP Evidence-Based Clinical Practice Guidelines
Chest. 2006;129:222s-231S
OBJECTIVE: review the literature to provide a comprehensive approach, including algorithms for the clinician to follow in evaluating and treating the patient with acute, subacute, and chronic cough. METHODS: We searched MEDLINE (through May 2004) for studies published in the English language since 1980 on human subjects using the medical subject heading terms "cough," "treatment of cough," and "empiric treatment of cough." We selected case series and prospective descriptive clinical trials. We also obtained any references from these studies that were pertinent to the topic. RESULTS: The relative frequency of the disorders (alone and in combination) that can cause cough as well as the sensitivity and specificity of many but not all diagnostic tests in predicting the cause of cough are known. An effective approach to successfully manage chronic cough is to sequentially evaluate and treat for the common causes of cough using a combination of selected diagnostic tests and empiric therapy. Sequential and additive therapy is often crucial because more than one cause of cough is frequently present. CONCLUSION: Algorithms that provide a "road map" that the clinician can follow are useful and are presented for acute, subacute, and chronic cough.

REVIEW:
Chang AB
Guidelines for Evaluating Chronic Cough in Pediatrics: ACCP Evidence-Based Clinical Practice Guidelines
Chest. 2006;129:260S-283S
OBJECTIVE: To review relevant literature and present evidence-based guidelines to assist general and specialist medical practitioners in the evaluation and management of children who present with chronic cough. METHODOLOGY: The Cochrane, MEDLINE, and EMBASE databases, review articles, and reference lists of relevant articles were searched and reviewed by a single author. The date of the last comprehensive search was December 5, 2003, and that of the Cochrane database was November 7, 2004. The authors' own databases and expertise identified additional articles. RESULTS/CONCLUSIONS: Pediatric chronic cough (*ie*, cough in children aged < 15 years) is defined as a daily cough lasting for > 4 weeks. This time frame was chosen based on the natural history of URTIs in children and differs from the definition of chronic cough in adults. In this guideline, only chronic cough will be discussed. Chronic cough is subdivided into specific cough (*ie*, cough associated with other symptoms and signs suggestive of an associated or underlying problem) and nonspecific cough (*ie*, dry cough in the absence of an identifiable respiratory disease of known etiology). The majority of this section focuses on nonspecific cough, as specific cough encompasses the entire spectrum of pediatric pulmonology. A review of the literature revealed few randomized controlled trials for treatment of nonspecific cough. Management guidelines are summarized in two pathways. Recommendations are derived from a systematic review of the literature and were integrated with expert opinion. They are a general guideline only, do not

substitute for sound clinical judgment, and are not intended to be used as a protocol for the management of all children with a coughing illness. Children (aged < 15 years) with cough should be managed according to child-specific guidelines, which differ from those for adults as the etiologic factors and treatments for children are sometimes different from those for adults. Cough in children should be treated based on etiology, and there is no evidence for using medications for the symptomatic relief of cough. If medications are used, it is imperative that the children are followed up and therapy with the medications stopped if there is no effect on the cough within an expected time frame. An evaluation of the time to response is important. Irrespective of diagnosis, environmental influences and parental expectations should be discussed and managed accordingly. Cough often impacts the quality of life of both children and parents, and the exploration of parental expectations and fears is often valuable in the management of cough in children.

REVIEW:
Rank MA
Taming chronic cough.
Ann Allergy Asthma Immunol 98:305-13
OBJECTIVE: To review the available evidence on treating chronic cough to relay a thoughtful, evidence-based approach for the diagnosis and treatment of chronic cough. DATA SOURCES: MEDLINE, PubMed, EMBASE, and CINAHL were searched using the following keywords: cough, asthma, gastroesophageal reflux, sinusitis, rhinitis (allergic, seasonal), postnasal drip, vocal cord dysfunction, lung disease (interstitial), bronchiectasis, and bronchoscopy. STUDY SELECTION: Studies were selected based on their relevance to the diagnosis and treatment of chronic cough. Because of a lack of randomized prospective studies, nonrandomized and retrospective studies were considered, with their strengths and limitations noted. RESULTS: Few randomized controlled trials have addressed the diagnosis and treatment of chronic cough. There are several prospective noncontrolled trials for adults with chronic cough that found a high percentage of cough resolution when using an approach that focused on the diagnosis and treatment of the most common causes: asthma, gastroesophageal reflux disease, and upper airway cough syndrome. Preliminary studies in children support an approach that distinguishes between a wet and dry cough, as well as an in-depth investigation of any specific symptoms that point to an underlying chronic illness. CONCLUSION: Allergists, as experts in treating upper airway and lower airway disorders, are uniquely poised to diagnose and treat chronic cough.

5. Drug Allergy (See dermatologic disorders and anaphylaxis)

a. General Reviews and Susceptibility States

REVIEW:
Greenberger PA
Drug Allergy (MiniPrimer)
J Allergy Clin Immunol 2006;117:S464-70
Drug reactions can be considered as being either predictable or unpredictable. A predictable reaction would be the result of the pharmacologic action of the medication. An unpredictable reaction might be idiosyncratic, might be drug intolerance, or might have or imply an immunologic basis, such as being IgE mediated. Immediate reactions that are not IgE mediated can be considered as pseudoallergic (non-IgE-mediated mast cell activation). This review will discuss allergic and immunologic reactions to immunomodulators, penicillins and cephalosporins,

sulfonamides, aspirin, and nonselective nonsteroidal anti-inflammatory drugs and consider the serious drug-related conditions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The field of drug "allergy" has expanded to include adverse reactions associated with immunosuppressive medications, anticytokine therapies, and mAbs. The cytokine release reaction that occurs with anti-CD20 antibody infusions in patients with leukemia and white blood cell counts of greater than 50 x 10(9)/L is associated with high concentrations of TNF, IL-6, and IL-8. Because of the findings of fever, dyspnea, rigors, and hypotension, this reaction resembles the Jarisch-Herxheimer reaction that occurs 60 to 90 minutes after penicillin administration in patients with secondary syphilis. Furthermore, the care of the patient with penicillin allergy has been made more difficult in the absence of the major determinant, penicilloyl-polylysine, in that from 34% to 84% of patients who have positive skin test reactions to penicillin have exclusively positive reactions to the major determinant. SJS and TEN typically are caused by medications within 1 to 8 weeks of initiation of therapy. Evidence for death of the keratinocytes through (1) drug-specific cytotoxicity with the perforin-granzyme B-mediated killing and (2) activation of Fas on keratinocytes have provided explanations for the sloughing of skin. Unfortunately, intravenous immunoglobulin therapy for SJS and TEN has been disappointing.

REVIEW:
Gruchalla R
Clinical Practice. Antibiotic Allergy
N Engl J Med 2006;354:601-9
This *Journal* feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

REVIEW:
Brackett CC
Sulfonamide allergy and cross reactivity
Curr Allergy Asthma Rep 2007;7:41-8.
Concerns about cross-allergenicity between sulfonamide antibiotics and nonantibiotic sulfonamide-containing drugs continue to complicate pharmacotherapy. Several elegant investigations have demonstrated unequivocal lack of interaction between the sulfonamide group and either cellular or humoral immunity. The immunologic determinant of type I immunologic responses to sulfonamide antibiotics is the N1 heterocyclic ring, and nonantibiotic sulfonamides lack this structural feature. Many non-type I hypersensitivity responses to sulfonamide antibiotics are attributable to reactive metabolites that cause either direct cytotoxicity or humoral or cellular responses. Metabolite formation is stereospecific to the N4 amino nitrogen of the sulfonamide antibiotics, a structure not found on any nonantibiotic sulfonamide drugs. Cellular immune responses to sulfonamide antibiotics are responsible for many non-immunoglobulin E-mediated dermatologic reactions; however, the stereospecificity of T-cell response renders cross-reactivity between sulfonamide antibiotics and nonantibiotics highly unlikely. Apparent cross-reactivity responses to sulfonamide-containing drugs likely represent multiple concurrent, rather than linked, drug hypersensitivities.

REVIEW:
Phillips, E

Drug hypersensitivity in HIV
Curr Opin Allergy Clinical Immunol 2007:7: 324–330
Drug hypersensitivity has been reported to occur 100 times more commonly in those living with HIV. In the first decade of HIV treatment, this mainly involved drugs used to treat HIV-related infections but now primarily includes drugs used to treat HIV. This review focuses on the current knowledge of the epidemiology, pathophysiology and clinical features of drug hypersensitivity reactions of drugs used in the management of the HIV-infected patient. Our understanding of the immunogenetics and host predisposition to drug hypersensitivity has been advanced considerably by the antiretroviral drugs abacavir and nevirapine. The association of abacavir hypersensitivity reaction with *HLA-B*5701* has been particularly important and provides a basis for genetic screening in the clinic setting. The increased predisposition of drug hypersensitivity disease in HIV will continue to provide a fertile ground for study of the diverse and complex processes that drive its pathophysiology. Our knowledge of drug hypersensitivity will also increase as the expanding armentarium of antiretroviral therapy is applied to more diverse populations in the developing world. The potential for widespread implementation of *HLA-B*5701* screening for abacavir hypersensitivity will set an important precedent for bringing individualized medicine to the clinic and the use of genetic testing to improve drug safety.

RESEARCH FRONTIER:
Pirmohamed M
Genetic Factors in the Predisposition to Drug-induced Hypersensitivity Reactions
AAPS Journal. 2006: 8; E20-E26
Drug hypersensitivity reactions can occur with most drugs, although the frequency, severity, and clinical manifestations vary. Case reports have suggested that there may be familial clustering of drug hypersensitivity suggesting a genetic predisposition. As with most other forms of drug response, predisposition to drug hypersensitivity reactions is likely to be multifactorial and multigenic. Given the immune pathogenesis of these reactions, it is perhaps not surprising that the most significant genetic associations have been identified in the major histocompatibility complex for drugs such as abacavir, carbamazepine, and allopurinol. For abacavir, it has been suggested that preprescription genotyping for HLA-B*5701 in whites may reduce the incidence of hypersensitivity. It is likely that as our knowledge of variation in the human genome improves, coupled with improvements in technology, many more significant genetic predisposing factors for drug hypersensitivity are likely to be identified in the next decade. However, as we search for these genetic factors, it is important that we do not forget environmental predisposition, and to bear in mind that a genetic marker for drug hypersensitivity in one population may not necessarily be relevant for another population. Notwithstanding the advances in genetic technologies, the ultimate determinant of success in this area of research will be the identification and careful phenotyping of patients with drug hypersensitivity reactions. As we progress to whole genome scanning, in order to satisfy the requirements for adequate statistical power, the identification of large numbers of carefully phenotyped patients will be feasible only through international collaborations.

RESEARCH FRONTIER:
Chung WH
Human leukocyte antigens and drug hypersensitivity
Curr Opin Allergy Clin Immunol 2007;317-23

PURPOSE OF REVIEW: The present article reviews the recent literature on the identification of human leukocyte antigen (HLA) alleles as major susceptible genes for drug hypersensitivity and discusses the clinical implications. RECENT FINDINGS: Several recent studies have reported strong genetic associations between HLA alleles and susceptibility to drug hypersensitivity. The genetic associations can be drug specific, such as HLA-B*1502 being associated with carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), HLA-B*5701 with abacavir hypersensitivity and HLA-B*5801 with allopurinol-induced severe cutaneous adverse reactions. A genetic association can also be phenotype-specific, as B*1502 is associated solely with carbamazepine-SJS/TEN, and not with either maculopapular eruption or hypersensitivity syndrome. Furthermore, a genetic association can also be ethnicity specific; carbamazepine-SJS/TEN associated with B*1502 is seen in south-east Asians but not in whites, which may be explained by the different allele frequencies. SUMMARY: The strong genetic association suggests a direct involvement of HLA in the pathogenesis of drug hypersensitivity when the HLA molecule presents an antigenic drug for T cell activation. The high sensitivity/specificity of some markers provides a plausible basis for developing tests to identify individuals at risk for drug hypersensitivity. Application of HLA-B*1502 genotyping as a screening tool before prescribing carbamazepine could be a valuable tool in preventing carbamazepine-induced SJS/TEN in south-east Asian countries.

REVIEW:
Sanderson JP
Role of Bioactivation in Drug-Induced Hypersensitivity Reactions.
AAPS Journal. 2006;8:E55-E64
Drug-induced hypersensitivity reactions are a major problem in both clinical treatment and drug development. This review covers recent developments in our understanding of the pathogenic mechanisms involved, with special focus on the potential role of metabolism and bioactivation in generating a chemical signal for activation of the immune system. The possible role of haptenation and neoantigen formation is discussed, alongside recent findings that challenge this paradigm. Additionally, the essential role of costimulation is examined, as are the potential points whereby costimulation may be driven by reactive metabolites. The relevance of local generation of metabolites in determining the location and character of a reaction is also covered.

LANDMARK PUBLICATION:
Brown BC, Price EV, Moore MD
Penicilloyl-polylysine as an intradermal test of penicillin sensitivity.
JAMA 1964;189:599-604.

b. Distinction between hypersensitivity and intolerance

REVIEW:
Demoly P
Classification and Epidemiology of Hypersensitivity Drug Reactions
Immunol Allergy Clin N Am 2004;24:345-56
Nonimmune hypersensitivity reactions are unpredictable adverse drug reactions that are clinically similar to allergic reactions for which no drug-specific antibodies or T lymphocytes are identified. Few tools allow a definite diagnosis, and most of the available ones need to be validated. True

epidemiologic data are limited, and most of the available information on the incidence, mortality, and socioeconomic impact should be discussed with caution.

REVIEW:
Volcheck G
Clinical Evaluation and Management of Drug Hypersensitivity
Immunol Allergy Clin N Am 2004;24:357-71
Adverse drug reactions are a major health problem in the inpatient and outpatient clinical setting. Although all of the immune mechanisms of drug reactions are not well characterized, a detailed medication history, knowledge of the signs and symptoms associated with known immune mechanisms, and knowledge of the types of medications typically associated with distinct immune reactions are helpful in implicating the causative drug. Standardized testing for drug reactions is limited, especially for non-IgE-mediated reactions. Management consists of stopping the offending drug, treating the acute reaction, and making a determination concerning future use of the drug.

c. Cytotoxic, immune complex and delayed hypersensitivity reactions

REVIEW:
Posadas SJ
Delayed Hypersensitivity reactions -new concepts
Clin Exp Allergy 2007;37:389-99.
Immune reactions to small molecular compounds such as drugs can cause a variety of diseases mainly involving skin, but also liver, kidney, lungs and other organs. In addition to the well-known immediate, IgE-mediated reactions to drugs, many drug-induced hypersensitivity reactions appear delayed. Recent data have shown that in these delayed reactions drug-specific CD4(+) and CD8(+) T cells recognize drugs through their T cell receptors (TCR) in an MHC-dependent way. Immunohistochemical and functional studies of drug-reactive T cells in patients with distinct forms of exanthems revealed that distinct T cell functions lead to different clinical phenotypes. Taken together, these data allow delayed hypersensitivity reactions (type IV) to be further subclassified into T cell reactions, which by releasing certain cytokines and chemokines preferentially activate and recruit monocytes (type IVa), eosinophils (type IVb), or neutrophils (type IVd). Moreover, cytotoxic functions by either CD4(+) or CD8(+) T cells (type IVc) seem to participate in all type IV reactions. Drugs are not only immunogenic because of their chemical reactivity, but also because they may bind in a labile way to available TCRs and possibly MHC-molecules. This seems to be sufficient to stimulate certain, probably preactivated T cells. The drug seems to bind first to the fitting TCR, which already exerts some activation. For full activation, an additional interaction of the TCR with the MHC molecules is needed. The drug binding to the receptor structures is reminiscent of a pharmacological interaction between a drug and its (immune) receptor and was thus termed the p-i concept. In some patients with drug hypersensitivity, such a response occurs within hours even upon the first exposure to the drug. The T cell reaction to the drug might thus not be due to a classical, primary response, but is due to peptide-specific T cells which happen to be stimulated by a drug. This new concept has major implications for understanding clinical and immunological features of drug hypersensitivity and a model to explain the frequent skin symptoms in drug hypersensitivity is proposed.

REVIEW:
Lopez S.

Non-immediate reactions of beta lactams
Curr Opin Allergy and Immunol 2007;7:310-6
PURPOSE OF REVIEW: Nonimmediate reactions to beta-lactams include several clinical entities, from maculopapular rash to severe reactions such as Steven-Johnson syndrome. Toxic epidermal necrolysis and organ-specific reactions may also occur. RECENT FINDINGS: Progress has been made in understanding the role of the immunological system in nonimmediate reactions to beta-lactams. Different T-cell subsets recognize beta-lactams after haptenation of serum or cell proteins in the context of major histocompatibility complex. Studies using T-cell lines and clones have shown that a heterogeneous response is generated, with the expression of different cytokine profiles. Betalactams also act on dendritic cells, inducing changes that enable them to interact with naïve lymphocytes, becoming memory T cells. Tissue-activated CD4 and CD8 cells express perforin and other cytotoxic mediators that elicit the lesions. Studies on the clinical course of these entities indicate that cells migrate, establishing a recirculation with homing to the skin and back to the circulation. These cells thus participate not only in skin lesions but probably also in the repair process. SUMMARY: Understanding the immunological mechanisms involved in nonimmediate reactions to beta-lactams has improved over the last few years, with better definition of the different T-cell subpopulations involved. Experimental studies and monitoring of the response support the implication of different cell subsets.

REVIEW:
Arndt PA
The Changing spectrum of Drug-Induced Immune Hemolytic Anemia
Sem Hematol 2007:42:137-144
Drug-induced immune hemolytic anemia (DIIHA) occurs rarely. To date, about 100 drugs have been implicated in causing DIIHA and/or a positive direct antiglobulin test (DAT). The most common drugs associated with DIIHA in the 1970s were methyldopa and penicillin; currently, they are cefotetan and ceftriaxone. Drug antibodies fall into two types: drug-independent ("autoantibodies") and drug-dependent ("penicillin type" or "immune complex type"); some patients have combinations of these antibodies. Some drugs cause nonimmunologic protein adsorption onto drug-treated red blood cells (RBCs). This is known to be the cause of positive indirect antiglobulin tests and is suspected to be a cause of positive DATs. This mechanism may be associated with hemolytic anemia. Twelve cephalosporins have been reported to cause DIIHA; five (primarily cefotetan and ceftriaxone) have been associated with fatalites. Patients with DIIHA due to cefotetan may only have received one dose of the drug prophylactically with surgery. Antibodies to cefotetan react to very high titers against drug-treated RBCs (and at lower titers against untreated RBCs without and/or with drug present). Patients with ceftriaxone-induced DIIHA have received the drug previously; reactions in children often occur minutes after ceftriaxone administration. Antibodies to ceftriaxone are only of the "immune complex type."

REVIEW:
Richard HA
Drug-induced immune cytopenias
Toxicology 2005:209:149-153
Drugs can induce thrombocytopenia by several mechanisms, including marrow suppression and destruction of platelets in the peripheral blood by non-immune and immune mechanisms. We will review here current understanding of the immune mechanisms by which drugs promote immune-

mediated platelet destruction resulting in thrombocytopenia. Immune cytopenia is a relatively common and poorly understood side effect of many drugs. Affected target cells include erythrocytes, leukocytes, platelets and, probably, hematopoietic precursor cells in the marrow. For unknown reasons, platelets are affected much more often than the other cell types. We will here consider drug-induced immune thrombocytopenia (DITP) as a model for drug-induced blood dyscrasias having an immunologic pathogenesis. Drug-induced antibodies cause platelet destruction by a number of different mechanisms, each of which will be discussed in turn.

REVIEW:
Roychowdhury S
Mechanisms of Drug-induced Delayed-type Hypersensitivity Reactions in the Skin.
AAPS J. 2005:7:80-5
Cutaneous drug reactions (CDRs) are the most commonly reported adverse drug reactions. These reactions can range from mildly discomforting to life threatening. CDRs can arise either from immunological or nonimmunological mechanisms, though the preponderance of evidence suggests an important role for immunological responses. Some cutaneous eruptions appear shortly after drug intake, while others are not manifested until 7 to 10 days after initiation of therapy and are consistent with delayed-type hypersensitivity. This review discusses critical steps in the initiation of delayed-type hypersensitivity reactions in the skin, which include protein haptenation, dendritic cell activation/migration and T-cell propagation. Recently, an alternative mechanism of drug presentation has been postulated that does not require bioactivation of the parent drug or antigen processing to elicit a drug-specific T-cell response. This review also discusses the role of various immune-mediators, such as cytokines, nitric oxide, and reactive oxygen species, in the development of delayed-type drug hypersensitivity reactions in skin. As keratinocytes have been shown to play a crucial role in the initiation and propagation of cutaneous immune responses, we also discuss the means by which these cells may initiate or modulate CDRs.

REVIEW:
Khalili B
Pathogenesis and recent therapeutic trends in Stevens-Johnson Syndrome and toxic epidermal necrolysis.
Ann Allergy Asthma Immunol 2006;272-80
OBJECTIVE: To review the current pathophysiologic mechanisms and recent therapeutic trends in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). DATA SOURCES: A MEDLINE search for SJS and TEN in combination with Fas, Fas ligand (FasL), cytotoxic T cells, intravenous immunoglobulin, and cyclosporine for articles published in English during 1966 to 2006. STUDY SELECTION: Information was derived from original research articles and reviews published in peer-reviewed journals. RESULTS: The hallmark of SJS and TEN is epidermal cell apoptosis, which may be mediated through keratinocyte Fas-FasL interaction or through cytotoxic T-cell release of perforin and granzyme B. Whereas systemic corticosteroid therapy showed contradictory results, intravenous immunoglobulin (IVIG) and cyclosporine have shown promising outcomes. IVIG contains anti-Fas antibodies that can abrogate apoptosis when preincubated with keratinocytes. Most studies on IVIG in SJS and TEN reported improvement in arresting disease progression and reduction in time to skin healing. Because of variations among studies, the findings cannot be optimally compared. In general, mortality varied from 0% to 12% in studies that supported the use of IVIG and 25% to 41.7% in those that did not demonstrate a beneficial

effect. Cyclosporine inhibits CD8 activation and thus may reduce epidermal destruction. Relatively few case reports and 1 case series have been published regarding the use of cyclosporine in SJS and TEN. In general, cyclosporine was associated with a significant improvement in time to disease arrest and to complete reepithelization, with no reported fatalities. CONCLUSIONS: Both IVIG and cyclosporine have been associated with enhanced healing and better survival through inhibition of apoptosis. Multicenter, randomized, placebo-controlled trials using a standardized design are needed to validate these findings.

RESEARCH FRONTIER:
Stur K
Soluble FAS ligand: a discriminating feature between drug-induced skin eruptions and viral exanthemas.
J Invest Derm 2007;127:802-7
The clinical spectrum of cutaneous eruptions comprises benign variants like maculopapular rashes (MPRs) and potentially life-threatening events such as toxic epidermal necrolysis (TEN). Apoptosis of keratinocytes is a common histopathological feature of all these drug eruptions. As in skin lesions of TEN and Stevens-Johnson syndrome patients, apoptosis of keratinocytes is often accompanied by an only sparse cellular infiltrate, a soluble fatty acid synthetase ligand (sFASL)-mediated mechanism of keratinocyte cell death is postulated. In MPR patients, evidence for the occurrence of a similar process could not be established so far. We therefore examined sera and lesional skin sections from patients with clinical variants of drug eruptions for FASL expression using a sandwich ELISA and immunohistochemistry, respectively. As controls, healthy persons and patients with other inflammatory skin diseases such as viral exanthema were nalyzed.Elevated levels of FASL were detected not only in TEN patients but also in sera and lesional skin of patients with MPR. In contrast, sFASL was repeatedly negative in all viral exanthemas and healthy controls tested. Thus, determination of sFASL serum concentration may represent a discriminating tool between drug rashes and viral exanthemas.

d. Aspirin and NSAID reactions

REVIEW:
Stevenson DD, Szczeklik A
Clinical and pathologic perspectives on aspirin sensitivity and asthma.
J Allergy Clin Immunology 2006:118:773-786
Aspirin and other nonsteroidal anti-inflammatory drugs that inhibit COX-1 induce unique nonallergic reactions, consisting of attacks of rhinitis and asthma. These hypersensitivity reactions occur in a subset of asthmatic subjects, thus identifying them as having this exclusive clinical presentation. We refer to these patients as having aspirin-exacerbated respiratory disease, a disease process that produces devastating eosinophilic inflammation of both the upper and lower respiratory tracts. This review focuses on a description of patients with aspirin-exacerbated respiratory disease, methods available to diagnose their condition, the unique ability of all nonsteroidal anti-inflammatory drugs that inhibit COX-1 to cross-react with aspirin, an update on pathogenesis, and current thoughts about treatment.

REVIEW:
Stevenson DD, Simon RA
Selection of patients for aspirin desensitization treatment

J Allergy Clin Immunology 2006;118:801-804
This article reviews candidates and procedures recommended for ASA desensitization.

e. Reactions to Vaccines

REVIEW:
Madaan A, Maddox DE:
Vaccine allergy: diagnosis and management.
Immunol Allergy Clin N Am 2003:23:555-88.
As a group, vaccines provide a safe and effective way of preventing infectious and allergic illness. Allergic reactions to vaccines and drug products have become important and common features of practice and demand heightened awareness. Serious adverse effects of vaccines are rare but have been reported to various components of different vaccines. Although there are few precise diagnostic tests available, patients usually can be diagnosed accurately after careful attention to the history and physical findings. Better understanding of these reactions can lead to proper vaccine selection and can improve immunization acceptance rates in the community. Prevention, avoidance, use of alternative agents, desensitization, and premedication remain the mainstays of therapy, even as more refined diagnostic and management tools are developed. VAERS data, in addition to the traditional uses (signal detection, large registry of rare vaccine adverse events), can serve as a source of cases for epidemiologic (eg, case-control) studies that evaluate biologic factors that may be related to vaccine-related adverse reactions. Additional studies that are aimed at identifying other causes of immediate hypersensitivity after immunization with live virus vaccines are warranted.

REVIEW:
Siegrist C.-A.
Mechanisms Underlying Adverse Reactions to Vaccines
J Comp Path 2007:137:546-550
A broad spectrum of adverse events is reported following human vaccination but such reactions are considered to be relatively rare. A variety of mechanisms has been proposed to account for such adverse events. These most commonly relate to the actual process of vaccination and range from the vagal reaction associated with anxiety about needle injection, to use of an inappropriate site of administration, or infection of the healthcare worker by accidental injection during needle-capping. Other adverse events directly associated with the vaccine include reversion to virulence of attenuated vaccine strains of organisms, or contamination of the vaccine product. Adverse events may involve immune-mediated phenomena triggered by exposure to the microbial or other components of vaccines. These include: classical IgE-mediated type I hypersensitivity reactions, and immune-complex type III hypersensitivity (Arthus) reactions. Such reactions may be localized or systemic in nature. A variety of autoimmune reactions has been suggested to be triggered by vaccination, but in general the evidence for such associations remains largely anecdotal. Finally, many reported adverse events are simply chance instances of infection or disease onset around the time of vaccination and are not causally associated with administration of vaccine.

REVIEW:
Nokleby H
Vaccination and anaphylaxis
Curr Allergy Asthma Rep 2006;6:9-13

The incidence of anaphylactic or severe allergic reactions to vaccines is very low, less than one case per million vaccine doses. Larger studies from later years report no deaths. The cause of the reaction is usually not the immunizing antigen itself, but rather some other vaccine ingredient such as egg protein from the production process or gelatin added as a stabilizer. Most people with egg allergy can be vaccinated without any reaction. Vasovagal reactions with or without hyperventilation are common after vaccination. They can be rather dramatic and are often istaken for anaphylactic reactions. Correct diagnosis is important in making it possible to vaccinate those who might otherwise run the risk of serious infections.

REVIEW:
Vaccine Adverse Event Reporting System
http://vaers.hhs.gov/
The Vaccine Adverse Event Reporting System is a cooperative program for vaccine safety of the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS is a post-marketing safety surveillance program, collecting information about adverse events (possible side effects) that occur after the administration of US licensed vaccines. This Web site provides a nationwide mechanism by which adverse events following immunization (AEFI) may be reported, analyzed and made available to the public. The VAERS Web site also provides a vehicle for disseminating vaccine safety-related information to parents/guardians, healthcare providers, vaccine manufacturers, state vaccine programs, and other constituencies.

f. Photoallergy, phototoxicity, drug fever, and serum sickness reactions

REVIEW:
Moore DE.
Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management.
Drug Safety 2002;25:345-72.
The interaction of sunlight with drug medication leads to photosensitivity responses in susceptible patients, and has the potential to increase the incidence of skin cancer. Adverse photosensitivity responses to drugs occur predominantly as a phototoxic reaction which is more immediate than photoallergy, and can be reversed by withdrawal or substitution of the drug. The bias and inaccuracy of the reporting procedure for these adverse reactions is a consequence of the difficulty in distinguishing between sunburn and a mild drug photosensitivity reaction, together with the patient being able to control the incidence by taking protective action. The drug classes that currently are eliciting a high level of adverse photosensitivity are the diuretic, antibacterial and nonsteroidal anti-inflammatory drugs (NSAIDs). Photosensitising chemicals usually have a low molecular weight (200 to 500 Daltons) and are planar, tricyclic, or polycyclic configurations, often with heteroatoms in their structures enabling resonance stabilisation. All absorb ultraviolet (UV) and/or visible radiation, a characteristic that is essential for the chemical to be regarded as a photosensitiser. The photochemical and photobiological mechanisms underlying the adverse reactions caused by the more photoactive drugs are mainly free radical in nature, but reactive oxygen species are also involved. Drugs that contain chlorine substituents in their chemical structure, such as hydrochlorthiazide, furosemide and chlorpromazine, exhibit photochemical activity that is traced to the UV-induced dissociation of the chlorine substituent leading to free radical reactions with lipids, proteins and DNA. The photochemical mechanisms for the NSAIDs

that contain the 2-aryl propionic acid group involve decarboxylation as the primary step, with subsequent free radical activity. In aerated systems, the reactive excited singlet form of oxygen is produced with high efficiency. This form of oxygen is highly reactive towards lipids and proteins. NSAIDs without the 2-arylpropionic acid group are also photoactive, but with differing mechanisms leading to a less severe biological outcome. In the antibacterial drug class, the tetracyclines, fluoroquinolones and sulfonamides are the most photoactive. Photocontact dermatitis due to topically applied agents interacting with sunlight has been reported for some sunscreen and cosmetic ingredients, as well as local anaesthetic and anti-acne agents. Prevention of photosensitivity involves adequate protection from the sun with clothing and sunscreens. In concert with the preponderance of free radical mechanisms involving the photosensitising drugs, some recent studies suggest that diet supplementation with antioxidants may be beneficial in increasing the minimum erythemal UV radiation dose.

REVIEW:
Stein KR
Drug-induced photoallergic and phototoxic reactions
Expert Opin Drug Saf. 2007;6:431-43
Drug-induced photosensitivity involves reactions to medication triggered by exposure of the skin to ultraviolet light. Medications that trigger reactions can be topical or oral. Following interaction of ultraviolet radiation with a chemical present in sufficient amounts in the skin, one of the several reactions may occur in susceptible patients, most commonly photoallergy or phototoxicity. These reactions can be diagnosed separately based on pathogenesis, clinical characteristics and histopathology. Phototoxic disorders have a higher incidence than photoallergic disorders. The action spectra for most photoallergens and phototoxins lie in the ultraviolet A range. Subtypes of drug-induced photosensitivity include dyschromia, pseudoporphyria, photo onycholysis, and lichenoid and telangiectatic reactions.

REVIEW:
Johnson DH
Drug fever
Inf Dis Clin N Amer 1996;10:85-91.
Drug fever is the febrile response to a drug without cutaneous manifestations. Although the exact incidence of drug fever remains unknown, it has been estimated to occur in approximately 10% of inpatients. The recognition of drug fever is of great clinical importance because, if drug fever is not recognized diagnostically, patients may be subjected to prolonged hospitalization and unnecessary testing or medications. Early diagnosis and treatment of drug fevers are essential in maintaining cost-effective, highquality medical care.

REVIEW:
Brychan M
Severe Serum Sickness Reaction to Oral and Intramuscular Penicillin
Pharmacotherapy 2006:26:705-08
Serum sickness is a type III hypersensitivity reaction mediated by immune complex deposition with subsequent complement activation, small-vessel vasculitis, and tissue inflammation. Although the overall incidence of serum sickness is declining because of decreased use of heterologous sera and improved vaccinations, rare sporadic cases of serum sickness from nonprotein drugs such as

penicillins continue to occur. Drug-induced serum sickness is usually self-limited, with symptoms lasting only 1–2 weeks before resolving. We report an unusual case of a severe and prolonged serum sickness reaction that occurred after exposure to an intramuscular penicillin depot injection (probable relationship by Naranjo score) and discuss how pharmacokinetics may have played a role. Clinicians should be familiar with serum sickness reactions particularly as they relate to long-acting penicillin preparations. Accurate diagnosis in conjunction with cessation of drug exposure and prompt initiation of antiinflammatory treatment with corticosteroids can produce complete recovery.

g. Clinical skills – specific testing and provocative challenges

REVIEW:
Romano A
Recent advances in the diagnosis of drug allergy
Curr Opin Allergy Clin Immunol 2007:7:299-303

The present review addresses the most recent literature regarding the diagnosis of drug hypersensitivity reactions, which can be classified as immediate or nonimmediate according to the time interval between the last drug administration and the onset. Immediate reactions occur within 1 h; nonimmediate ones occur after more than 1 h. Clinical and immunological studies suggest that type-I (IgE-mediated) and type-IV (cell-mediated) pathogenic mechanisms are involved in most immediate and nonimmediate reactions, respectively. New diagnostic tools, such as the basophil activation test and the lymphocyte activation test, have been developed and are under validation. In diagnosis, the patient's history is fundamental; the allergologic examination includes in-vivo and in-vitro tests selected on the basis of the clinical features. Prick, patch, and intradermal tests are the most readily available forms of allergy testing. Determination of specific IgE levels is still the most common in-vitro method for diagnosing immediate reactions. The sensitivity of allergologic tests is not 100%; in selected cases, therefore, provocation tests are necessary. The routine use of the basophil activation test and the lymphocyte activation test could increase the sensitivity of diagnostic work-ups, thus reducing the need for drug provocation tests.

REVIEW:
Demoly P
Anaphylactic reactions—value of skin and provocation tests
Toxicology April 2006:209: 221-223

Drug hypersensitivity reactions may affect up to 5% of hospitalised patients and can be life threatening. A variety of reaction types have been described. These include: (i) non-immunological reactions, (ii) IgE-mediated allergic reactions in the form of immediate anaphylactic shock, generalised urticaria, angioedema and/or bronchospasm, (iii) non-immediate allergic reactions (which may occur several days after the last drug has been administered) such as urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome or drug reaction with eosinophilia and systemic symptoms. Reactions occurring within a few hours following the last administration of the drug may due to IgE-dependent or non-immunological mechanisms. The former could be lethal. The latter occur in only a small percentage of patients and in general cannot be predicted. The etiologies of these reactions include non-specific histamine release (e.g. opiates, radiocontrast media and vancomycin), bradykinin accumulation (angiotensin-converting enzyme inhibitors), complement activation (radiocontrast media and protamine), induction of leukotriene synthesis (non-steroidal anti-inflammatory drugs)

and bronchospasm (e.g. S02 released by drug preparations containing sulphites). Moreover, some reactions such as urticaria could even be not related to the drug itself, but to the underlying (e.g. infectious) disease. Therefore, a complete drug allergy work up is required, which includes a detailed clinical history and physical examination, followed by one or more of the following procedures: skin tests, laboratory tests and ultimately, drug provocation tests. This paper discusses the principles on the establishment of clinical tools for the daily practice.

REVIEW:
Aberer W
Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations.
Allergy 2003;58:854-63.
A drug provocation test (DPT) is the controlled administration of a drug in order to diagnose drug hypersensitivity reactions. DPTs are performed under medical surveillance, whether this drug is an alternative compound, or structurally/pharmacologically related, or the suspected drug itself. DPT is sometimes termed controlled challenge or reexposure , drug challenge , graded or incremental challenge , test dosing , rechallenge , or testing for tolerance. DPT is recommended by some specialized centers, allergy societies, and text books, whereas other societies advise against performing DPTs , and some review articles and textbooks do not even mention the method. The topic DPT is controversial in general and the test procedures not validated in most instances. Therefore it is considered important to develop general guidelines for performing DPT. Specific protocols for every single drug or at least group of drugs would be helpful, where indication, contraindication, substance, dosing, grading of the reaction and test as well as scoring criteria are defined. However, the development of individual DPT protocols is impractical because of the countless drugs that may cause numerous kinds of hypersensitivity reactions, allergic and non-allergic, with different time courses, severity and outcome, the individual situation of every person, and other factors that might possibly influence the test reaction. This paper sets out general guidelines for DPT that can be adapted for the specific problem under investigation.

REVIEW:
Phillips JF
Approach to patients with suspected hypersensitivity to local anesthetics
Am J Med Sci 2007;334:190-6
Adverse reactions to local anesthetics are relatively common, but true IgE-mediated hypersensitivity is extremely rare. Fortunately, the vast majority of adverse reactions occur via nonimmunologic means, but considerable confusion still exists among providers. We conducted a review of the literature to determine if earlier estimates of IgE-mediated allergy are consistent with current reports and whether current management strategies are consistent with these findings. We identified several confounding variables involved in the evaluation, including the roles of preservatives/additives, epinephrine, latex, and inadequate testing procedures. These problems may cause significant diagnostic challenges for clinicians. It is in fact much more likely that there is an alternate diagnosis, and in many cases clinicians can begin the evaluation in the office. When local anesthetic allergy is still suspected, the patient should be referred to an allergist for testing to determine if the suspected culprit drug can be safely used, or, if necessary, identify a suitable alternative.

REVIEW:
Kelso J
Immunization of egg allergic individuals with egg or chicken-derived vaccines
Immunol Allergy Clin N Am 2003:23:635-48
Viruses used in several vaccines are propagated in embryonated eggs. These vaccines contain variable quantities of residual egg or chicken proteins and pose risks when administered to egg- or chicken-sensitive persons. This article highlights differences in how vaccines are prepared, with emphasis on the quantitation of residual egg-derived protein in each vaccine. Published reports on the frequency and severity of these vaccine-induced allergic reactions are reviewed, and an algorithm is provided for the preimmunization evaluation of egg-sensitive persons.

REVIEW:
Macy E
Aspirin challenge & desensitization for ASA-exacerbated respiratory disease:a practice paper.
Ann Allergy Asthma Immunol 2007:98:172-174
Aspirin desensitization is indicated for patients who have aspirin-exacerbated respiratory disease and whose asthma and/or rhinosinusitis is suboptimally controlled with inhaled corticosteroids and leukotriene-modifying drugs. In this practice paper, the general requirements for aspirin desensitization are presented, the locations where desensitizations can be safely performed are outlined, prechallenge patient preparation is discussed, an oral aspirin challenge protocol is presented, treatment of adverse reactions is reviewed, and maintenance of aspirin desensitization is discussed.

REVIEW:
Gollapudi
Aspirin Sensitivity: Implications for Patients With Coronary Artery Disease
JAMA 2004;292:3017-23
CONTEXT: Although acetylsalicylic acid (aspirin) is commonly used for patients with chronic cardiovascular disease, a minority of patients have a sensitivity to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. OBJECTIVE: To provide a diagnostic strategy for evaluating and treating patients with aspirin sensitivity, with additional consideration for issues specific to patients with coronary artery disease (CAD). EVIDENCE ACQUISITION: Published articles were identified through a search of MEDLINE and the Cochrane databases using the dates 1966 to June 2004 and the search terms aspirin allergy, coronary artery disease, aspirin desensitization, and aspirin sensitivity. References of retrieved articles were also reviewed for pertinent studies. Articles were included in this review if they were controlled studies, published in the English language, and appeared in a peer-reviewed journal. EVIDENCE SYNTHESIS: The prevalence of aspirin-exacerbated respiratory tract disease is approximately 10% and for aspirin-induced urticaria the prevalence varies from 0.07% to 0.2% of the general population. Aspirin sensitivity is most often manifested as rhinitis and asthma or urticaria/angioedema induced by cross-reacting nonsteroidal anti-inflammatory drugs that inhibit cyclooxygenase 1. The primary mechanism of sensitivity is less often related to drug-specific IgE antibody production leading to urticaria/angioedema and rarely to anaphylaxis. Most patients with acetylsalicylic acid sensitivity are able to undergo desensitization therapy safely and successfully except in cases of chronic idiopathic urticaria. However, there have not been any randomized trials that specifically focus on

the efficacy of aspirin desensitization. Furthermore, experience with acetylsalicylic acid desensitization in patients with CAD is very limited. After successful desensitization, acetylsalicylic acid therapy must be indefinitely continued to prevent resensitization. CONCLUSIONS: Acetylsalicylic acid sensitivity is common and desensitization can be performed safely in many patients. Large-scale trials are warranted to determine the safety and efficacy of acetylsalicylic acid desensitization therapy in patients with concomitant CAD because data are currently limited to small case series.

REVIEW:
Solensky R
Drug Desensitization
Immunol Allergy Clin N Am 2004;24:425-43
The term drug allergy is loosely applied to many drug reactions. Consequently, when properly evaluated, most patients who are labeled allergic are found to lack hypersensitivity and are able to tolerate the implicated medication. A proportion of patients who undergo a thorough evaluation by allergists/immunologists are determined to be drug allergic. Although the usual recommendation for allergic patients is to avoid the medication in question, some clinical situations may necessitate re-administration. This article focuses on the approach to drug-allergic patients when administration of the sensitizing drug, or a cross-reacting one is required.

REVIEW:
Castells M
Rapid Desensitization for hypersensitivity reactions to chemotherapy agents
Curr Opin Allergy Clin Immunol 2006;6:271-7
PURPOSE OF REVIEW: Hypersensitivity reactions (HSRs) to chemotherapy agents have limited their use for fear of inducing severe reactions or death. Alternative regimens may be limited by tumor sensitivity and the need to provide first-line therapy. Rapid desensitizations allow patients to be treated with medications to which they have presented a HSR. The purpose of this review is to highlight the indications and recent developments in chemotherapy rapid desensitization protocols. RECENT FINDINGS: Intravenous and oral rapid desensitization protocols are available for taxenes, platinums, doxorubicin, monoclonal antibodies and others. Candidate patients present mild to severe type I hypersensitivity, mast cell/IgE-dependent reactions, as seen with platinums. Anaphylactoid reactions, such as those with taxenes, can be treated with the same protocols. Repeat desensitizations in outpatient settings are well tolerated and allow patients to remain in clinical studies/trials. Breakthrough symptoms during desensitizations are less severe than the initial reaction and no deaths have been reported. Cancer remissions are similar to those for nondesensitized patients. SUMMARY: The use of rapid desensitization protocols for cancer patients with HSRs to chemotherapy depends on their demonstrated tolerability and efficacy in selected populations. Education of nurses, pharmacists, and oncology and allergy specialists is needed to improve their universal application as standard of care.

GUIDELINE PRACTICE PARAMETER:
Joint Task Force
Disease management of drug hypersensitivity: a practice parameter.
Ann Allergy Asthma Immunol. 1999;83:665-700

NOTE: Updates of practice parameters entitled “Drug Allergy and Intolerance: An Updated Practice Parameter” and “Allergy Diagnostic Testing: An Updated Practice Parameter”were circulated in draft form during 2007 and final versions prepared by by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology should be available in the near future.

6. Adverse reactions to ingestants

a. Food sensitivities – IgE mediated, food intolerance, gluten sensitivity

REVIEW:
Food allergy: a practice parameter
Ann Allergy Asthma Immunol 2006 96(3 Suppl 2): S1-68.

REVIEW:
Lack, G.
Clinical practice. Food allergy
N Engl J Med2008; 359(12): 1252-60.

CUTTING EDGE:
Sicherer, S. H. and H. A. Sampson.
Food Allergy: Recent Advances in Pathophysiology and Treatment
Annu Rev Med 2008
Food allergies, defined as an adverse immune response to food proteins, affect as many as 6% of young children and 3%-4% of adults in westernized countries, and their prevalence appears to be rising. In addition to well-recognized acute allergic reactions and anaphylaxis triggered by IgE antibody-mediated immune responses to food proteins, there is an increasing recognition of cell-mediated disorders such as eosinophilic gastroenteropathies and food protein-induced enterocolitis syndrome. We are gaining an increasing understanding of the pathophysiology of food allergic disorders and are beginning to comprehend how this disease results from a failure to establish or maintain normal oral tolerance. Many food allergens have been characterized at a molecular level, and this knowledge, combined with an increasing appreciation of the nature of humoral and cellular immune responses resulting in allergy or tolerance, is leading to novel therapeutic approaches. Currently, management of food allergies consists of educating the patient to avoid ingesting the responsible allergen and initiating therapy if ingestion occurs. However, numerous strategies for definitive treatment are being studied, including sublingual/oral immunotherapy, injection of anti-IgE antibodies, cytokine/anticytokine therapies, Chinese herbal therapies, and novel immunotherapies utilizing engineered proteins and strategic immunomodulators. Expected final online publication date for the Annual Review of Medicine Volume 60 is January 07, 2009. Please see http://www.annualreviews.org/catalog/pubdates.aspx for revised estimates.

CUTTING EDGE:
Burks, A. W., S. Laubach, et al.
Oral tolerance, food allergy, and immunotherapy: implications for future treatment
J Allergy Clin Immunol 2008; 121(6): 1344-50.

The lumen of the gastrointestinal tract is exposed daily to an array of dietary proteins. The vast majority of proteins are tolerated through suppression of cellular or humoral responses, a process known as oral tolerance. However, in approximately 6% of children and 4% of adults in the United States, tolerance to a given dietary antigen either is not established or breaks down, resulting in food hypersensitivity. Although food allergies can result in sudden and life-threatening symptoms, their prevalence is remarkably low considering the complexities of the gut-associated mucosal system. Suppression involves signaling by an array of nonprofessional antigen-presenting cells, dendritic cells, and regulatory T cells, as well as lymphocyte anergy or deletion. Several factors, including antigen properties, route of exposure, and genetics and age of the host, contribute to the development of oral tolerance. Although the current standard of care for patients with food allergies is based on avoidance of the trigger, increased understanding of the mechanisms involved in tolerance has shifted focus of treatment and prevention toward inducing tolerance. Data from early-phase clinical trials suggest both sublingual and oral immunotherapy are effective in reducing sensitivity to allergens. In this article we review the mechanisms of tolerance, discuss aberrations in oral tolerance, and provide information on novel prevention and treatment paradigms for food allergy.

REVIEW:
Enrique, E. and A. Cistero-Bahima
Specific immunotherapy for food allergy: basic principles and clinical aspects
Curr Opin Allergy Clin Immunol 2006; 6(6): 466-9.
PURPOSE OF REVIEW: Food allergy may be life threatening and its management continues to consist of avoiding relevant allergens and, in the case of accidental ingestion, initiation of appropriate emergency therapy. The aim of this article is to describe current treatment approaches and discuss attempts to use specific immunotherapy for food-allergy treatment. RECENT FINDINGS: A recent study reports the use of sublingual immunotherapy for hazelnut food allergy in hazelnut-allergic patients. A significant increase in tolerance to hazelnuts after sublingual immunotherapy as assessed by double-blind, placebo-controlled food challenge, and good tolerance to this treatment, have been observed. SUMMARY: The purpose of this review is to highlight the most promising novel approaches for treating food allergy beyond allergen avoidance. Some of these approaches alone, such as traditional Chinese herbal medicine, anti-immunoglobulin E therapy or sublingual immunotherapy for food allergy, or the combination of different approaches, would probably offer the best treatment option for food-allergic patients in the near future.

REVIEW:
Pajno, G. B.
Sublingual immunotherapy: the optimism and the issues
J Allergy Clin Immunol 2007; 119(4): 796-801.
The acceptability of sublingual immunotherapy (SLIT) in guidelines or statements has recently increased. SLIT is currently used in Europe, Asia, and Australia for the treatment of allergic respiratory diseases. Four meta-analyses have shown that SLIT is an effective tool for the treatment of patients with asthma and/or rhinitis, and only conflicting results were reported for children with allergic rhinitis. Moreover, it offers logistic advantages and is safe. However, some unmet needs are to be faced, such as the difficulty of manufacturers to achieve the homogeneity of standardized vaccines, the magnitude of their clinical efficacy, and the pivotal question of an early

intervention with SLIT in young children with IgE-mediated disorders. Altogether, SLIT has already given convincing results in respiratory diseases both in adults and children. In the future, this route of administration of allergic vaccines may improve even the treatment of patients with IgE-mediated food allergy. These patients indeed deserve better than allergen avoidance. The immunomodulatory treatment of allergic diseases probably has found a new tool; however, a more balanced understanding of this form of allergen immunotherapy is needed. This aim could be achieved through: (1) the improvement of products standardization quality; (2) an attempt to modify in children the natural course of allergic diseases; and (3) new research on mechanisms of action.

REVIEW:
Green, P. H. and C. Cellier
Celiac disease
N Engl J Med 2007; 357(17): 1731-43.

REVIEW:
Hoffenberg, E. J. and E. Liu
Celiac disease for the allergist: who and how to screen
Allergy Asthma Proc 2007; 28(1): 20-4.
This article is meant to guide the allergist in clinical practice. Current understanding of the pathogenesis and epidemiology of celiac disease is reviewed. Issues of screening and genetic testing are discussed and current controversies and additional resources are highlighted.

b. Food-additive reactions

REVIEW:
Spergel JM. Fiedler J.
Food allergy and additives: triggers in asthma
Immunol Allergy Clin N Am 2005; 25; 149-167
Exposure to food allergens can cause a varied pattern of respiratory symptoms, with allergic responses ranging from asthma symptoms to occupational asthma. Food allergy in a patient presenting as asthma tends to indicate a more severe disease constellation. Patients with underlying asthma experience more severe and life-threatening allergic food reactions. When a food reaction involves respiratory symptoms, it is almost always a more severe reaction compared with reactions that do not involve the respiratory tract. Susceptible patients may even react to a causative food on inhalation without ingestion. However, isolated asthma or rhinitis symptoms without concomitant cutaneous or gastrointestinal symptoms are rare events.

c. Eosinophilic esophagitis and gastroenteritis

REVIEW:
Straumann A.
Idiopathic eosinophilic gastrointestinal diseases in adults.
Best Pract Res Clin Gastroenterol. 2008;22(3):481-96.

REVIEW:

Rothenberg ME.
Eosinophilic gastrointestinal disorders (EGID).
J Allergy Clin Immunol. 2004 Jan;113(1):11-28; quiz 29.

REVIEW:
Assa'ad, A.,
Eosinophilic esophagitis: association with allergic disorders.
Gastrointest Endosc Clin N Am, 2008. 18(1): p. 119-32; x.

d. Clinical Skills

REVIEW:
Bernstein, I. L., J. T. Li, et al.
Allergy diagnostic testing: an updated practice parameter
Ann Allergy Asthma Immunol 2008; 100(3 Suppl 3): S1-148.

REVIEW:
Maloney, J. M., M. Rudengren, et al.
The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy
J Allergy Clin Immunol 2008; 122(1): 145-51.
BACKGROUND: The gold standard for diagnosing food allergy is the double-blind, placebo-controlled food challenge. Diagnostic food-specific IgE levels might assist in diagnosing food allergies and circumventing the need for food challenges. OBJECTIVES: The purpose of this study was to determine the utility of food-specific IgE measurements for identifying symptomatic peanut, tree nut, and seed allergies and to augment what is known about the relationships among these foods. METHODS: Patients referred for suspected peanut or tree nut allergies answered a questionnaire about their perceived food allergies. Allergen-specific diagnoses were based on questionnaire, medical history, and, when relevant, skin prick tests and serum specific IgE levels. Sera from the patients were analyzed for specific IgE antibodies to peanuts, tree nuts, and seeds by using ImmunoCAP Specific IgE (Phadia, Inc, Uppsala, Sweden). RESULTS: Three hundred twenty-four patients (61% male; median age, 6.1 years; range, 0.2-40.2 years) were evaluated. The patients were highly atopic (57% with atopic dermatitis and 58% with asthma). The majority of patients with peanut allergy were sensitized to tree nuts (86%), and 34% had documented clinical allergy. The relationship between diagnosis and allergen-specific IgE levels were estimated by using logistic regression. Diagnostic decision points are suggested for peanut and walnut. Probability curves were drawn for peanut, sesame, and several tree nuts. High correlations were found between cashew and pistachio and between pecan and walnut. CONCLUSIONS: Quantification of food-specific IgE is a valuable tool that will aid in the diagnosis of symptomatic food allergy and might decrease the need for double-blind, placebo-controlled food challenges.

REVIEW:
Niggemann, B. and K. Beyer
Pitfalls in double-blind, placebo-controlled oral food challenges
Allergy 2007; 62(7): 729-32.
Although controlled oral food challenges are considered to be the gold-standard in the diagnosis of food related symptoms, especially if performed in a double-blind, placebo-controlled food

challenges (DBPCFC) manner, there are still many unanswered questions and newer aspects, which may explain some pitfalls encountered during oral food challenges. For stopping an oral food challenge and declaring a challenge as positive or negative, symptoms should be objective and/or repetitive. The time interval between administering the food and observing the clinical reaction is an ambivalent factor. Possible reasons for false negative assessments include inadvertent drug use during oral challenges, and the fact that a short-term specific oral tolerance induction (SOTI) may be induced as increasing amounts of the offended food are administered during a titrated oral food challenge. Possible reasons for false positive assessments are the difficulty to maintain an appropriate strict diet throughout the oral challenge procedure, and that the elimination diet implemented before the oral food challenge in children with atopic eczema and suspected food related symptoms may itself be responsible for immediate type clinical symptoms, which had not been reported by the parents before. Finally augmentation factors are among the most plausible explanations for the inadequate reproducibility of an oral food challenge. Although a 100% standardization of the challenge procedure does not seem realistic, efforts should be made to improve the methodology used so far. On the contrary, the possible relation of DBPCFC and SOTI may offer potential advantages for future therapeutic approaches of food allergy.

7. Anaphylaxis and Anaphylactoid Reactions

WEB-BASED LEARNING TOOLS:

UpToDate (www.uptodateonline.com) is a subscription medical knowledge database to which many university medical centers subscribe and it includes a number of quality, well-referenced anaphylaxis articles that have been written and edited by allergist-immunologists commonly linked to the topic. Version 16.2 has ten anaphylaxis cards (articles).

LANDMARK PUBLICATION:

Smith PL, Kagey-Sobotka A, Bleecker ER, et al. Physiologic manifestations of human anaphylaxis. J Clin Invest 1980;66:1072-80.

The authors conducted a controlled study to evaluate different forms of immunotherapy for subjects with insect-sting hypersensitivity, and observed 11 subjects who had generalized urticaria and 3 subjects who experienced anaphylactic shock characterized by severe hypotension attributed to peripheral vasodilation. Plasma histamine levels correlated with the severity and duration of the cardiopulmonary changes observed during anaphylactic shock. The two subjects with the most severe shock showed reductions in Factor V, Factor VIII, fibrinogen, and high molecular weight kininogen, as well as changes in complement components. This study also documents the paradoxical occurrence of bradycardia in the setting of anaphylactic shock (one subject).

a. Causes (ingestants, exercise, allergy immunotherapy, latex, radiocontrast media) case definition and common presentations.

REVIEW:

Sampson HA, Muñoz-Furlong A, Campbell RL, et al.: Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–397.

Proposes working definition for anaphylaxis and reviews many of its salient features and controversies.

Simons FER. Anaphylaxis, killer allergy: long-term management in the community. J Allergy Clin Immunol 2006;117:367–377.
Good overview of the topic and relevant issues in diagnosis, treatment, and patient education. It includes helpful education resources (e.g., sample anaphylaxis emergency action plan).

Simons FER. Anaphylaxis. J Allergy Clin Immunol 2008:121:S402-7.
Worthy of its inclusion in a primer, it updates the former and includes some helpful figures.

Pumphrey R. Anaphylaxis: can we tell who is at risk of a fatal reaction? Curr Opin Allergy Clin Immunol 2004;4:285–290.
A valuable review of mortality data and the conclusions the author reached. Among other findings, an analysis of 202 anaphylaxis fatalities occurring in the United Kingdom from 1992 to 2001 revealed the interval between initial onset of food anaphylaxis symptoms and fatal cardiopulmonary arrest averaged 25-35 minutes, which was longer than for insect stings (10-15 minutes) or for drugs (mean, 5 minutes in-hospital; 10-20 minutes pre-hospital). He also alludes to the potential importance of recumbent posture in the prevention of pulseless electrical activity in anaphylactic shock.

Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. Ann Allergy Asthma Immunol 2006;97:39–43.
In a study of patients referred to a university-affiliated allergy-immunology practice in Memphis, Tennessee, food was the cause of anaphylaxis in 34% of patients, medications in 20%, and exercise in 7% (anaphylaxis due to insect stings or subcutaneous immunotherapy injections were excluded from the study). The cause of anaphylaxis was undetermined in 59% of patients (i.e., they were diagnosed with idiopathic anaphylaxis).

Lieberman P. Biphasic anaphylactic reactions. Ann Allergy Asthma Immunol 2005;95:217–226.
This is a comprehensive review on biphasic anaphylaxis, which includes summaries of reports published to 2005 and discusses various theories concerning its pathogenesis.

Finkelman FD. Anaphylaxis: lessons from mouse models. J Allergy Clin Immunol 2007;120:506-15.
Updates an earlier 2005 article and provides a good overview of the pathophysiology of anaphylaxis in the mouse model and how it contrasts with human anaphylaxis. Potential research implications are also discussed.

b. Laboratory evaluation of anaphylactic episode, allergy testing, tryptase

REVIEW:

Vadas P, Gold M, Perelman B, Liss GM, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. N Engl J Med 2008;358:28-35.
The authors report findings from a two-part study in which they prospectively study PAF and PAF acetylhydrolase activity in peanut anaphylaxis patients and controls presenting to an emergency department and then retrospectively analyze PAF acetylhydrolase activity in fatal anaphylaxis cases. Not surprisingly, PAF levels were elevated in anaphylaxis compared to controls. The authors also observed a significant increase in relation to clinical severity and an inverse

correlation between PAF and PAF acetylhydrolase levels. Serum PAF acetylhydrolase activity was significantly lower in fatal episodes.

c. Treatment of Anaphylaxis including Cardiopulmonary Resuscitation

i. Acute treatment

REVIEW:

Kemp SF, Lockey RF, Simons FER, on behalf of the World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization [position paper]. Allergy 2008;63:1061-70.

The authors examine evidence for the role of epinephrine in the treatment of anaphylaxis, especially focusing on the risk vs. benefit of use and many of the factors that might influence the decision to use it. They conclude that epinephrine is currently underutilized and dosed suboptimally and that therapeutic benefits exceed the risk when epinephrine is provided for acute anaphylaxis. Numerous evidence-rated references, case scenarios and informational links are additional features.

Sheikh A, Shehata YA, Brown SG, Simons FE. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock. Cochrane Database Syst Rev 2008 Oct 8;(4):CD006312.

The researchers found no high quality evidence on which to offer any new recommendations on the use of epinephrine for the treatment of anaphylaxis. They posit that randomized, double-blind, placebo-controlled clinical trials of high methodological quality are unlikely to be performed in individuals with anaphylaxis and indeed might be unethical because prompt treatment with epinephrine is deemed to be critically important for survival in anaphylaxis. They also acknowledge that such studies would be difficult to conduct because anaphylactic episodes "usually occur without warning, often in a non-medical setting, and differ in severity both among individuals and from one episode to another in the same individual". Accordingly, they recommend that intramuscular epinephrine injections should still be regarded as first-line treatment for the management of anaphylaxis.

Sheikh A, ten Broek V, Brown SGA, Simons FER. H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review Allergy 2007;62:830-37.

The researchers found no high quality evidence for or against the use of H1 antihistamines in anaphylaxis.

ii. Patient education, use of Epi-pen

NOTE:

A variety of patient education material regarding anaphylaxis, including the use of self-administered epinephrine can be found at the following website**:**
www.anaphylaxis.com/pro/6_4_5.cfm

8. Insect Hypersensitivity

REVIEW:

Golden DBK

Insect sting allergy and venom immunotherapy: A model and a mystery

J Allergy Clin Immunol 2005;115:439-447

Allergic reactions to stinging insects of the order Hymenoptera have been recognized for millennia, but only in the last century have they been subject to scientific investigation. Since we began our investigations at Johns Hopkins more than 30 years ago, the diagnosis and treatment of insect sting allergy has been viewed as a model in many ways.1 As a model of anaphylaxis, insect sting allergy illustrates most of the dilemmas in the immunology, pathophysiology, diagnosis, and prevention of anaphylaxis. This condition and its treatment have also been a model for the use of standardized allergens, a model for allergen challenge procedures, and a model for the study and application of immunotherapy. After 3 decades, this model has lived up to many of these expectations, but some mysteries remain.

REVIEW:
Freeman TM
Hypersensitivity to Hymenoptera Stings
N Engl J Med 2004;351:1978-84
Insects of the order Hymenoptera, which includes ants, bees, hornets, wasps, and yellow jackets, have a stinging apparatus at the tail end of their abdominal segment and are capable of delivering between 100 ng (fire ants) and 50 μg (bees) of venom. Although the venoms have various peptide and protein components, some of which are capable of inducing toxic or vasoactive responses, it has been estimated that about 1500 stings would be required to deliver a lethal dose of hymenoptera venom for a nonallergic adult who weighs 70 kg. Despite this estimate, about 40 deaths a year are attributed to hymenoptera stings; these deaths are ascribed to anaphylaxis occurring in persons with a history of prior stings in whom specific IgE antibodies developed to various venom components.

PRACTICE PARAMETER GUIDELINE:
Moffitt JE, Golden DBK, Reisman RE
Stinging insect hypersensitivity: A practice parameter update
J Allergy Clin Immunol, *2004;114:869 -886*
This parameter was developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology. The objective of ‘‘Stinging insect hypersensitivity: A practice parameter update’’ is to improve the care for patients with stinging insect hypersensitivity. This parameter is intended to refine guidelines for the use and interpretation of diagnostic methods and for the institution and implementation of measures to manage stinging insect hypersensitivity, with particular emphasis on the appropriate use of immunotherapy.

LANDMARK PUBLICATION:
Hunt KJ, Valentine MD, Sobotka AK et al
A controlled trial of immunotherapy in insect hypersensitivity
N Engl J Med 1978;299:157-161
Insect hypersensitivity is currently treated by immunization using whole-body extracts. We compared this regimen with immunotherapy using insect venoms or placebo in groups of 20 patients matched for history and sensitivity, as judged by venom skin test, histamine release and IgE antibody to venom. After six to 10 weeks of immunization, systemic reactions to stings occurred in seven of 12, seven of 11, and one of 18 patients treated with placebo, whole-body

extract, and venom, respectively. Placebo and wholebody extract gave similar results and were significantly less effective than venom immunotherapy (P less than 0.01). The 14 patients with failure of treatment with wholebody extract and placebo were subsequently provided with venom immunotherapy; one reacted to a subsequent sting. We conclude that venom immunotherapy is clinically superior to therapy on whole-body extract or placebo.

LANDMARK PUBLICATION:
Barnard JH
Studies of 400 Hymenoptera sting deaths in the United States
J Allergy Clin Immunol 1973:52;259-64
Data from 400 cases of Hymenoptera sting deaths in. the United States have been collected. These included 100 cases seen at autopsy and the results of postmortem abnormalities and certain other correlations ore tabulated.

INVESTIGATION:
Armentia A, Pineda F, Fernandez S
Wine-Induced Anaphylaxis and Sensitization to Hymenoptera Venom
N Engl J Med 2007;357:719 *Correspondence*
Alcoholic drinks have been described as triggering or initiating anaphylactoid reactions. Although little is known about the pathogenesis of these reactions, wine contains many biologic and chemical components derived from grapevines, yeast, bacteria, and insects (including those of the order Hymenoptera) that might explain the observed symptoms. We report on five patients who presented with symptoms after drinking grape juice or newly pressed wines (both red and white). Three of the patients had an oral allergy syndrome and facial flushing, one had asthmatic symptoms, and one had anaphylaxis. Skin tests with conventional allergens, including commercial grape extract, egg white, and wines aged for up to 1 year, were negative. None of the patients had a history of ingesting drugs containing sulfites that was concomitant with these symptoms, nor had any of them been stung by Hymenoptera species. Yet all had positive skin tests for specific IgE antibodies (levels >0.35 kU per liter, CAP, Phadia) to Hymenoptera (*Apis mellifera* and vespula and polistes species) and to an extract of the wine or grape juice under suspicion for causing the symptoms.

RESEARCH FRONTIER:
Akdis CA. Blesken T. Akdis M et al
Role of interleukin 10 in specific immunotherapy
J Clin Invest. 1998;102:98-106.
The induction of allergen-specific anergy in peripheral T cells represents a key step in specific immunotherapy (SIT). Here we demonstrate that the anergic state results from increased IL-10 production. In bee venom (BV)-SIT the specific proliferative and cytokine responses against the main allergen, the phospholipase A2 (PLA), and T cell epitope-containing PLA peptides were significantly suppressed after 7 d of treatment. Simultaneously, the production of IL-10 increased during BV-SIT. After 28 d of BV-SIT the anergic state was established. Intracytoplasmic cytokine staining of PBMC combined with surface marker detection revealed that IL-10 was produced initially by activated CD4(+)CD25(+), allergen-specific T cells, and followed by B cells and monocytes. Neutralization of IL-10 in PBMC fully reconstituted the specific proliferative and cytokine responses. A similar state of IL-10-associated T cell anergy, as induced in BVSIT, was

found in hyperimmune individuals who recently had received multiple bee stings. The addition of IL-10 to soluble CD40 ligand IL-4-stimulated PBMC or purified B cells inhibited the PLA-specific and total IgE and enhanced the IgG4 formation. Accordingly, increased IL-10 production by SIT causes specific anergy in peripheral T cells, and regulates specific IgE and IgG4 production toward normal IgG4-related immunity.

a. Classes of insects associated with hypersensitivity

REVIEW:
Guralnick MW,
Benton AW Entomologic Aspects of Insect Sting Allergy.
In Monograph on Insect Allergy, edition 4, editors Levine MI, Lockey RF
American Academy of Allergy, Asthma and Immunology, 2003;11-25

b. Skin prick, intradermal and in vitro testing to stinging insects

REVIEW:
Bil BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JNG, EAACI Interest Group on Insect Venom Hypersensitivity
Diagnosis of Hymenoptera venom allergy
Allergy 2005;60:1339–1349

The purpose of diagnostic procedure is to classify a sting reaction by history, identify the underlying pathogenetic mechanism, and identify the offending insect. Diagnosis of Hymenoptera venom allergy thus forms the basis for the treatment. In the central and northern Europe vespid (mainly Vespula spp.) and honeybee stings are the most prevalent, whereas in the Mediterranean area stings from Polistes and Vespula are more frequent than honeybee stings; bumblebee stings are rare throughout Europe and more of an occupational hazard. Several major allergens, usually glycoproteins with a molecular weight of 10–50 kDa, have been identified in venoms of bees, vespids. and ants. The sequences and structures of the majority of venom allergens have been determined and several have been expressed in recombinant form. A particular problem in the field of cross-reactivity are specific immunoglobulin E (IgE) antibodies directed against carbohydrate epitopes, which may induce multiple positive test results (skin test, in vitro tests) of still unknown clinical significance. Venom hypersensitivity may be mediated by immunologic mechanisms (IgE-mediated or non-IgE-mediated venom allergy) but also by nonimmunologic mechanisms. Reactions to Hymenoptera stings are classified into normal local reactions, large local reactions, systemic toxic reactions, systemic anaphylactic reactions, and unusual reactions. For most venom-allergic patients an anaphylactic reaction after a sting is very traumatic event, resulting in an altered health-related quality of life. Risk factors influencing the outcome of an anaphylactic reaction include the time interval between stings, the number of stings, the severity of the preceding reaction, age, cardiovascular diseases and drug intake, insect type, elevated serum tryptase, and mastocytosis. Diagnostic tests should be carried out in all patients with a history of a systemic sting reaction to detect sensitization. They are not recommended in subjects with a history of large local reaction or no history of a systemic reaction. Testing comprises skin tests with Hymenoptera venoms and analysis of the serum for Hymenoptera venom-specific IgE. Stepwise skin testing with incremental venom concentrations is recommended. If diagnostic tests are negative they should be repeated several weeks later. Serum tryptase should be analyzed in patients with a history of a severe sting reaction.

INVESTIGATION:
Sturm GJ, Heinemann A, Schuster C, et al.
Influence of total IgE levels on the severity of sting reactions in Hymenoptera venom allergy
Allergy 2007: 62: 884–889
Background: Detection of specific IgE for Hymenoptera ***venoms*** and skin tests are well established diagnostic tools for the diagnosis of insect ***venom*** hypersensitivity. The aim of our study was to analyze the effect of total IgE levels on the outcome of generalized anaphylactic reactions after a Hymenoptera sting. Methods: Two hundred and twenty patients allergic to bee, wasp, or European hornet ***venom*** were included in the study. Their specific and total IgE levels, serum tryptase levels, skin tests, and sting history were analyzed. Results: In patients with mild reactions (grade I, generalized skin symptoms) we observed higher total IgE levels (248.0 kU/l) compared to patients with moderate reactions (grade II, moderate pulmonary, cardiovascular, or gastrointestinal symptoms; 75.2 kU/l) and severe reactions (grade III, bronchoconstriction, emesis, anaphylactic shock, or loss of consciousness; 56.5 kU/l; $P < 0.001$). Accordingly, 25% of the patients with low levels of total IgE (<50 kU/l), but no individual with total IgE levels >250 kU/l, developed loss of consciousness ($P = 0.001$). Additionally, specific IgE levels were related to total IgE levels: Specific IgE levels increased from 1.6 to 7.1 kU/l in patients with low (<50 kU/l) and high (>250 kU/l) total IgE levels, respectively ($P < 0.001$). Specific IgE levels correlated inversely to the clinical reaction grades, however, this trend was not statistically significant ($P = 0.083$). Conclusion: Patients with Hymenoptera ***venom allergy*** and high levels (>250 kU/l) of total IgE, predominantly develop grade I and grade II reactions and appear to be protected from grade III reactions. However, this hypothesis should be confirmed by extended studies with sting challenges.

INVESTIGATION:
Golden DB, Kagey-Sobotka A, Norman PS et al
Insect sting allergy with negative venom skin test responses.
J Allergy Clin Immunol 2001;107:897-901
Background: In our 1976 controlled venom immunotherapy trial, 33% of 182 patients with a history of systemic reactions to insect stings were excluded because of negative venom skin test responses. There have been reports of patients with negative skin test responses who have had severe reactions to subsequent stings. Objective: Our aim is to increase awareness about the patient with a negative skin test response and insect sting allergy and to determine the frequency and significance of negative skin test responses in patients with a history of systemic reactions to insect stings. Methods: We prospectively examined the prevalence of negative venom skin test responses in patients with a history of systemic reactions to stings. In patients who gave informed consent, we analyzed the outcome of retesting and sting challenge. Results: Of 307 patients with positive histories screened for our sting challenge study, 208 (68%) had positive venom skin test responses (up to 1 μg/mL concentration), and 99 (32%) had negative venom skin test responses. In 36 (36%) of the 99 patients with negative skin test responses, the venom RAST result was a low positive (1-3 ng/mL), or repeat venom skin test responses were positive; another 7 (7%) patients had high venomspecific IgE antibody levels (4-243 ng/mL). Notably, 56 (57%) of 99 patients with positive histories and negative skin test responses had negative RAST results. In patients with positive skin test responses, sting challenges were performed in 141 of 196 patients, with 30 systemic reactions. Sting challenges were performed on 37 of 43 patients with negative skin test responses and positive venom-specific IgE and in 14 of 56 patients with negative skin test responses and negative

RAST results. There were 11 patients with negative skin test responses who had systemic reactions to the challenge sting: 2 had negative RAST results, and 9 had positive RAST results at 1 ng/mL. The frequency of systemic reaction was 21% in patients with positive skin test responses and 22% in patients with negative skin test responses (24% in those with positive RAST results and 14% in those with negative RAST results. Conclusions: Venom skin test responses can be negative in patients who will subsequently experience another systemic sting reaction. Venom skin test responses are negative in many patients with a history of systemic allergic reactions to insect stings and may be associated with positive serologic test responses for venom-specific IgE antibodies (sometimes strongly positive results). Venom skin test responses should be repeated when negative, along with a serologic IgE antivenom test. Better diagnostic skin test reagents are urgently needed.

LANDMARK PUBLICATION:
Golden DBK, Marsh DG, Freidhoff LR, et al.
Natural history of Hymenoptera venom sensitivity in adults
J Allergy Clin Immunol 1997;100:760-6

Background: Epidemiologic studies of Hymenoptera venom allergy in adults show a prevalence of positive venom skin test results, RASTs of 15% to 25%, or both, but most such individuals have had no systemic reactions to stings. The clinical significance and natural history of this apparently common sensitivity is uncertain. Objective: We sought to determine the natural history of venom sensitization by observing the rate of decrease or increase in sensitivity in normal adults over 5 to 10 years. The clinical significance of these findings is related to the frequency of systemic reactions to stings during the period of observation. Methods: Serial observations were planned in 520 volunteers and randomly selected subjects. Two follow-up visits were attempted , once after 2 to 3 years and again after 5 to 9 years, to perform repeat venom skin tests and RASTs and to review any history of interim stings and their outcomes. Results: Follow-up visits were conducted with 398 subjects (375 early visits and 205 late visits). Overall, in the 398 subjects with one or more visits after a mean of 4 years, skin test responses changed from positive to negative in 44 of 98 (45%) and from negative to positive in 27 of 309 (8.7%) of the subjects. Skin test responses changed from positive to negative in 29 of 87 (33%) subjects after 2.5 years and in 43 of 54 (80%) after 6.8 years. Even when the skin test response became negative, venom-specific IgE remained positive in 11 of 29 (38%) subjects after 2.5 years and in 13 of 43 (30%) after 6.8 years. The rate of loss of sensitivity was 12% per year, similar to retrospective estimates. Skin test sensitivity to venoms disappears more rapidly in these subjects without symptoms (half-life, 4 years) than in patients receiving venom immunotherapy (half-life, 7 years). Skin test responses changed from negative to positive in 23 of 288 (8%) subjects after 2.5 years and in 9 of 151 (6%) after 6.8 years. Insect stings caused no reaction in 120 subjects with a negative skin test response, but 17% (11 of 65) of subjects with a positive skin test response (but with a negative history) had systemic reactions when stung. There was no difference between the early and late visits in the frequency of systemic reactions reported. The risk may be higher than 17% for the specific individuals (67% after 2.5 years and 20% after 6.8 years) whose positive skin test responses persist for years. This risk is lower than that of patients with a positive history (50%) but higher than that of "normal" adults or venomtreated patients (<2%). It is still not clear whether any subset of adults with a positive skin test response but a negative history can be identified, in whom the risk of systemic sting reaction would justify venom immunotherapy even before any reaction occurs. Conclusion: Asymptomatic venom sensitization in adults is common but transient, disappearing at the rate of

12% per year. However, the risk of a systemic reaction to a subsequent sting is significant in adults without symptoms but with positive venom skin test responses (17%) and may be higher when skin test sensitivity does persist for years.

c. Predictive value of clinical history and testing for adult and pediatric population

REVIEW:

Moffitt JE, Golden DBK, Reisman RE

Stinging insect hypersensitivity: A practice parameter update

J Allergy Clin Immunol, *2004;114:869 –886*

This parameter was developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology

LANDMARK PUBLICATION:

Outcomes of Allergy to Insect Stings in Children, with and without Venom Immunotherapy

Golden DBK, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM

N Engl J Med 2004:351;668-74.

Background - Children are thought to “outgrow” the allergy to insect stings, but there are no reports documenting the natural history of this reaction. We studied the outcome of allergic reactions to insect stings in childhood 10 to 20 years afterward in patients who had not received venom immunotherapy and in those who had been treated. Methods - Between 1978 and 1985, we diagnosed allergic reaction to insect stings in 1033 children, of whom 356 received venom immunotherapy. We conducted a survey of these patients by telephone and mail between January 1997 and January 2000, to determine the outcome of stings that occurred in the period from 1987 through 1999. Results - Of the 1033 patients, 512 patients (50 percent) responded, with a mean follow-up period of 18 years, a mean duration of venom immunotherapy of 3.5 years in treated patients, and an incidence of stings of 43 percent. Systemic reactions occurred less frequently in patients who had received venom immunotherapy (2 of 64 patients, or 3 percent) than in untreated patients (19 of 111 patients, or 17 percent; P=0.007). Patients - with a history of moderate-to-severe reactions had a higher rate of reaction if they had not been treated (7 of 22 patients, or 32 percent) than if they had received venom immunotherapy (2 of 43 patients, or 5 percent; P=0.007). In patients who had been treated and who had a history of mild (cutaneous) systemic reaction (i.e., one with only cutaneous manifestations), none of the 21 subjects who received stings had a systemic reaction. Conclusions - A clinically important number of children do not outgrow allergic reactions to insect stings. Venom immunotherapy in children leads to a significantly lower risk of systemic reaction to stings even 10 to 20 years after treatment is stopped, and this prolonged benefit is greater than the benefit seen in adults.

d. History positive, test neg, stinging insect reactive patient.

REVIEW:

Golden DB. Tracy JM. Freeman TM. Hoffman DR. Insect Committee of the American Academy of Allergy, Asthma and Immunology

Negative venom skin test results in patients with histories of systemic reaction to a sting.

J Allergy Clin Immunol 2003;112:495-8.

For more than 20 years venom immunotherapy has been the preferred treatment for Hymenoptera allergy and venom skin testing the preferred diagnostic test. Most allergists consider venom skin tests to be highly accurate and interpret a negative venom skin test result to indicate the absence of insect allergy. Furthermore, current practice guidelines do not adequately address the question of how best to manage the patient with a convincing history of insect allergy but negative skin test results. Recent case reports and published studies have forced us to reexamine this important management issue and to consider what role in vitro venom testing might have in the management of insect allergy. We reviewed the current status of what is known about the management of individuals with a history of insect allergy but negative venom skin test results and suggested modifications of current working guidelines.

e. Venoms, formulation, schedule and duration of immunotherapy.

REVIEW:

Moffitt JE, Golden DBK, Reisman RE

Stinging insect hypersensitivity: A practice parameter update

J Allergy Clin Immunol, 2004;114:869 –886

This parameter was developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology

REVIEW:

Bonifazi F, Jutel M, Bil BM, Birnbaum J, Muller U Oude-Elberink JNG, EAACI Interest Group on Insect Venom Hypersensitivity

Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice

Allergy 2005;60: 1459–1470

Based on the knowledge of the living conditions and habitat of social Aculeatae a series of recommendations have been formulated which can potentially greatly minimize the risk of field re-sting. After a systemic sting reaction, patients should be referred to an allergy specialist for evaluation of their allergy, and if necessary venom immunotherapy (VIT). An emergency medical kit should be supplied, its use clearly demonstrated and repeatably practised until perfected. This should be done under the supervision of a doctor or a trained nurse. Epinephrine by intramuscolar injection is regarded as the treatment of choice for acute anaphylaxis. H1-antihistamines alone or in combination with corticosteroids may be effective in mild to moderate reactions confined to the skin and may support the value of treatment with epinephrine in full-blown anaphylaxis. Up to 75% of the patients with a history of systemic anaphylactic sting reaction develop systemic symptoms once again when re-stung. Venom immunotherapy is a highly effective treatment for individuals with a history of systemic reaction and who have specific IgE to venom allergens. The efficacy of VIT in yellow jacket venom allergic patients has been demonstrated also by assessing healthrelated quality of life. If both skin tests and serum venom specific IgE turn negative, VIT may be stopped after 3 years. After VIT lasting 3–5 years, most patients with mild to moderate anaphylactic symptoms remain protected following discontinuation of VIT even with positive skin tests. Longer term or lifelong treatment should be considered in high-risk patients. Because of the small but relevant risk of re-sting reactions, in these patients, emergency kits, including epinephrine auto-injectors, should be discussed with every patient when stopping VIT.

LANDMARK PUBLICATION:
Freeman TM, Hylander R, Ortiz A, Martin ME
Imported fire ant immunotherapy:m Effectiveness of whole body extracts
J Allergy Clin Immunol 1992:90;210-5
The purpose of this study was to determine if whole body extract (WBE) immunotherapy for Imported fjre ant (IFA) hypersensitivity is effective. This evaluation was carried out by retrospectively interviewing 76 patients with a history of generalized allergic reactions to IFA stings and positive skin tests to IFA-WBE. The study groups consisted of 65 patients onimmunotherapy and 11 similar patients who were not treated for various reasons. In addition, an IFA sting challenge was performed in 30 volunteers of the 65 patients on immunotherapy. The retrospective review showed that of the 65 patients on immunotherapy there had been 112 Subsequent field-sting episodes in 47 patients. Only one sting episode in this group (2.1%) produced an anaphylactic reaction. Six of the 11 patients not on immunotherapy have had subsequent field re-sting episodes, and each has had a systemic reaction. Repeat skin testing on 31 of the 65 patients in the immunotherapy group showed persistent positive responses in five (16%), but each was at a lower dilution than initially. Responses of the other 26 of the 31 patients who had skin testing had become negative. The four untreated patients who were available for skin testing continued to have positive responses at comparable dilutions on skin testing. Sting challenges carried out on 30 volunteers from the 65 patients (all from the 31 who had repeat skin tests) on immunotherapy resulted in only local reactions. Therefore it appears IFA-WBE is effective in decreasing the incidence of anaphylaxis during subsequent field stings; reducing specific immunoglobulin E as demonstrated by skin testing; and protecting against systemic reactions provoked by a sting challenge with a single IFA.

LANDMARK PUBLICATION:
Golden DBK, Kagey-Sobotka A, Lichtenstein LM
Survey of patients after discontinuing venom immunotherapy
J Allergy Clin Immunol 2000;105:385-90
Background: Venom immunotherapy rapidly reduces the risk of a systemic sting reaction in adults from 30% to 70% to less than 2%. When venom immunotherapy is stopped after 5 years or longer, the risk of a systemic sting reaction is 5% to 15% during the first few years after stopping treatment. It is uncertain whether systemic sting reactions will occur more than 5 years after discontinuing venom immunotherapy and whether treatment can be safely stopped in some patients after less than 5 years. Objective: The purpose of this study is to estimate the risk of systemic reaction to a sting 10 years after discontinuing treatment and the relative risk after 3 years of treatment compared with that after 5 years or more of treatment. Methods: Among all patients who had venom immunotherapy at our center, we identified 395 patients who stopped treatment: some had dropped out of therapy early (6-24 months), some stopped after 3 to 4 years, and most completed 5 years or more of venom immunotherapy and were advised to stop by the allergist (many as part of our reported studies of discontinuing venom immunotherapy). Results: Contact was made with 194 patients, including telephone interviews for sting history and requests to visit the office for skin testing and blood sampling. Of these patients, 74 had been included in our original study of patients who had 5 years or more of venom immunotherapy and had sting challenges after 1 to 5 years off venom immunotherapy, as previously reported. Of the 74 in that original study, 61 were reached for this survey, and 30 reported recent stings, with 5 systemic sting reactions. Another 133 patients who had stopped venom immunotherapy were reached: 82 had 5 or

more years of venom immunotherapy, 20 had 3 to 4 years of venom immunotherapy, and 31 had less than 2 years of venom immunotherapy. Of 51 patients stung from this group, 27 had 5 or more years of venom immunotherapy (no systemic sting reactions), and 24 had less than 5 years of venom immunotherapy (3 systemic sting reactions). We have now observed a total of 113 patients who had 5 or more years of venom immunotherapy and were stung after stopping. Sixteen (14%) had systemic sting reactions; most were mild, but 4 were severe. Systemic sting reactions occurred in 12 (10.7%) of 112 patients stung in the first 4 years off venom immunotherapy and 5 (10%) of 50 stung more than 5 years off venom immunotherapy. In 4 of 8 patients with current systemic sting reactions, the skin test response was negative, although the venom-IgE response was positive at the previous encounter. All systemic sting reactions were similar in pattern and severity to prevenom immunotherapy reactions in the same patient. Conclusions:We conclude that the risk of systemic sting reactions when venom immunotherapy is stopped after 5 years or longer remains in the reported range of 5% to 15% in the 5 to 10 years after stopping venom immunotherapy. This risk of systemic sting reactions does not seem to decrease over time, unlike the progressive decline in immunologic markers (skin test and venom-IgE responses). To prospectively assess the risk of recurrent systemic sting reactions, there is a need for sting challenge studies of patients who have been off venom immunotherapy for 5 to 10 years and patients who have stopped venom immunotherapy after just 3 to 4 years treatment.

LANDMARK PUBLICATION:
Ruëff F, Wenderoth A, Przybilla B
Patients still reacting to a sting challenge while receiving conventional Hymenoptera venom immunotherapy are protected by increased venom doses
J Allergy Clin Immunol 2001;108:1027-32
Background: Up to 20% of patients allergic to Hymenoptera venom are not protected by conventional venom immunotherapy (VIT) with 100 μg of any single venom. Objective:We sought to evaluate the efficacy of an increased venom dose in patients allergic to Hymenoptera venom still reacting systemically to a sting challenge despite immunotherapy with 100 μg of venom every 4 weeks. Methods: In this retrospective study patients were included who still had reacted systemically to a sting challenge with a living bee or wasp despite VIT with a maintenance dose of 100 μg every 4 weeks. The maintenance dose was increased to 150 or 200 μg every 4 weeks, and a second sting challenge was performed. If a patient reacted again, the dose was further increased. Baseline mast-cell tryptase levels were assessed by using a fluoroenzyme immunoassay in stored patient sera. Results: While receiving a maintenance dose of 100 μg of venom every 4 weeks for 7 to 38 months, 18 patients reacted systemically to a bee sting and 22 reacted to a wasp sting. After an increase of the maintenance dose to 150 μg, 2 of 4 patients allergic to bee venom (BV) and 6 of 6 patients allergic to yellow jacket venom (YJV) no longer reacted systemically to the sting challenge. The respective rates of full protection were 13 of 14 and 15 of 16 in patients with an increase of the maintenance dose to 200 μg from the start. Of those 4 individuals not protected by the first dose increase, one patient allergic to BV (prior dose of 150 μg) and one patient allergic to YJV (prior dose of 200 μg) did not react systemically to a further sting challenge while receiving 200 μg of BV or 250 μg of YJV, respectively. One patient allergic to BV who had a systemic reaction to the sting challenge while receiving 150 μg was not protected after a dose increase to 200 μg; she later received a dose of 400 μg of BV, and no further sting challenge was performed. The patient allergic to BV who still reacted systemically after a first dose increase to 200 μg was a female patient with urticaria pigmentosa. She had repeated systemic adverse

reactions to further BV immunotherapy, necessitating discontinuation of the treatment; however, she tolerated well VIT with 200 µg of YJV. In all other patients, no unusual adverse reactions to the increased venom doses were observed. Baseline serum tryptase levels were elevated above 13.5 µg/L (95th percentile in normal subjects) in 9 (28.1%) of 32 patients. Conclusions: The majority of patients allergic to Hymenoptera venom who still reacted systemically to a sting challenge despite VIT with a dose of 100 µg every 4 weeks can be fully protected by an increased maintenance dose. This dose increase is well tolerated by most patients. The rather high proportion of patients with elevated baseline serum tryptase levels necessitates further investigation of a possible association between mastocytosis and treatment failure of conventionally dosed VIT.

INVESTIGATION:
Golden DBK, Kwiterovich KA, Kagey-Sobotka A, et al
Discontinuing venom immunotherapy: Extended observations
J Allergy Clinical Immunol 1998;101:298-302
Background: Our studies of discontinuing venom immunotherapy after at least 5 years have led to the conclusion that the residual risk of a systemic reaction to a sting was in the range of 5% to 10% in adults, and no severe or life-threatening reaction occurred with 270 challenge stings in 74 patients after 1 to 5 years without venom immunotherapy. Objective: The objective of this study was to extend our observation of patients who discontinue venom immunotherapy over 5 to 10 years and to determine which patients are at higher risk for a reaction. Methods: Patients who discontinued venom immunotherapy were surveyed for 3 consecutive years to determine the frequency of systemic reactions to field stings and the fate of venom sensitivity. The evaluation included the 74 patients previously studied (group 1) and 51 additional patients followed after stopping therapy in our clinical center (group 2). Results: Of the original 74 patients, 11 had field stings again after 3 to 7 years without venom immunotherapy, with one systemic reaction (dyspnea). Of the 51 patients in the other group, 15 were stung, of whom four (26%) had systemic reactions, including respiratory symptoms requiring epinephrine. Review of group 1 and group 2 revealed that half of the patients who had systemic reactions to a sting after stopping venom immunotherapy had a history of a systemic reaction occurring during venom immunotherapy (to an injection or a sting). Systemic reactions occurred in three patients who had negative skin test reactions; all three had very low but detectable venom-specific serum IgE antibody levels as determined by RAST and had a history of systemic reactions during venom immunotherapy. Greater severity of the pretreatment reaction was not associated with higher frequency of reaction to stings after stopping therapy but was associated with greater severity if a reaction did occur. Conclusions: Venom immunotherapy (yellow jacket/mixed vespid) in adults can be discontinued after 5 to 6 years with a 5% to 10% residual risk of a systemic reaction. Risk factors may include history of a systemic reaction during venom immunotherapy, persistent strongly positive skin test sensitivity, and the severity of the pretreatment reaction.

INVESTIGATION:
Goldberg A, Confino-Cohen R.
Maintenance venom immunotherapy administered at 3-month intervals is both safe and efficacious.
J Allergy Clin Immunol 2001;107:902-6
Background: Maintenance venom immunotherapy (MVIT) is usually administered to patients with venom allergy at 4- to 6-week intervals for at least 3 to 5 years. The small number of studies

assessing the possibility of extending the maintenance interval (MI) included either too small a population and patients with only vespid and not bee venom (BV) allergy or relied on reaction to field stings only. Objective: We sought to assess the safety and efficacy of MVIT given at 3-month intervals to a large population of patients allergic to both yellow jacket venom and BV. Methods: In all patients undergoing venom immunotherapy, MI was gradually extended to 3 months. Systemic reactions (SRs) to immunotherapy injections or to field stings were regularly recorded. Some of the patients were also deliberately sting challenged during the 3-month interval. Patients discontinuing MVIT were interviewed regarding their responses to field re-stings, and in some of them, an in-hospital sting challenge was performed. Results: One hundred sixty patients mostly allergic to BV were enrolled in the study. Failure to reach the 3-month interval was observed in 6 (3.8%) patients, originating in failure to reach the full maintenance dose in most of them. SRs to MVIT administered at 3-month intervals were observed in 2.6% of the patients. One of 36 patients who experienced a field sting during the 3-month interval had an objective mild SR (2.8%). Two (4.5%) of 44 patients who were deliberately stung during the 3-month interval had mild SRs. After discontinuation of MVIT, 2 (8.3%) of 24 patients who experienced a field sting had an SR. Both were allergic to yellow jacket venom. Three to 82 months after discontinuation of MVIT, 22 patients allergic to BV were sting challenged. Only one (4.5%) patient had a mild objective SR. Conclusions: The conventional 4- to 6-week MI can easily be extended to 3 months in most patients without any adverse events. MVIT given at a 3-month interval is safe and effective while being administered, as well as after its discontinuation. This fact should be applied to almost every patient allergic to insect venom.

INVESTIGATION:
Goldberg A, Confino-Cohen R
Effectiveness of maintenance bee venom immunotherapy administered at 6-month intervals.
Ann Allergy Asthma Immunol 2007:99;352-7

Background: Extension of the intervals at which maintenance venom immunotherapy (MVIT) is administered has been attempted for many years. However, published evidence on its effect, especially in intervals of longer than 3 months, is sparse. Objective: To examine whether the administration of a bee venom (BV) maintenance dose at 6-month intervals is safe and efficacious. Methods: The 3-month intervals at which venom-allergic patients were receiving their MVIT were gradually extended to 6 months. Systemic reactions (SRs) to immunotherapy injections or to field stings were regularly recorded. Patients who were allergic to BV alone or also to other venoms were deliberately sting challenged by a honeybee after reaching the 6-month interval. Results: The 3-month intervals were extended in 47 patients. A single patient (2%) developed an SR after receiving the injection at an interval of 4 months. Two field stings in 2 patients resulted in a mild SR in 1 patient. Of 14 sting-challenged patients, 3 (21%) developed an SR after the challenge. The 3 SRs occurred only among the 8 patients (38%) who were allergic to BV alone. The 3 patients with the SR to the challenge continued to receive the regular maintenance dose at monthly intervals 3 to 5 more times. Repeated sting challenges were then well tolerated in all 3 patients. Conclusion: The administration of MVIT at 6-month intervals does not provide suitable protection in BV-allergic patients, and they should continue MVIT at the accepted 1- to 3-month intervals.

INVESTIGATION:
Oude Elberink JNG, van der Heide S, Guyatt GH, Dubois AEJ

Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis
J Allergy Clin Immunol 2006:118;699-704
Background: Venom immunotherapy (VIT) is a treatment with established efficacy for the prevention of repeated anaphylactic reactions in patients with Hymenoptera allergy, which also allows patients to discontinue carrying an EpiPen. Despite their merits, both treatments can have negative aspects potentially important to patients. Objective: We examined possible negative aspects of the EpiPen in comparison with VIT as perceived by patients. Methods: Positive and negative aspects of both treatments were measured by using a burden of treatment questionnaire together with statements about the EpiPen. Results: One hundred ninety-three patients were included, of whom 94 consented to randomization: 47 received VIT, and 47 received the EpiPen. Of the remaining 99, 75 chose VIT, and 26 chose the EpiPen. Of the patients receiving VIT, 91.5% were (extremely) positive about their treatment, and 85% would choose VIT again. Of the patients receiving the EpiPen, only 48% were positive about their treatment, and even of these patients, 68% preferred to be treated with VIT after 1 year of carrying the EpiPen. Although most patients indicated that it is reassuring to carry an EpiPen and makes them feel safe, many patients also indicated that it is inconvenient and troublesome. Especially patients who were negative about the EpiPen indicated that they would not dare use the EpiPen if necessary and were afraid at possible side effects. Conclusion: In contrast to VIT, the EpiPen is perceived as burdensome by most patients with venom allergy. For most patients, an EpiPen is an unsuitable definitive treatment. Clinical implications: As VIT enables patients with venom allergy to get rid of the EpiPen, patients should be offered VIT.

INVESTIGATION:
Gonzalez de Olano D, lvarez-Twose IA, Esteban-Lopez MI, et al.
Safety and effectiveness of immunotherapy in patients with indolent systemic mastocytosis presenting with Hymenoptera venom anaphylaxis
J Allergy Clin Immunol 2008;121:519-26
Background: Anaphylaxis after Hymenoptera sting has been described in patients with mastocytosis. Venom immunotherapy (VIT) is a safe and effective way to treat patients with Hymenoptera anaphylaxis, but few studies have addressed its usefulness in patients with systemic mastocytosis. Objective: To study the effectiveness and safety of VIT in patients with systemic mastocytosis having anaphylaxis after Hymenoptera sting. Methods: A total of 21 mastocytosis patients—4 women (19%) and 17 men (81%) with a median age of 50 years (range, 29-74 years)—with Hymenoptera sting anaphylaxis who were treated with VIT and followed for a median of 52 months (range, 2-250 months) were studied. Results: In 18 of 21 patients—16 of them lacking skin involvement—anaphylaxis was the presenting symptom. Six patients (29%) experienced adverse reactions during VIT, 3 during initiation and 3 during maintenance. Twelve patients (57%) were restung while undergoing VIT; 9 (75%) presented local reactions and 3 (25%) systemic reactions, 1 of which required intubation. The Hymenoptera specific IgE decreased from 4.15 kU/L (range, 0.44-100 kU/L) before immunotherapy to 1.2 kU/L (range, 0.34-69.4 kU/L) after 4 years ($P < .003$). Conclusion: Venom immunotherapy is effective to treat IgE-mediated Hymenoptera anaphylaxis in patients with mastocytosis. Its use is recommended despite a relatively high risk of adverse reactions during the build-up phase because it provides protection from anaphylaxis in around 3/4 of the patients.

INVESTIGATION:
Mu¨ller UR, Haeberli G
Use of b-blockers during immunotherapy for Hymenoptera venom allergy
J Allergy Clin Immunol 2005;115:606-10
Background: B-Blockers may aggravate anaphylactic reactions and interfere with treatment. There is therefore concern about their use in patients who have a history of anaphylaxis or are on allergen immunotherapy. Immunotherapy is the best available treatment for prevention of life-threatening anaphylaxis to Hymenoptera stings, which is often observed in elderly patients who have cardiovascular disease and therefore are on b-blocker treatment. Objective: To analyze the risk of b-blocker treatment during venom immunotherapy. Methods: We screened all 1682 patients with Hymenoptera venom allergy seen during a period of 34 months for immunotherapy, cardiovascular disease, and treatment with b-blockers. Results: Of the 1389 patients in whom immunotherapy was recommended, 11.2% had cardiovascular disease, and 44 of these were on b-blockers before immunotherapy. In 31 of those, the drug was replaced before starting treatment. In 3 with coronary heart disease and 1 with severe ventricular arrhythmia, the drug was continued throughout immunotherapy. In 9, it was reintroduced after reaching the maintenance dose. In an additional 12 patients, b-blockers were newly started during immunotherapy. Of 25 patients on b-blockers during immunotherapy, 3 (12%) developed allergic side effects, compared with 23 (16.7%) of 117 with cardiovascular disease but without b-blockers. Systemic allergic symptoms after re-exposure by sting challenge or field sting were observed in 1 of 7 (14.3%) with and 4 of 29 (13.8%) without b-blockade. No severe reactions to treatment or sting reexposure were observed in patients with b-blockade. Conclusion: Combination of b-blockers with venom immunotherapy may be indicated in heavily exposed patients with severe cardiovascular disease.

INVESTIGATION:
White KM, England RW
Safety of angiotensin-converting enzyme inhibitors while receiving venom immunotherapy
Ann Allergy Asthma Immunol 2008:101;426-430
Background: Case reports have raised concern about concurrent use of angiotensin-converting enzyme inhibitors (ACE-Is) in patients receiving venom immunotherapy (VIT). No surveys have been performed on the number of venom allergic patients who take ACE-Is and their outcomes. Objective: To survey the use of ACE-Is and systemic reaction (SR) characteristics in patients receiving VIT. Methods: A retrospective medical record review was performed on all patients evaluated for Hymenoptera venom allergy at a single center from 2000 to 2005. Patient records were evaluated for presenting symptoms, specific IgE testing, VIT treatment course, ACE-I use during VIT, and the presence of any SRs to field stings or VIT. Results: Of 288 patients evaluated from 2000 to 2005 for Hymenoptera venom allergy, 157 were found to have venom specific IgE. Of these 157 patients, 79 (50%) of those with Hymenoptera venom allergy underwent VIT. Seventeen of these 79 patients (21%) were taking an ACE-I during VIT. The mean overlap of a patient taking an ACE-I with the time they were receiving VIT was 30.9 months (range, 3-114 months). Patients taking ACE-Is were older (mean age, 56.2 vs 36.4 years; $P < .001$) and received VIT for a longer period (mean, 72.3 vs 29.9 months; $P < .04$). Thirteen of 62 patients not taking an ACE-I (21%) experienced an SR during their VIT. No patients taking an ACE-I experienced an SR to VIT while taking an ACE-I ($P = .03$). Conclusions: This study suggests that there is not an association between ACE-I use and increased frequency of SRs to venom immunotherapy.

RESEARCH FRONTIER:

Severino MG, Cortellini G, Bonadonna P, Francescato E, Panzini I, Macchia D, Campi P, Spadolini I, Canonica WG, Passalacqua G

Sublingual immunotherapy for large local reactions caused by honeybee sting: A double-blind, placebo-controlled trial

J Allergy Clin Immunol 2008;122:44-8.

Background: Sublingual immunotherapy (SLIT) proved effective and safe in respiratory allergy, and thus its use in hymenoptera allergy can be hypothesized. Objective: We sought to assess, in a proof-of-concept study, whether SLIT might potentially be beneficial in hymenoptera allergy. The sting challenge in large local reactions (LLRs) was used to test this hypothesis. Methods: We performed a randomized, double-blind, placebocontrolled study involving patients with LLRs who were monosensitized to honeybee. After the baseline sting challenge, they were randomized to either SLIT or placebo for 6 months. The treatment (Anallergo, Florence, Italy) involved a 6-week build-up period, followed by maintenance with 525 mg of venom monthly. The sting challenge was repeated after 6 months. Results: Thirty patients (18 male patients; mean age, 44.5 years) were enrolled, and 26 completed the study, with 1 dropout in the active group and 3 dropouts in the placebo group. In the active group the median of the peak maximal diameter of the LLRs decreased from 20.5 to 8.5 cm (P 5 .014), whereas no change was seen in the placebo group (23.0 vs 20.5 cm, P 5 not significant). The diameter was reduced more than 50% in 57% of patients. One case of generalized urticaria occurred in a placebo-treated patient at sting challenge. No adverse event caused by SLIT was reported. Conclusion: Honeybee SLIT significantly reduced the extent of LLRs, and its safety profile was good. Although LLRs are not an indication for immunotherapy, this proof-of-concept study suggests that SLIT in hymenoptera allergy deserves further investigation. Trials involving systemic reactions and dose-ranging studies are needed.

RESEARCH FRONTIER:

Mu¨ller UR, Jutel M, Reimers A, et al.

Clinical and immunologic effects of H1 antihistamine preventive medication during honeybee venom immunotherapy

J Allergy Clin Immunol 2008;122:1001-7

Background: H1 antihistamines increase safety during allergenspecific immunotherapy and might influence the outcome because of immunoregulatory effects. Objective: We sought to analyze the influence of 5 mg of levocetirizine (LC) on the safety, efficacy, and immunologic effects of ultrarush honeybee venom immunotherapy (BVIT). Method: In a double-blind, placebo-controlled study 54 patients with honeybee venom allergy received LC or placebo from 2 days before BVIT to day 21. Side effects during dose increase and systemic allergic reactions (SARs) to a sting challenge after 120 days were analyzed. Allergen-specific immune response was investigated in skin, serum, and allergen-stimulated T-cell cultures. Results: Side effects were significantly more frequent in patients receiving placebo. Four patients receiving placebo dropped out because of side effects. SARs to the sting challenge occurred in 8 patients (6 in the LC group and 2 in the placebo group). Seven SARs were only cutaneous, and 1 in the placebo group was also respiratory. Difference of SARs caused by the sting challenge as insignificant. Specific IgG levels increased significantly in both groups. Major allergen phospholipase A2-stimulated T cells from both groups showed a slightly decreased proliferation. The decrease in IFN-g and IL-13 levels with placebo was not prominent with LC, whereas IL-10 levels showed a significant increase in the LC group only. Decreased histamine receptor (HR)1/HR2 ratio in allergen-specific T cells on day 21 in the

placebo group was prevented by LC. Conclusions: LC reduces side effects during dose increase without influencing the efficacy of BVIT. LC modulates the natural course of allergen-specific immune response and affects the expression of HRs and cytokine production by allergenspecific T cells.

9. Economic costs of diagnosis and treatment of allergic diseases

REVIEW ECONOMICS OF RHINITIS:
Nathan, Robert A
The Burden of Allergic Rhinitis. Allergy and Asthma Proceedings, Volume 28, Number 1, January-February 2007, pp. 3-7

Although formerly regarded as a nuisance disease, allergic rhinitis (AR) has a considerable effect on quality of life and can have significant consequences if left untreated. The total burden of this disease lies not only in impaired physical and social functioning but also in a financial burden made greater when considering evidence that AR is a possible causal factor in comorbid diseases such as asthma or sinusitis. Compared with matched controls, patients with AR have an approximate twofold increase in medication costs and 1.8-fold the number of visits to health practitioners. Hidden direct costs include the treatment of comorbid asthma, chronic sinusitis, otitis media, upper respiratory infection, and nasal polyposis. Nasal congestion, the most prominent symptom in AR, is associated with sleep-disordered breathing, a condition that can have a profound effect on mental health, including increased psychiatric disorders, depression, anxiety, and alcohol abuse. Furthermore, sleep-disordered breathing in childhood and adolescence is associated with increased disorders of learning performance, behavior, and attention. In the United States, AR results in 3.5 million lost workdays and 2 million lost schooldays annually. Patients struggle to alleviate their misery, frequently self-adjusting their treatment regimen of over-the-counter and prescription medications because of lack of efficacy, deterioration of efficacy, lack of 24-hour relief, and bothersome side effects. Ironically, health care providers overestimate patient satisfaction with therapy. Therefore, improvement in patient-practitioner communication may enhance patient adherence with prescribed regimens.

REVIEW PHARMACOECONOMICS OF ASTHMA:
JW Cheng, RJ Arnold
Pharmacoeconomic review of medical management of persistent asthma.
Allergy Asthma Proc.2008 Mar-Apr,29(2):109-22

Asthma affects 20 million Americans and causes a substantial loss of productivity. Medications help to increase symptom-free days and improve quality of life. Examining the cost-effectiveness of different treatments, in addition to their clinical efficacy, allows us to choose the optimal strategy in managing patients. This study reviews published pharmacoeconomic analyses of different medications used for asthma management, with a focus on medications available in the United States. English language, peer-reviewed articles, or abstracts were identified from MEDLINE and Current Contents databases (both 1966 to March 1, 2006) using the search terms asthma, pharmacoeconomics, cost-effectiveness, steroids, beta(2)-agonists, cromolyn, methylxanthines, leukotriene receptor antagonists, and omalizumab. Citations from available articles were reviewed also for additional references. Pharmacoeconomic analysis from a payer's perspective has shown that salmeterol/fluticasone is a cost-effective treatment option for moderate persistent asthma management, when compared with fluticasone with or without the addition of leukotriene modifiers. Leukotriene modifiers are less cost-effective than inhaled corticosteroids or

combined inhaled steroids and long-acting beta(2)-agonists for mild or moderate persistent asthma. Anti-IgE antibody has been shown inconsistently, to be cost-effective in patients with moderate to severe allergic asthma. Although the acquisition cost of levalbuterol is higher, one study showed that it may be more cost-effective than albuterol after taking into account reduction in hospitalizations. Cost-effectiveness analyses and clinical efficacy of medications, together with other patient-specific factors, are important information to be considered when selecting treatment regimens for asthma. Future economic analysis should focus on finding better ways to evaluate productivity lost due to asthma, in addition to hospitalization.

10. Psychosocial aspects of allergic diseases and chronic illness, failure of adherence to therapy

REVIEW PSYCHOSOCIAL ASPECTS OF CHRONIC ILLNESS:
Julie Schmittdiel, David M. Mosen, Russell E. Glasgow, Judith Hibbard, Carol Remmers and Jim Bellows.
Patient Assessment of Chronic Illness Care (PACIC) and Improved Patient-centered Outcomes for Chronic Conditions. Journal of General Internal Medicine. Vol.23 (1):77-80. November 21, 2007 (online)
BACKGROUND: The Patient Assessment of Chronic Illness Care (PACIC) has potential for use as a patient-centered measure of the implementation of the Chronic Care Model (CCM), but there is little research on the relationship between the PACIC and important behavioral and quality measures for patients with chronic conditions. OBJECTIVE: To examine the relationship between PACIC scores and self-management behaviors, patient rating of their health care, and self-reported quality of life. DESIGN: Cross-sectional survey with a 61% response rate. PARTICIPANTS: Included in the survey were 4,108 adults with diabetes, chronic pain, heart failure, asthma, or coronary artery disease in the Kaiser Permanente Medical Care program across 7 regions nationally. MEASUREMENTS: The PACIC was the main independent variable. Dependent variables included use of self-management resources, self-management behaviors such as regular exercise, self-reported adherence to medications, patient rating of their health care, and quality of life. RESULTS: PACIC scores were significantly, positively associated with all measures (odds ratio [ORs] ranging from 1.20 to 2.36) with the exception of self-reported medication adherence. CONCLUSIONS: Use of the PACIC, a practical, patient-level assessment of CCM implementation, could be an important tool for health systems and other stakeholders looking to improve the quality of chronic disease care.

B. Immunodeficiency Diseases

REVIEW PRACTICE GUIDELINE Primary Immunodeficiency:
Bonilla F, Bernstein IL,Khan DA, et al.
Practice parameter for the diagnosis and management of primary immunodeficiency.
Ann Allergy Asthma Immunol, 2005;94:S1-63.
A principal aim of this Practice Parameter is to organize current knowledge and practice in thediagnosis and management of primary immunodeficiency diseases. Preparation of this Practice Parameter included a review of the medical literature, mainly via the PubMed database. Published clinical studies or reports were rated by category of evidence and used to establish the strength of a clinical recommendation. There are few randomized trials in the diagnosis and management of primary immunodeficiency. Thus, most of these recommendations represent evidence from published case series or reports or the opinions of experts in the field.

REVIEW:
Fischer A.
Human primary immunodeficiency diseases: a perspective.
Nat Immunol 2004;5:23-30.
Primary immunodeficiency diseases consist of a group of more than 100 inherited conditions, mostly monogenic, predisposing individuals to different sets of infections, allergy, autoimmunity and cancer. Primary immunodeficiencies therefore represent exquisite models of various immunopathological settings. The identification of the associated genes, 100 so far, has generated a plethora of information about the immune system and spurred the analysis of many aspects of the development, function and regulation of both innate and adaptive immunity. These findings can potentially contribute to improved care of affected individuals by providing new diagnostic and/or therapeutic tools.

RESEARCH FRONTIER:
Fischer A. Hacein-Bey-Abina S. Cavazzana-Calvo M.
Gene therapy for immunodeficiency diseases.
Semin Hematol. 2004;41:272-8.
Primary immunodeficiency diseases represent good targets for hematopoietic stem cell-targeted gene therapy. Severe combined immunodeficiencies (SCID) have been the first examples of successful gene therapy based on the ex vivo usage of retroviral vectors. New advances in the technology of gene transfer should further promote gene therapy as a safe and effective therapeutic strategy of immunodeficiency diseases.

1. Combined immunodeficiencies syndromes

REVIEW:
Simonte, SJ Cunningham-Rundles C.
Update on primary immunodeficiency: defects of lymphocytes.
Clinical Immunol 2003;109:109-18, 2003.
The recent identification of the genes involved in many primary immunodeficiency disorders has led to a significant increase in our understanding of the pathogenesis of these defects. Many of these disorders share a clinical phenotype with common features such as recurrent infections, chronic inflammation, and autoimmunity. Although some of these immune defects have mild presentations and better outcomes, others result in severe infections and significant morbidity and mortality. For these, early diagnosis and treatment are critical. This review provides an overview of the genetic defects and clinical features of primary immune deficiencies due to defects in lymphocytes.

REVIEW:
Schroeder HW Jr. Schroeder HW 3rd. Sheikh SM.
The complex genetics of common variable immunodeficiency.
Journal Invest Med 2004;.52:90-103.
Immunoglobulin (Ig)A deficiency and common variable immunodeficiency (CVID) are the most common primary immunodeficiency disorders in North America and Europe. These diseases appear to comprise a familial spectrum of immunodeficiency that ranges from partial IgA deficiency to a complete absence of serum immunoglobulin. The CVID phenotype is typically

acquired and can spontaneously revert to IgG and IgM sufficiency. Family studies suggest thevpresence of at least two susceptibility loci within the major histocompatibility complex on the short arm of chromosome 6: one located near the class II region and the other located near the junction between the class III and class I regions. Inheritance of these susceptibility genes may yield an additive risk for the development of immunodeficiency. First-degree family members of patients with CVID are at risk throughout their lives for the development of these diseases and should be monitored with a high index of suspicion.

a. Predominant antibody deficiencies

REVIEW:
Ballow M.
Primary immunodeficiency disorders: antibody deficiency.
J Allergy Clin Immunol. 2002;109:581-91.

As a group, antibody deficiencies represent the most common types of primary immune deficiencies in human subjects. Often symptoms do not appear until the latter part of the first year of life, as passively acquired IgG from the mother decreases to below protective levels. As with the T-cell immune deficiencies, the spectrum of antibody deficiencies is broad, ranging from the most severe type of antibody deficiency with totally absent B cells and serum Igs to patients who have a selective antibody deficiency with normal serum Ig. In addition to the increased susceptibility to infections, a number of other disease processes (eg, autoimmunity and malignancies) can be involved in the clinical presentation. Fortunately, the availability of intravenous immune serum globulin has made the management of these patients more complete. Recently, molecular immunology has led to identification of the gene or genes involved in many of these antibody deficiencies. As discussed in this review, this has led to a better elucidation of the B-cell development and differentiation pathways and a more complete understanding of the pathogenesis of many of these antibody deficiencies.

b. Other well defined immunodeficiency syndromes

REVIEW NEMO:
Orange JS, Jain A, Ballas ZK, Schneider LC, Geha RS, Bonilla FA.
The presentation and natural history of immunodeficiency caused by nuclear factor kappaB essential modulator mutation.
J Allergy Clin Immunol. 2004;113;725-723

An increasing number of rare genetic defects are associated with immunodeficiency and impaired ability to activate gene transcription through nuclear factor (NF) kappaB. Hypomorphic mutations in the NFkappaB essential modulator (NEMO) impair NFkappaB function and are linked to both immunodeficiency and ectodermal dysplasia (ED), as well as susceptibility to atypical mycobacterial infections. OBJECTIVE: We sought to investigate the clinical and immunologic natural history of patients with NEMO mutation with immunodeficiency (NEMO-ID). METHODS: Patients with severe bacterial infection and ED or unexplained mycobacterial sensitivity were evaluated for NEMO mutation. Laboratory investigations and clinical data were retrospectively and prospectively accumulated and reviewed. RESULTS: We have given a diagnosis of NEMO-ID to7 boys; 6 had ED, and 5 had gene mutations in the 10th exon of NEMO. Our resulting estimated incidence of NEMO-ID is 1:250,000 live male births. All patients had serious pyogenic bacterial illnesses early in life, and the median age of first infection was 8.1 months. Most boys had mycobacterial disease (median age, 84 months), and a minority had

herpesviral infections. Initial immunologic assessments showed hypogammaglobulinemia (median IgG, 170 mg/dL) with variable IgM (median, 41 mg/dL) and IgA (median, 143 mg/dL) levels. Two patients had increased IgM levels, and 5 had increased IgA levels. All patients evaluated had normal lymphocyte subsets with impaired proliferative responses, specific antibody production, and natural killer cell function. Two patients died from complications of mycobacterial disease (ages 21 and 33 months). CONCLUSION: NEMO-ID is a combined immunodeficiency with early susceptibility to pyogenic bacteria and later susceptibility to mycobacterial infection. Specific features of particular NEMO mutations in these patients provide insight into the role of this gene in immune function.

REVIEW Wiskott Aldrich:
Rengan R. Ochs HD.
Molecular biology of the Wiskott-Aldrich syndrome.
Rev Immunogen.2000; 2:243-55
The Wiskott-Aldrich syndrome (WAS) is an X-linked primary immunodeficiency associated with thrombocytopenia, bloody diarrhea, eczema, recurrent infections, and a high incidence of malignancies. X-linked thrombocytopenia (XLT) is a milder form with predominant platelet abnormalities. Both are caused by mutations of the cytoplasmic WAS protein (WASP). To date, mutations of WASP have been identified in over 340 families and consist of missense and nonsense mutations, deletions and insertions, and splice site mutations. There is a striking correlation between phenotype and genotype. The complex gene product of WASP has multiple functional domains that contribute to actin polymerization, cell motility, intracellular signaling, and apoptosis. Understanding the molecular basis of WAS/XLT not only explains the highly variable clinical phenotype, but also affects the medical management of this serious congenital disorder.

CUTTING EDGE ARTICLE:
Friedrich W, Schütz C, Schulz A, Benninghoff U, Hönig M.
Results and long-term outcome in 39 patients with Wiskott-Aldrich syndrome transplanted from HLA-matched and -mismatched donors.
Immunol Res. 2008 Oct 10. [Epub ahead of print]
In this report, we present an analysis in 39 WAS patients treated by hematopoietic stem cell transplantation (HSCT) in our center since 1983. Fifteen patients received transplants from HLA-identical unrelated donors, 15 from nonidentical parental donors, and 9 from matched siblings. The overall survival rate is 90% in patients with matched donors and 50% in patients after nonidentical transplantation, with a mean follow-up time of 11 years. Treatment failures in the latter group were mainly related to graft rejections and to GvHD and infections following repeat transplants. Long-term survivors in both patient groups remain with few exceptions free of late complications and with stable graft function and complete donor cell chimerism. Based on our findings, we recommend early and prompt treatment of each diagnosed WAS patient if an HLA-matched, related or unrelated, donor can be identified. If this is not the case, HLA-nonidentical donor transplantation represents an alternative to be considered early in patients with severe disease.

REVIEW X-linked lymphoproliferative disease:
Gilmour KC. Gaspar HB.
Pathogenesis and diagnosis of X-linked lymphoproliferative disease.

Expert Rev Molec Diag. 2003;3:549-61.
X-linked lymphoproliferative syndrome (XLP) is a rare, often fatal, primary immunodeficiency that has profound and damaging effects on the immune system of affected individuals. It is characterized by a dysregulated immune response, most commonly to Epstein-Barr viral infection. The defective gene in this syndrome has been identified as SAP-SLAM (signaling lymphocyte activation molecule)-associated protein. It is an adapter molecule that is required for appropriate function of the SLAM-related receptors. There is now a greater understanding of the molecular associations and cellular pathogenesis of SAP and this review will summarize the most recent findings. Clinically, XLP may be difficult to diagnose as a result of its varied clinical phenotype, and protein and genetic assays are currently used to make a definitive diagnosis. With the advances in gene analysis and genomics technology, it is likely that better and more rapid diagnostic techniques will become available.

REVIEW TYPE I INTERFERON DEFICIENCIES:
Jouanguy E, Zhang SY, Chapgier A, Sancho-Shimizu V, Puel A, Picard C, Boisson-Dupuis S, Abel L, Casanova JL.
Human primary immunodeficiencies of type I interferons.
Biochimie. 2007 Jun-Jul;89(6-7):878-83. Epub 2007 May 8.
Type I interferons (IFN-alpha/beta and related molecules) are essential for protective immunity to experimental infection by numerous viruses in the mouse model. In recent years, human primary immunodeficiencies affecting either the production of (UNC-93B deficiency) or the response to (STAT1 and TYK2 deficiencies) these IFNs have been reported. Affected patients are highly susceptible to certain viruses. Patients with STAT1 or TYK2 deficiency are susceptible to multiple viruses, including herpes simplex virus-1 (HSV-1), whereas UNC-93B-deficient patients present isolated HSV-1 encephalitis. However, these immunological defects are not limited to type I IFN-mediated immunity. Impaired type II IFN (IFN-gamma)-mediated immunity plays no more than a minor role in the pathogenesis of viral diseases in these patients, but the contribution of impaired type III IFN (IFN-lambda)-mediated immunity remains to be determined. These novel inherited disorders strongly suggest that type I IFN-mediated immunity is essential for protection against natural infections caused by several viruses in humans.

REVIEW RAG DEPENDENT IMMUNODEFICIENCIES:
Sobacchi C, Marrella V, Rucci F, Vezzoni P, Villa A.
RAG-dependent primary immunodeficiencies.
Hum Mutat. 2006 Dec;27(12):1174-84.
Mutations in recombination activating genes 1 and 2 (RAG1 and RAG2) cause a spectrum of severe immunodeficiencies ranging from classical T cell-B cell-severe combined immunodeficiency (T(-)B(-)SCID) and Omenn syndrome (OS) to an increasing number of peculiar cases. While it is well established from biochemical data that the specific genetic defect in either of the RAG genes is the first determinant of the clinical presentation, there is also increasing evidence that environmental factors play an important role and can lead to a different phenotypic expression of a given genotype. However, a better understanding of the mechanisms by which the molecular defect impinges on the cellular phenotype of OS is still lacking. Ongoing studies in knock-in mice could better clarify this aspect. (c) 2006 Wiley-Liss, Inc.

REVIEW IPEX AND APECED:

Moraes-Vasconcelos D, Costa-Carvalho BT, Torgerson TR, Ochs HD.
Primary immune deficiency disorders presenting as autoimmune diseases: IPEX and APECED.
J Clin Immunol. 2008 May;28 Suppl 1:S11-9. Epub 2008 Feb 9.
BACKGROUND: Several primary immune deficiency disorders are associated with autoimmunity and malignancy, suggesting a state of immune dysregulation. The concept of immune dysregulation as a direct cause of autoimmunity in primary immune deficiency disorders (PIDDs) has been strengthened by the recent discovery of distinct clinical entities linked to single-gene defects resulting in multiple autoimmune phenomena including immune dysregulation, polyendocrinopathy, enteropathy and X-linked (IPEX) syndrome, and autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy (APECED) syndrome. CONCLUSION: reviewing recent advances in our understanding of the small subgroup of PIDD patients with defined causes for autoimmunity may lead to the development of more effective treatment strategies for idiopathic human autoimmune diseases.

REVIEW MHC CLASS II DEFICIENCIES:
Chen X, Jensen PE.
MHC class II antigen presentation and immunological abnormalities due to deficiency of MHC class II and its associated genes.
Exp Mol Pathol. 2008 Aug;85(1):40-4. Epub 2008 Apr 13.
Antigen presentation by Major Histocompatibility Complex (MHC) class II molecules plays an important role in controlling immunity and autoimmunity. Multiple co-factors including the invariant chain (Ii), HLA-DM and HLA-DO are involved in this process. While the role for Ii and DM has been well defined, the biological function of DO remains obscure. Our data indicate that DO inhibits presentation of endogenous self-antigens and that developmentally-regulated DO expression enables antigen presenting cells to preferentially present different sources of peptide antigens at different stages of development. Disruption of this regulatory mechanism can result in not only immunodeficiency but also autoimmunity. Despite the fact that deletion of each of the three genes in experimental animals is associated with profound immunological abnormalities, no corresponding human diseases have been reported. This discrepancy suggests the possibility that primary immunodeficiencies due to a genetic defect of Ii, DM and DO in humans are under diagnosed or diagnosed as "common variable immunodeficiency", a category of immunodeficiency of heterogeneous or undefined etiology. Clinical tests for any of these potential genetic defects are not yet available. We propose the use of multi-color flow cytometry in conjunction with intracellular staining to detect expression of Ii, DM, DO in peripheral blood B cells as a convenient reliable screening test to identify individuals with defects in antigen presentation.

c. Complement deficiencies including hereditary acquired C1 inhibitor deficiency

REVIEW:
Wen L. Atkinson JP. Giclas PC.
Clinical and laboratory evaluation of complement deficiency.
J Allergy Clin Immunol 2004;113:585-93.
The complement system provides innate defense against microbial pathogens and is a "complement" to humoral (antibody-mediated) immunity. Consisting of plasma and membrane

proteins, this proinflammatory system works in part by a cascade involving limited proteolysis whereby one component activates the next, resulting in a dramatic amplification. The overall goal is deposition of complement fragments on pathologic targets for the purposes of opsonization, lysis, and liberation of peptides that promote the inflammatory response. Deficiencies of complement components predispose to infections and autoimmune syndromes. Even though total deficiency of a complement component is rare, patients presenting with certain bacterial infections and autoimmune syndromes, especially SLE, have a much greater incidence of deficiency. This review will summarize the clinical manifestations and pathophysiology of congenital and acquired complement deficiency diseases. We will also present an algorithm for laboratory diagnosis of complement deficiency and discuss current and future therapeutic options.

REVIEW:
Kaplan AP.
C1 inhibitor deficiency: hereditary and acquired forms.
J Invest Allergol Clin Immunol 2001;11:211-9.
C1 inhibitor deficiency can be hereditary or acquired. The hereditary disorder has two types, each of which is inherited as a dominant disorder, with genetic mechanisms leading either to low levels of normal C1 INH and little or no mutant problem as a result of mRNA or protein synthetic defects or degradative mechanisms (Type I) or with point mutations and synthesis of a functionless protein product with transinhibition of the normal allele (Type II). The acquired disorder with low C1q is due to C1 INH consumption associated with lymphoma or connective tissue disease (Type I) and/or autoimmune mechanisms (Type II). The swelling of all types is due to absence of inhibition of the plasma kinin forming cascade with liberation of bradykinin while complement activation, a critical marker of the disorder, is not responsible for the swelling. Treatment employs androgenic compounds, antifibrinolytic agents, or replacement therapy.

REVIEW:
Gompels MM. Lock RJ. Abinun M. et al.
C1 inhibitor deficiency: consensus document
Clin Exp Immunol 2005. 139:379-94
We present a consensus document on the diagnosis and management of C1 inhibitor deficiency, a syndrome characterized clinically by recurrent episodes of angio-oedema. In hereditary angiooedema, a rare autosomal dominant condition, C1 inhibitor function is reduced due to impaired transcription or production of non-functional protein. The diagnosis is confirmed by the presence of a low serum C4 and absent or greatly reduced C1 inhibitor level or function. The condition can cause fatal laryngeal oedema and features indistinguishable from gastrointestinal tract obstruction. Attacks can be precipitated by trauma, infection and other stimulants. Treatment is graded according to response and the clinical site of swelling. Acute treatment for severe attack is by infusion of C1 inhibitor concentrate and for minor attack attenuated androgens and/or tranexamic acid. Prophylactic treatment is by attenuated androgens and/or tranexamic acid. There are a number of new products in trial, including genetically engineered C1 esterase inhibitor, kallikrein inhibitor and bradykinin B2 receptor antagonist. Individual sections provide special advice with respect to diagnosis, management (prophylaxis and emergency care), special situations (childhood, pregnancy, contraception, travel and dental care) and service specification.

REVIEW:
Zuraw BL
Clinical practice. Hereditary angioedema.
N Engl J Med. 2008 Sep 4;359(10):1027-36.
This journal feature beings with a case vignette highlighting a clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

d. Congenital defects of phagocytic number, function and adhesion

REVIEW Phagocyte Deficiency:
Rosenzweig SD. Holland SM.
Phagocyte immunodeficiencies and their infections.
J Allergy Clin Immunol 2004;113:620-6.
Primary immunodeficiencies (PIDs) primarily affecting the phagocytes (neutrophils and macrophages) typically predispose patients to infections. However, one of the most clinically important features of these disorders is their relatively narrow spectrum of disease-specific infections. Invasive aspergillosis in the absence of immune suppression is essentially seen only in chronic granulomatous disease; disseminated nontuberculous mycobacterial infection in the absence of immune suppression is seen predominantly in patients with defects of the IFN-gamma/IL-12 axis. In contrast, infections that are relatively common in some of the PIDs affecting the lymphoid system (Pneumocystis jiroveci and Streptococcus pneumoniae) are extremely uncommon in PIDs affecting phagocytes. Therefore careful attention to the microbiology laboratory early in the course of evaluation of a patient with recurrent infections and suspected of having a PID will help steer the workup in the appropriate direction. Over the last few years, there have been major advances in the molecular and cellular understandings of PIDs affecting phagocytes. As the field of PIDs becomes broader and more clinical and molecular definition becomes available, it is increasingly important to be able to identify likely pathways for investigation early in the evaluation. Here we have updated some of the more rapidly evolving aspects of PIDs affecting phagocytes, with a special emphasis on the associated microbiology.

REVIEW CGD:
Yu G, Hong DK, Dionis KY, Rae J, Heyworth PG, Curnutte JT, Lewis DB.
Focus on FOCIS: the continuing diagnostic challenge of autosomal recessive chronic granulomatous disease.
Clin Immunol. 2008 Aug;128(2):117-26.
Chronic granulomatous disease (CGD) is a primary immunodeficiency of defective neutrophil oxidative burst activity due to mutations in the genes CYBA, NCF-1, NCF-2, and CYBB, which respectively encode the p22-phox, p47-phox, p67-phox, and gp91-phox subunits. CGD usually presents in early childhood with recurrent or severe infection with catalase-positive bacteria and fungi. We present an unusual case of CGD in which Burkholderia cepacia lymphadenitis developed in a previously healthy 10-year-old girl. Flow cytometric analysis of dihydrorhodamine (DHR)-labeled neutrophils performed by a CLIA-approved outside reference laboratory was reported as normal. However, we found that this patient's neutrophil oxidative burst activity in DHR assays was substantially reduced but not absent. A selective decrease in intracellular staining for p67-phox suggested the diagnosis of autosomal recessive CGD due to NCF-2 gene mutations,

and a novel homozygous and hypomorphic NCF-2 gene mutation was found. The potential mechanisms for this delayed and mild presentation of CGD are discussed.

CUTTING EDGE CGD:
Ott MG, Seger R, Stein S, Siler U, Hoelzer D, Grez M.
Advances in the treatment of Chronic Granulomatous Disease by gene therapy.
Curr Gene Ther. 2007 Jun;7(3):155-61.
Gene transfer into hematopoietic stem cells has been successfully used to correct immunodeficiencies affecting the lymphoid compartment. However, similar results have not been reported for diseases affecting myeloid cells, mainly due to low engraftment levels of gene-modified cells observed in unconditioned patients. Here we review the developments leading to a gene therapy approach for the treatment of Chronic Granulomatous Disease (CGD), a primary life threatening immunodeficiency caused by a defect in the oxidative antimicrobial activity of phagocytes. Although the disease can be cured by bone marrow transplantation, this treatment is only available to patients with HLA-identical sibling or matched unrelated donors. One therapeutic option for patients without suitable donor is the genetic modification of autologous hematopoietic stem cells. Although early attempts to correct CGD by gene therapy were unsuccessful, these studies demonstrated the safety and limitations of gene transfer into hematopoietic stem cells (HSC) of CGD patients using retroviral vectors. The recent development of advanced gene transduction protocols together with improved retroviral vectors, combined with low intensity chemotherapy conditioning, allowed partial correction of the granulocytic function with a significant clinical benefit in treated patients. These results may have important implications for future applications of gene therapy in myeloid disorders and inherited diseases using hematopoietic stem cells.

REVIEW Leukocyte Adhesion Deficiencies:
Etzioni A.
Leukocyte adhesion deficiencies: molecular basis, clinical findings, and therapeutic options.
Adv Exp Med Biol. 2007; 601:51-60.
Leukocyte trafficking from bloodstream to tissue is important for the continuous surveillance for foreign antigens, as well as for rapid leukocyte accumulation at sites of inflammatory response or tissue injury. Leukocyte interaction with vascular endothelial cells is a pivotal event in the inflammatory response and is mediated by several families of adhesion molecules. The crucial role of the beta2-integrin subfamily in leukocyte emigration was established after leukocyte adhesion deficiency (LAD) I was discovered. Patients with this disorder suffer from life-threatening bacterial infections, and in its severe form, death usually occurs in early childhood unless bone marrow transplantation is performed. The LAD II disorder clarifies the role of the selectin receptors and their fucosylated ligands. Clinically, patients with LAD II suffer from a less severe form of disease, resembling the moderate phenotype of LAD I. LAD III emphasizes the importance of the integrin activation phase in the adhesion cascade. Although the primary defect is still unknown, it is clear that all hematopoietic integrin activation processes are defective, which lead to severe infection as observed in LAD I and to marked increase tendency for bleeding problems.

CUTTING EDGE LAD:
Kilic SS, Etzioni A.

The Clinical Spectrum of Leukocyte Adhesion Deficiency (LAD) III due to Defective CalDAG-GEF1.
J Clin Immunol. 2008 Aug 16. [Epub ahead of print]
INTRODUCTION: Leukocyte adhesion deficiency (LAD) type III is a rare syndrome characterized by severe recurrent infections, leukocytosis, and increased bleeding tendency. All integrins are normally expressed yet a defect in their activation leads to the observed clinical manifestations. MATERIALS AND METHODS: Less than 20 patients have been reported world wide and the primary genetic defect was identified in some of them. Here we describe the clinical features of patients in whom a mutation in the calcium and diacylglycerol-regulated guanine nucleotide exchange factor 1 (CalDAG GEF1) was found and compare them to other cases of LAD III and to animal models harboring a mutation in the CalDAG GEF1 gene. DISCUSSION: The hallmarks of the syndrome are recurrent infections accompanied by severe bleeding episodes distinguished by osteopetrosis like bone abnormalities and neurodevelopmental defects.

REVIEW Hyper IgE Syndrome:
Paulson ML, Freeman AF, Holland SM.
Hyper IgE syndrome: an update on clinical aspects and the role of signal transducer and activator of transcription 3.
Curr Opin Allergy Clin Immunol. 2008 Dec; 8(6):527-533.
PURPOSE OF review Hyper IgE syndrome (HIES) is a primary immunodeficiency characterized by eczema, recurrent skin and lung infections, elevated serum IgE, and connective tissue and skeletal abnormalities. We present newly recognized aspects of the clinical phenotype and discuss recent genetic and immunologic findings. RECENT FINDINGS: In 2007, mutations in signal transducer and activator of transcription 3 (STAT3) were determined to be the cause of autosomal-dominant HIES. Mutations lead to disruption of STAT3-dependent pathways, which are crucial for signaling of many cytokines, including IL-6 and IL-10. On the one hand, cells from STAT3-defective patients have a proinflammatory profile with elevated TNFalpha and IFNgamma; on the other hand, STAT3 mutations result in the inability to produce IL-17 or form Th17 cells. SUMMARY: HIES was previously defined on the basis of clinical manifestations and laboratory markers that were not specific to the disease. With the identification of STAT3 mutations as the cause of HIES, we can definitively characterize the disease at molecular and immunologic levels. Future study of HIES and STAT3 will help us understand eczema, IgE regulation, infection susceptibility, coronary artery disease, scoliosis, and bronchiectasis as well as provide mechanistic insights into treatment.

CUTTING EDGE HIES:
Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, Kanno Y, Spalding C, Elloumi HZ, Paulson ML, Davis J, Hsu A, Asher AI, O'Shea J, Holland SM, Paul WE, Douek DC.
Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome.
Nature. 2008 Apr 10;452(7188):773-6. Epub 2008 Mar 12.
The autosomal dominant hyper-IgE syndrome (HIES, 'Job's syndrome') is characterized by recurrent and often severe pulmonary infections, pneumatoceles, eczema, staphylococcal abscesses, mucocutaneous candidiasis, and abnormalities of bone and connective tissue. Mutations presumed to underlie HIES have recently been identified in stat3, the gene encoding STAT3

(signal transducer and activator of transcription 3) (refs 3, 4). Although impaired production of interferon-gamma and tumour-necrosis factor by T cells, diminished memory T-cell populations, decreased delayed-type-hypersensitivity responses and decreased in vitro lymphoproliferation in response to specific antigens have variably been described, specific immunological abnormalities that can explain the unique susceptibility to particular infections seen in HIES have not yet been defined. Here we show that interleukin (IL)-17 production by T cells is absent in HIES individuals. We observed that ex vivo T cells from subjects with HIES failed to produce IL-17, but not IL-2, tumour-necrosis factor or interferon-gamma, on mitogenic stimulation with staphylococcal enterotoxin B or on antigenic stimulation with Candida albicans or streptokinase. Purified naive T cells were unable to differentiate into IL-17-producing (T(H)17) T helper cells in vitro and had lower expression of retinoid-related orphan receptor (ROR)-gammat, which is consistent with a crucial role for STAT3 signalling in the generation of T(H)17 cells. T(H)17 cells have emerged as an important subset of helper T cells that are believed to be critical in the clearance of fungal and extracellular bacterial infections. Thus, our data suggest that the inability to produce T(H)17 cells is a mechanism underlying the susceptibility to the recurrent infections commonly seen in HIES.

e. Clinical skills for diagnosis and treatment

REVIEW PRACTICE GUIDELINE Primary Immunodeficiency:
Bonilla F, Bernstein IL, Khan DA, et al.
Practice parameter for the diagnosis and management of primary immunodeficiency.
Ann Allergy Asthma Immunol, 2005;94:S1-63.
A principal aim of this Practice Parameter is to organize current knowledge and practice in the diagnosis and management of primary immunodeficiency diseases. Preparation of this Practice Parameter included a review of the medical literature, mainly via the PubMed database. Published clinical studies or reports were rated by category of evidence and used to establish the strength of a clinical recommendation. There are few randomized trials in the diagnosis and management of primary immunodeficiency. Thus, most of these recommendations represent evidence from published case series or reports or the opinions of experts in the field.

REVIEW:
Weiler CR. Bankers-Fulbright JL.
Common variable immunodeficiency: test indications and interpretations.
Mayo Clin Proc.2005; 80:1187-2000
Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder that can present with multiple phenotypes, all of which are characterized by hypogammaglobulinemia, in a person at any age. A specific genetic defect that accounts for all CVID phenotypes has not been identified, and it is likely that several distinct genetic disorders with similar clinical presentations are responsible for the observed variation. In this review, we summarize the known genetic mutations that give rise to hypogammaglobulinemia and how these gene products affect normal or abnormal B-cell development and function, with particular emphasis on CVID. Additionally, we describe specific phenotypic and genetic laboratory tests that can be used to diagnose CVID and provide guidelines for test interpretation and subsequent therapeutic intervention.

REVIEW:
Paul ME.
Diagnosis of immunodeficiency: clinical clues and diagnostic tests.

Curr Allergy Asthma Rep 2002. 2:349-55.
Recognition of immunodeficiency allows steps to be taken to minimize morbidity and mortality. Immunodeficiency can be secondary to viral infection, most importantly secondary to HIV-1 worldwide, medications, disruption of the usual infection clearance mechanisms, or secondary to a myriad of systemic disorders. Immunodeficiency may also be due to one of the growing list of primary immunodeficiency disorders. In infancy, lymphopenia should trigger an evaluation investigating the possibility of severe combined immunodeficiency. Evaluations of children should be done keeping in mind that normal numbers of lymphocytes are higher in children than in adults, immunoglobulin levels in children are lower than in adults in younger age groups, and antibody production in response to polysaccharide antigens is not usually fully developed in the less-than 2-year-old child.

REVIEW:
Tangsinmankong N. Bahna SL. Good RA.
The immunologic workup of the child suspected of immunodeficiency.
Ann Allergy Asthma Immunol 2001; 87: 362-9.
This review is intended to provide an outline for the evaluation of patients suspected of having immunodeficiency, a problem that is frequently encountered in clinical practice. DATA SOURCES: Information was obtained through a MEDLINE literature search as well as from standard textbooks in immunology. Also included is information that reflects the authors' clinical experience in the field. RESULTS: In general clinical practice, many physicians feel inadequate to evaluate patients with suspected immune deficiencies. They also think that the process of evaluation is time consuming, which results in misdiagnosis of a substantial percentage of such disorders. Hence, the prevalence of immunodeficiency disorders is much higher than generally thought. At present, there are >80 unique primary immunodeficiency conditions and >50 syndromes that are associated with various immunologic defects. The prevalence of secondary immunodeficiency has also been increasing because of the tragic epidemic of HIV infection, more usage of immunosuppressive medications and bone marrow stem cell transplantation, and the severe degree of malnutrition in underdeveloped countries. It is necessary for clinicians, particularly the specialists in allergy and immunology, to be able to evaluate the status of the immune system. CONCLUSIONS: Very valuable information can be gathered from the medical history and physical examination that may exclude or increase the suspicion of immunologic defect. Laboratory tests can then be appropriately selected to define the specific defect. Once the diagnosis has been settled, proper medical management can be instituted with subsequent improvement in morbidity and mortality of such disorders.

REVIEW:
Durandy A. Wahn V. Petteway S. Gelfand EW.
Immunoglobulin replacement therapy in primary antibody deficiency diseases--maximizing success.
Inter Archiv Allergy Immunol 2005; 136: 217-29.
Antibody or humoral immunodeficiencies comprise the largest group of primary immunodeficiency diseases. Since the first description of patients with low gammaglobulin levels more than four decades ago, a great wealth of information has been accumulated. Especially in the last several years, the application of molecular and genetic techniques has unraveled many of these disorders, identifying disorders of B cell development, failure of class switch recombination and

abnormalities of specific antibody production. Regardless of the underlying defect, the mainstay of therapy has been and remains immunoglobulin (Ig) replacement therapy, currently by intravenous infusion or subcutaneous injection. With advances in manufacturing, a number of products are not only safe for intravenous administration but doses can be increased to provide even more effective infection prophylaxis. However, manufacturing processes, methods of viral inactivation and removal and final composition differ widely among the available preparations. How these variables impact clinical outcome is not clear, but they have the potential to do so. As a result, careful selection of an intravenous immunoglobulin (IVIG), matching patient needs and risks to those risks associated with a specific IVIG, is necessary to optimize outcomes and maximize the success of Ig replacement therapy.

REVIEW PRACTICE GUIDELINE Use of IVIg:
Orange JS, Hossny EM , Weiler CR, et al.
Use of intravenous immunoglobulin in human disease: A REVIEW: of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology
J Allergy Clin Immunol 2006;117:S525-53.
Human immunoglobulin prepared for intravenous administration (IGIV) has a number of important uses in the treatment of disease. Some of these are in diseases for which acceptable treatment alternatives do not exist. In this review we have evaluated the evidence underlying a wide variety of IGIV uses and make specific recommendations on the basis of these data. Given the potential risks and inherent scarcity of IGIV, careful consideration of the indications for and administration of IGIV is warranted.

REVIEW:
Illoh OC.
Current applications of flow cytometry in the diagnosis of primary immunodeficiency diseases.
Arch Pathol Laboratory Med 2004;128:23-31.
To review the applications of flow cytometry in the diagnosis and management of primary immunodeficiency disease. DATA SOURCES: Articles describing the use of flow cytometry in the diagnosis of several primary immunodeficiency diseases were obtained through the National Library of Medicine database. STUDY SELECTION: Publications that described novel and known applications of flow cytometry in primary immunodeficiency disease were selected. Review articles were included. Articles describing the different immunodeficiency diseases and methods of diagnosis were also selected. DATA EXTRACTION: Approximately 100 data sources were analyzed, and those with the most relevant information were selected. DATA SYNTHESIS: The diagnosis of many primary immunodeficiency diseases requires the use of several laboratory tests. Flow cytometry has become an important part of the workup of individuals suspected to have such a disorder. Knowledge of the pathogenesis of many of these diseases continues to increase, hence we acquire a better understanding of the laboratory tests that may be helpful in diagnosis. CONCLUSIONS: Flow cytometry is applicable in the initial workup and subsequent management of several primary immunodeficiency diseases. As our understanding of the pathogenesis and management of these diseases increases, the use of many of these assays may become routine in hospitals.

REVIEW STEM CELL TRANSPLANTATION:
Filipovich A.
Hematopoietic cell transplantation for correction of primary immunodeficiencies.
Bone Marrow Transplant. 2008 Aug;42 Suppl 1:S49-S52.
The first hematopoietic cell transplants in humans with durable success were reported in 1968, in three patients with primary immunodeficiencies who received grafts from HLA-matched siblings (two with SCID and one with Wiskott-Aldrich syndrome). Significant progress has been made in correcting lethal primary immunodeficiencies (PIDs) with hematopoietic transplantation in the ensuing 40 years due to several factors: (1) ability to phenotype and quantitate (CD34+) hematopoietic stem cells, (2) advent of high-resolution tissue typing, (3) availability of closely matched unrelated donor bone marrow, peripheral blood stem cells, and cord blood, and (4) the application of reduced intensity conditioning regimens pre-transplant. Furthermore, the genetic basis of the majority of lethal PIDs has been defined, allowing more accurate studies of the natural history of the disorders without HCT intervention, and providing a compelling rationale for early transplantation in disorders with median survivals of 15-20 years. In the current era, we can identify several factors, which influence the ultimate success of HCT for PID. These include the age at transplant and general health of the patient. Young age is associated with fewer comorbidities and less frequent pre-transplant exposure to herpes family and enteric viruses, thus lowering the risks of related post-transplant complications. The careful selection of pre-transplant conditioning can significantly reduce early TRM in patients with certain immunodeficiencies, and increase the probability of durable engraftment in others. Because of the specific needs of children with PIDs, HCT from unrelated donors should, ideally, be performed in centers with extensive expertise and experience in the treatment of such disorders. In such centers, donor selection based on high-resolution tissue typing, younger age and specific viral immunity has led to survival rates following matched unrelated donor HCT for PIDs, which are very similar to those obtained with HCT from matched sibling donors. While ultimate success rates are similar, transplant-related management of children receiving unrelated grafts is considerably more complicated and prolonged than following matched sibling HCT.

2. Acquired immunodeficiency diseases

a. Due to infection, AIDS and other

REVIEW:
Sleasman JB, Goodenow MM
HIV-1 infection
J Allergy Clin Immunol 2003;111:S582-92.
This review is intended to provide a fundamental perspective on the dynamic interplay between HIV-1 and the immune system, an essential aspect in defining the pathogenesis and treatment of AIDS**.** HIV-1 infection, the cause of AIDS**,** is a worldwide pandemic with enormous adverse health and economic implications, particularly in the developing world. This bloodborne and sexually transmitted disease, which evolved from simian immunodeficiency virus, infects and replicates in helper T cells and macrophages and utilizes CD4 and a chemokine coreceptor for entry. Immune deficiency occurs as a result of virally induced attrition of CD4 T cells, resulting in the development of opportunistic infections and malignancy. Prophylaxis against opportunistic infections is required according to the extent of immune deficiency. HIV-specific immunity can control viral replication and delay disease progression but does not clear infection. Antiretroviral

treatment consists of inhibitors that target for viral entry, reverse transcriptase, and viral protease. Therapy can control viral replication, restore immunity, and delay disease progression, but it cannot eliminate infection. Thus chronic infection persists even in treated patients. Antiretroviral drugs have been highly effective in preventing mother-to-child transmission and for postexposure prophylaxis. Several novel vaccines in development hold promise for either effective infection prevention or attenuation of disease progression.

REVIEW:
Ambinder RF.
Epstein-Barr virus-associated lymphoproliferative disorders.
Rev Clin Exp Hematol. 2003 :362-74
Epstein-Barr virus (EBV) is a ubiquitous member of the herpesvirus family that is associated with a variety of lymphomas and lymphoproliferative diseases. It encodes a multitude of genes that drive proliferation or confer resistance to cell death. Among these are two key viral proteins which mimic the effects of the activated cellular signaling proteins. EBV-associated lymphomas include Burkitt's lymphoma; natural killer (NK)/T-cell lymphoma, lymphoma and lymphoproliferative diseases in immunocompromized populations, and Hodgkin's lymphoma. The character of the viral association differs among these entities with some consistently associated with EBV in all populations and all parts of the world, and others associated with the virus only in particular circumstances. An example of the former is nasal NK/T-cell lymphoma, while an example of the latter is Burkitt's lymphoma. The pattern of viral gene expression also varies among tumor types with different viral genes playing key roles in different tumors and conferring sensitivity to immune surveillance. Thus some of the post-transplant lymphoproliferative diseases are exquisitely sensitive to CD8 T-cell immunosurveillance, while other tumors such as Burkitt's lymphoma may be nearly impervious to such surveillance. Knowledge of the EBV association is not only important for understanding the pathogenesis of these tumors, but is increasingly important for diagnosis, monitoring and treatment.

REVIEW:
Rouse BT, Sarangi PP, Suvas S
Regulatory T cells in virus infections.
Immunol Rev. 2006 Aug; 212:272-86
This review discusses situations when the magnitude and function of immune responses to virus infection are influenced by regulatory T cells (Tregs). The focus is on CD4+ CD25+ forkhead box protein 3+ natural Tregs (nTregs). The immune response may be limited in magnitude and efficacy when animals with normal nTreg function are infected with virus. This limitation can be observed both in vitro and in vivo. In the case of herpes simplex virus (HSV), animals depleted of nTregs prior to infection more effectively control the virus. With some virus infections, Treg responses (either nTregs or interleukin-10-dependent adaptive Tregs) appear to contribute to immune dysfunction, accounting for viral persistence and chronic tissue damage. This may occur with hepatitis C virus and some retrovirus infections that include human immunodeficiency virus (HIV). Under other circumstances, the nTreg response is judged to be beneficial, as it may help limit the severity of tissue damage associated with an immunoinflammatory reaction to virus infection. Such a situation occurs in HSV-induced immunopathological lesions in the eye. With HIV, nTregs may help limit chronic immune activation that may precede collapse of the immune system. This review also discusses how virus infections become recognized by nTreg responses

and how such responses might be manipulated to increase immunity or to limit virus-induced immunopathology

REVIEW:
Hammer, SM, Eron JJ, Reiss P et al.
Antiretroviral Treatment of Adult HIV Infection: 2008 Recommendations of the International AIDS Society USA Panel. JAMA 2008; 300(5): 555-570.
This review highlights the rapidly changing landscape of HIV therapy. It covers appropriate drug choices, timing of therapy, and optical use of medications. It serves as a useful document to refer to when caring for patients with HIV/AIDS

REVIEW:
Ohshima K.
Pathological features of diseases associated with human T-cell leukemia virus type 1. Cancer Sci 2007; 98(6): 772-8.
HTLV-1 was the first human retrovirus discovered in the early 1980's and has been associated with the development of malignancy: adult T-cell leukemia/lymphoma. In addition, it is associated with immunodeficiency resulting in opportunistic infections. This review covers the features of this infection and the different pathological conditions which can occur.

b. Nutrition and metabolic related

REVIEW:
Cunningham Rundles. C
Mechanisms of nutrient modulation of the immune response
J Allergy Clin Immunol 2005;115:1119-1128
Lack of adequate macronutrients or selected micronutrients, especially zinc, selenium, iron, and the antioxidant vitamins, can lead to clinically significant immune deficiency and infections in children. Undernutrition in critical periods of gestation and neonatal maturation and during weaning impairs the development and differentiation of a normal immune system. Infections are both more frequent and more often become chronic in the malnourished child. Recent identification of genetic mechanisms is revealing critical pathways in the gastrointestinal immune response. New studies show that the development of tolerance, control of inflammation, and response to normal mucosal flora are interrelated and linked to specific immune mechanisms. Nutrients act as antioxidants and as cofactors at the level of cytokine regulation. Protein calorie malnutrition and zinc deficiency activate the hypothalamic-pituitary-adrenal axis. Increased circulating levels of glucocorticoids cause thymic atrophy and affect hematopoiesis. Chronic undernutrition and micronutrient deficiency compromise cytokine response and affect immune cell trafficking. The combination of chronic undernutrition and infection further weakens the immune response, leading to altered immune cell populations and a generalized increase in inflammatory mediators. Obesity caused by excess nutrition or excess storage of fats relative to energy expenditure is a form of malnutrition that is increasingly seen in children. Leptin is emerging as a cytokine-like immune regulator that has complex effects in both overnutrition and in the inflammatory response in malnutrition. Because the immune system is immature at birth, malnutrition in childhood might have long-term effects on health.

REVIEW:

Kim CH. Regulation of FoxP3+ Regulatory T Cells and Th 17 cells by retinoids. Clin Dev Immunol. 2008; 1-12.
Vitamin A has both positive and negative regulatory functions in the immune system. Vitamin A is critical for the development of normal immune cells and epithelial cell barriers. Vitamin A deficiency can lead to inflammation. This review looks at the role of retinoids in the generation of immune-suppressive FoxP3+ regulatory T cells which they suppress the T cell differentiation into pro-inflammatory Th17 T cells in such sites as the intestine. The review also looks at Fox P3+ T cells in immune tolerance.

c. Associated with malignancy and infectious processes

REVIEW:
Schwartz RS
Immunodeficiency, Immunosuppression, and Susceptibility to Neoplasms
J Natl Cancer Inst Monogr. 2001;28:5-9
A review of the association of altered immune function and the risk of malignancy.

REVIEW:
Ambinder RF.
Epstein-Barr virus-associated lymphoproliferative disorders.
Rev Clin Exp Hematol. 2003 :362-74
Epstein-Barr virus (EBV) is a ubiquitous member of the herpesvirus family that is associated with a variety of lymphomas and lymphoproliferative diseases. It encodes a multitude of genes that drive proliferation or confer resistance to cell death. Among these are two key viral proteins which mimic the effects of the activated cellular signaling proteins. EBV-associated lymphomas include Burkitt's lymphoma; natural killer (NK)/T-cell lymphoma, lymphoma and lymphoproliferative diseases in immunocompromized populations, and Hodgkin's lymphoma. The character of the viral association differs among these entities with some consistently associated with EBV in all populations and all parts of the world, and others associated with the virus only in particular circumstances. An example of the former is nasal NK/T-cell lymphoma, while an example of the latter is Burkitt's lymphoma. The pattern of viral gene expression also varies among tumor types with different viral genes playing key roles in different tumors and conferring sensitivity to immune surveillance. Thus some of the post-transplant lymphoproliferative diseases are exquisitely sensitive to CD8 T-cell immunosurveillance, while other tumors such as Burkitt's lymphoma may be nearly impervious to such surveillance. Knowledge of the EBV association is not only important for understanding the pathogenesis of these tumors, but is increasingly important for diagnosis, monitoring and treatment.

REVIEW:
Pratt G, Goodyear O and Moss P. Immunodeficiency and immunotherapy in multiple myeloma.
Br. J Haematol. 2007; 138(5): 563-79.
Multiple myeloma is a malignant tumor of plasma cells that remains incurable for the vast majority of patients, with a median survival of 2-3 years. It is characterized by the patchy accumulation of tumor cells within bone marrow leading to variable anemia, bone destruction, hypercalcemia, renal failure and infections. Immune dysfunction is an important feature of the disease and leads to infections that are both a major cause of morbidity and mortality and may promote tumor growth

and resistance to chemotherapy. Numerous defects of the immune system have been described in multiple myeloma although the relative clinical importance of these remains elusive. There has been considerable interest in the identification of an autologous response against myeloma. Although T cells and humoral responses directed against myeloma-associated antigens have been described, it is uncertain if the immune system plays a role in preventing or controlling myeloma cell growth. There is increasing interest in the potential role of immunotherapy but the success of these interventions is likely to be modified by the immunologically hostile environment associated with multiple myeloma. This review attempts to summarize the current knowledge relating to the immune defects found in multiple myeloma.

d. Iatrogenic immunodeficiency

REVIEW:
Nelson RP, Ballow M
Immunomodulation and Immunotherapy: Drugs, Cytokines, Cytokine Receptors, and Antibodies
J Allergy Clin Immunol 2003; 111: S720-32.
The preceding chapters in this primer have provided an overview of the immune response that serves as a background for understanding potential sites for immune modulation and immunotherapy. A number of soluble growth and activation factors are released from various cell populations involved in the immune response. They play vital roles in the initiation, propagation, and regulation of immunologic responses. Pharmacologic immunomodulators include suppressive and stimulatory agents. Immunosuppressive therapies include antimetabolites, cytotoxic drugs, radiation, adrenocortical glucocorticosteroids, immunophilins, and therapeutic antibodies. The field of clinical immunostimulation is emerging as an important therapeutic modality for a number of immunodeficiency diseases, chronic viral infections, and cancer. These compounds will be discussed in terms of general principles, molecular targets, major indications, and adverse effects.

REVIEW:
Giovanbattista I, Mauro R, . Pellegrini C et al.
Incidence of cancer after immunosuppressive treatment for heart transplantation.
Crit Rev Oncol Hematol. 2005;56:101-13.
Prolonged or intensive immunosuppressive therapy used after organ transplantation is complicated by an increased incidence of cancer. Striking differences in incidence are observed in heart and heart-lung transplant recipients when compared with renal transplant patients. The most significant increase was in the incidence of lymphomas in cardiac versus renal patients. Moreover, a two-fold greater increase of all neoplasms was found in cardiac recipients, with nearly a six-fold increase in visceral tumors. Several factors may account for these differences. In cardiac allograft recipients, intensive immunosuppression is frequently used to reverse acute rejection and the highest number of cardiac transplants was performed in the era of polypharmacy, usually consisting of triple therapy.

REVIEW:
Koo S, Baden LR.
Infectious complications associated with immunomodulating monoclonal antibodies used in the treatment of hematologic malignancy.
J Natl Compr Cancer Netwk 2008 (2): 202-13.

Review of the literature with regards to infectious complications with immuno-suppressive therapies.

e. Clinical skills for diagnosis and treatment

NOTE: HIV related immunodeficiency: HIV related evaluation and treatment is frequently updated. For the most recent CDC recommendations in regard to the evaluation and treatment visit the website:
www.cdc.gov/hiv/resources/guidelines/index.htm

NOTE: **Non HIV-related immunodeficiency:** Evaluation of immune system function is similar in primary and secondary immunodeficiency disorders and methods for systematic evaluation can be found in the following reviews:

REVIEW Diagnosis of Immunodeficiency:
Ballow M.
Approach to the Patient with Recurrent Infections.
Clinic Rev Allerg Immunol 2008; 34:129-140.
This is comprehensive review to the work up of children with recurrent infections including the more recently described immunodeficiencies.

REVIEW PRACTICE GUIDELINE Primary Immunodeficiency:
Bonilla F, Bernstein IL,Khan DA, et al.
Practice parameter for the diagnosis and management of primary immunodeficiency.
Ann Allergy Asthma Immunol, 2005;94:S1-63.
A principal aim of this Practice Parameter is to organize current knowledge and practice in the diagnosis and management of primary immunodeficiency diseases. Preparation of this Practice Parameter included a review of the medicalliterature, mainly via the PubMed database. Published clinical studies or reports were rated by category of evidence and used to establish the strength of a clinical recommendation. There are few randomized trials in the diagnosis and management of primary immunodeficiency. Thus, most of these recommendations represent evidence from published case series or reports or the opinions of experts in the field.

REVIEW PRACTICE GUIDELINE Use of IVIg:
Orange JS, Hossny EM , Weiler CR, et al.
Use of intravenous immunoglobulin in human disease
J Allergy Clin Immunol 2006;117:S525-53.
Human immunoglobulin prepared for intravenous administration (IGIV) has a number of important uses in the treatment of disease. Some of these are in diseases for which acceptable treatment alternatives do not exist. In this review we have evaluated the evidence underlying a wide variety of IGIV uses and make specific recommendations on the basis of these data. Given the potential risks and inherent scarcity of IGIV, careful consideration of the indications for and administration of IGIV is warranted.

C. Immunoregulatory Disorders Interpretation of physical findings, diagnostic tests and management of:

1. The Vasculitides (Small, Medium and Large vessels)

REVIEW:
Jennette JC, Falk RJ
REVIEW: Article: Small Vessel Vasculitis
N Engl J Med. 1997; 337(21):1512-23
Excellent and still relevant review article on Small-vessel vasculitis.
Comment in:
N Engl J Med. 1998 Apr 2;338(14):994-5.

REVIEW:
Weyand CM. Gorozny JJ
Medium- and large-vessel vasculitis
N Engl J Med 2003;349:160-9
Despite differences in presentation and the clinical course, giant-cell arteritis, polymyalgia rheumatica, and Takayasu's arteritis share many pathogenic principles, and similar rules apply in the diagnostic and therapeutic approaches. The following discussion of pathogenic pathways will focus mostly on giant-cell arteritis, a reflection of the accessibility of inflamed vascular tissue that has facilitated mechanistic studies.

REVIEW:
Narula N, Gupta S, Narula J
The primary vasculitides: a clinicopathologic correlation.
Am J Clin Pathol. 2005;124 :S84-95
Primary vasculitis is the inflammation and necrosis of vessel walls not associated with infections, drugs, and autoimmune and lymphoproliferative disorders. It is important to make the correct diagnosis of different types of vasculitis, as their prognosis may be significantly different. classification of vasculitis based on the size of the vessel is helpful, but there is often an overlap. Whereas the criteria proposed by the American College of Rheumatology are primarily clinical, the definitions set forth by the Chapel Hill Consensus Conference are based only on histologic observations. Correct diagnosis requires appropriate incorporation of the clinical history, laboratory parameters, and the histologic data. Incorporation of antineutrophil cytoplasmic antibodies in defining the pathogenesis of vasculitis has been particularly useful in diagnosing those small vessel vasculitides that are life threatening and need immediate intervention.

REVIEW Vasculitis diagnostic tests:
Bosch X, Guilabert A, Font J.
Antineutrophil cytoplasmic antibodies
Lancet. 2006;368:404-18
Much like other autoantibodies (eg, anti-double stranded DNA in systemic lupus erythematosus or antiglomerular basement membrane antibodies in Goodpasture's syndrome), antineutrophil cytoplasmic antibodies (ANCA) have provided doctors with a useful serological test to assist in diagnosis of small-vessel vasculitides, including Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, and their localised forms (eg, pauci-immune necrotizing and crescentic glomerulonephritis). 85-95% of patients with Wegener's granulomatosis, microscopic polyangiitis, and pauci-immune necrotising and crescentic glomerulonephritis have

serum ANCA. ANCA directed to either proteinase 3 or myeloperoxidase are clinically relevant, yet the relevance of other ANCA remains unknown. Besides their diagnostic potential, ANCA might be valuable in disease monitoring. In addition, data seem to confirm the long-disputed pathogenic role of these antibodies. Present treatments for ANCA-associated vasculitis are not free from side-effects and as many as 50% of patients relapse within 5 years. Accurate understanding of the key pathogenic points of ANCA-associated vasculitis can undoubtedly provide a more rational therapeutic approach.

REVIEW:
Chung SA, Seo P
Advances in the use of biologic agents for the treatment of systemic vasculitis
Curr Opin Rheumatol. 2009 Jan;21(1):3-9
PURPOSE OF REVIEW: Due to the well known toxicities of cyclophosphamide, substantial interest exists in finding other therapies to treat primary systemic vasculitis. Biologic agents have been proposed as an alternative to cyclophosphamide for these disorders because of their recent success in treating other rheumatic diseases. This article reviews the current state-of-the-art therapy with regards to the use of biologic agents as treatments for systemic vasculitis. RECENT FINDINGS: The greatest amount of experience with these agents for the treatment of systemic vasculitis is with antitumor necrosis factor agents, pooled intravenous immunoglobulin, and anti-B-cell therapies such as rituximab. Intravenous immunoglobulin is already a standard therapy for Kawasaki's disease, but should also be considered for the treatment of vasculitis associated with antineutrophil cytoplasmic antibodies when standard therapies are either ineffective or contraindicated. Early experience with tumor necrosis factor inhibitors indicates that they may be effective for the treatment of Takayasu's arteritis, but their role in the treatment of other forms of vasculitis remains controversial. Early experience with rituximab for the treatment of several forms of vasculitis has been quite promising, but must be confirmed by ongoing randomized clinical trials. SUMMARY: Biologic agents represent the next evolution in treatment for the primary systemic vasculitides. Greater understanding of these diseases has allowed us to move further away from nonspecific, highly toxic therapies toward a more directed approach. As our experience with these agents increases, they will likely form the keystone of treatment in the near future.

REVIEW:
Phillip R, Luqmani R
Clin Exp Rheumatol. 2008 Sep-Oct;26(5 Suppl 5):S94-104
Mortality in systemic vasculitis: a systematic review.
There has been a considerable improvement in the survival of patients with systemic vasculitis since the introduction of immunosuppressive therapy and improved diagnostic tools to allow earlier diagnosis. We review the published literature on current risk of mortality in patients with small vessel antineutrophil cytoplasm antibody- (ANCA) associated vasculitis including Wegener's granulomatosis (survival rate of approximately 75% at 5 years), microscopic polyangiitis (survival rate of 45% to 75% at 5 years), Churg-Strauss syndrome (survival rate of 68% to 100% at 5 years), and Henoch-Schönlein purpura (survival rate of 75% in adult-onset, greater in childhood onset); medium vessel vasculitis including polyarteritis nodosa (survival rate of 75% to 80% at 5 years), Kawasaki disease (survival rate of greater than 99% at 5 years); large vessel vasculitis including giant cell arteritis (survival rate equivalent to the age-matched

population), and Takayasu arteritis (survival of 70% to 93% at 5 years). Mortality rates are falling as a result of more effective intervention but remain elevated substantially in severe disease. Early deaths are usually attributable to active vasculitis with multiorgan failure or infection, or both. The incidence of late deaths may be increased by long-term effects of therapy and development of comorbidities. These findings highlight the need to improve early diagnosis and initiation of targeted therapy, thereby reducing treatment-related toxicity and comorbidities.

REVIEW Pediatric Vasculitis:
Dhillon MJ
Childhood vasculitis.
Lupus. 1998;7(4):259-65
Vasculitis can and does occur in childhood. Apart from the relatively common vasculitides (Henoch-Schonlein purpura, Kawasaki disease and in world wide terms Takayasu disease) there are a number of important but comparatively rare disorders affecting children. These include macroscopic and microscopic polyarteritis, cutaneous polyarteritis, Wegener's granulomatosis, Churg-Strauss syndrome, primary angiitis of the central nervous system, hypersensitivity angiitis, hypocomplimentaemic urticarial vasculitis, vasculitis associated with various connective tissue disorders and vasculitis associated with conditions such as Behcets syndrome, familial Mediterranean fever and Cogan's syndrome. Distinguishing these conditions from other disorders is often difficult and requires clinical acumen and appropriate investigative procedures. With modern therapeutic agents, it is possible to implement appropriate therapy but in spite of this, there remains a not inconsequential morbidity and mortality.

REVIEW:
Zwerina J, Eger G, Englbrecht M, Manger B, Schett G.
Churg-Strauss Syndrome in Childhood: A Systematic Literature Review and Clinical Comparison with Adult Patients.
Semin Arthritis Rheum. 2008 Jul 16. [Epub ahead of print]
OBJECTIVE: To describe the clinical characteristics of children with Churg-Strauss syndrome (CSS) in comparison with adult patients. MATERIALS AND METHODS: A systematic literature analysis was performed in the Medline database up to November 2007 and in rheumatology and pulmonology meeting scientific abstracts 2003-2007. Articles with reported childhood CSS cases were retrieved; clinical data were recorded. Descriptive statistical analyses and a comparison with 2 published adult CSS cohorts were performed. RESULTS: Thirty-three cases of childhood CSS were identified. The mean age was 12 years and the male-to-female ratio was 0.74. All patients had significant eosinophilia and asthma. Histological evidence of eosinophilia and/or vasculitis was present in virtually all patients. Antineutrophil cytoplasmic antibodies were found in 25% of children with CSS. Initial treatment was corticosteroid monotherapy in 76% of childhood CSS patients, while 24% received additional immunosuppressive therapy. Another 18% required further immunosuppression at follow-up due to frequent relapses. Six deaths (18%), all related to the underlying disease, occurred after a mean disease duration of 14 months. As compared with adult CSS patients, children had a predominance of cardiopulmonary disease manifestations, a lower rate of peripheral nerve involvement, and higher mortality. CONCLUSIONS: Many aspects of CSS are similar in childhood and adult patients. However, pulmonary and cardiac involvement is predominant in pediatric CSS and mortality is substantial.

REVIEW:
Weiss PF, Feinstein JA, Luan X, Burnham JM, Feudtner C.
Effects of corticosteroid on Henoch-Schönlein purpura: a systematic review.
Pediatrics. 2007 Nov;120(5):1079-87.

Comment in:
Pediatrics. 2008 Apr;121(4):870-1; author reply 871-2.
OBJECTIVE: No consensus exists among general pediatricians or pediatric rheumatologists regarding whether corticosteroid therapy ameliorates the acute manifestations of Henoch-Schönlein purpura or mitigates renal injury. Therefore, we sought to synthesize the reported experimental and observational data regarding corticosteroid use. METHODS: We performed a meta-analysis based on a comprehensive review of the literature in the Medline database (1956 to January 2007) and the Cochrane Controlled Trials Register. On the basis of reported outcomes among patients with Henoch-Schönlein purpura who were treated at diagnosis with corticosteroids compared with patients treated with supportive care only, we calculated odds ratios for the resolution of abdominal pain, the need for surgical intervention secondary to severe pain or intussusception, the likelihood of Henoch-Schönlein purpura recurrence, and the development of transient or persistent renal disease. RESULTS: Of 201 articles retrieved from the initial literature search, 15 were eligible for inclusion. Corticosteroid treatment did not reduce the median time to resolution of abdominal pain but did significantly reduce the mean resolution time and increased the odds of resolution within 24 hours. Early corticosteroid treatment significantly reduced the odds of developing persistent renal disease. In addition, although the results were not statistically significant, the prospective data suggest reduced odds of both surgical intervention and recurrence. CONCLUSIONS: Corticosteroids, given early in the course of illness, seem to produce consistent benefits for several major clinically relevant Henoch-Schönlein purpura outcomes.

REVIEW:
Akikusa JD, Schneider R, Harvey EA, et al
Clinical features and outcome of pediatric Wegener's granulomatosis
Arthritis Rheum. 2007 15;57(5):837-44
OBJECTIVE: Wegener's granulomatosis (WG) is a predominantly small-vessel vasculitis associated with antineutrophil cytoplasmic antibodies (ANCAs). There are few reports describing its clinical features and outcome in children. We report on the experience at a single tertiary referral center over 21 years. METHODS: We conducted a retrospective chart review of all patients diagnosed with WG at The Hospital for Sick Children between 1984 and 2005. RESULTS: Twenty-five patients were identified. Median age at diagnosis and median followup were 14.5 years and 32.7 months, respectively. Male-to-female ratio was 1:4. Median duration of symptoms before diagnosis was 2 months. Of 22 patients, 21 were ANCA positive during their disease course (classic ANCA 78.9%). Constitutional symptoms were the most common clinical feature at presentation (24 of 25). Glomerulonephritis was present in 22 patients at presentation. Only 1 of 11 patients who presented with or developed renal impairment had normalization of serum creatinine. Upper airway involvement occurred in 21 patients at presentation and 24 over followup; only 1 had subglottic stenosis. Twenty patients had initial pulmonary involvement, most commonly nodules (44%) and pulmonary hemorrhage (44%). Five patients required ventilation for pulmonary hemorrhage. Four patients (16%) had venous thrombotic events (VTEs). Treatment included prednisone (100%), cyclophosphamide (76%), azathioprine (40%), and methotrexate

(32%). CONCLUSION: Pediatric WG typically presents in adolescence and has a female predominance. Glomerulonephritis and pulmonary disease are common at diagnosis and frequently present as a pulmonary-renal syndrome. Loss of renal function is common and rarely completely reversible. As in adults, children with WG are at risk of VTEs.

2. Immune rheumatic disorders

REVIEW:
Davidson A., Diamond B.
Advances in Immunology: Autoimmune Diseases
N Engl J Med 2001; 345:340-350
Autoimmune diseases, with the exception of rheumatoid arthritis and autoimmune thyroiditis, are individually rare, but together they affect approximately 5 percent of the population in Western countries. They are a fascinating but poorly understood group of diseases. In this review, we define an autoimmune disease as a clinical syndrome caused by the activation of T cells or B cells, or both, in the absence of an ongoing infection or other discernible cause. We will discuss a classification of autoimmune disease that distinguishes diseases caused by generalized defects in lymphocyte selection or homeostasis from those caused by aberrant responses to particular antigens. We will consider genetic susceptibility to autoimmune disease, environmental and internal triggers of autoreactivity, changes in pathologic processes as the disease progresses, and multiple mechanisms of tissue injury, and we will conclude with a survey of new therapeutic approaches.

REVIEW:
Lee, SJ. Kavanaugh, A
Autoimmunity, vasculitis, and autoantibodies
J Allergy Clin Immunol. 2006; 117:S445-50
Autoimmune diseases are distinct clinical syndromes characterized by various alterations in normal immune responsiveness, such that there is a loss of tolerance to particular host constituents. In most cases, despite years of intense investigation, the etiopathogenic antigens initiating these systemic inflammatory conditions remain undefined. However, a great deal has been learned about the changes in components of the immune response relevant to the propagation and sustenance of these often chronic disorders. In addition, various hormonal, environmental, physiologic, and other influences that affect their expression have been identified. The expression and ultimate clinical outcome of autoimmune diseases usually relate to inflammation-related damage to the target organ with subsequent dysfunction. Certain immune conditions, such as autoimmune thyroid disease, largely affect a single organ, whereas others, such as systemic lupus erythematosus, heterogeneously affect sundry organ systems. Autoantibodies directed against normal host antigens are a common feature of many autoimmune diseases. In some cases they are pathogenic, whereas in others they serve as markers for organ involvement or outcomes. Clinical descriptions of autoimmune diseases date back many decades in some cases. Recent efforts at formulating classification criteria have allowed clearer distinctions and more accurate stratification. Greater understanding of the immunopathogenesis of autoimmune conditions has led to the development and introduction into the clinic of novel immunomodulatory therapies and treatment paradigms that have substantially improved the outcomes for patients affected by these serious conditions.

REVIEW:

Schmerling RH
Diagnostic tests for rheumatic disease: clinical utility revisited
South Med J. 2005; 98:704-11
Establishing a diagnosis of systemic rheumatic disease requires an integration of a patient's symptoms, physical examination findings, and the results of diagnostic testing. There is often a temptation by clinicians to rely heavily on objective measures such as the presence or absence of an autoantibody. Medical textbooks and the medical literature may overestimate the diagnostic utility of many commonly ordered tests for rheumatic disease because the tests are usually analyzed among patients with established rheumatic disease rather than among patients with an uncertain cause of symptoms as is common in practice. Few diagnostic tests are highly sensitive, though the antinuclear antibody in systemic lupus erythematosus (SLE) and the erythrocyte sedimentation rate in temporal arteritis are notable exceptions. Conversely, few diagnostic tests are highly specific; anti-proteinase-3 and antimyeloperoxidase antibodies (types of antineutrophilic cytoplasmic antibodies) among patients with Wegener granulomatosis (and related vasculitides) and anti-double-stranded and anti-Smith antibodies among patients with SLE may be particularly helpful in the proper clinical settings due to their high specificity. Anticitrullinated cyclic protein (anti-CCP), a newly described autoantibody that may be highly specific for rheumatoid arthritis, requires additional study as its utility in clinical practice is uncertain.

THERAPY REVIEW:
Scott D.L., Kingsley G.H.
Tumor Necrosis Factor Inhibitors for Rheumatoid Arthritis
N Engl J Med 2006; 355:704-712
Rheumatoid arthritis developed in a 25-year-old woman, who was found to have a positive rheumatoid factor (150 IU per milliliter); she had no periarticular radiologic erosions or extraarticular disease. Oral methotrexate was started and incrementally increased to 20 mg weekly. Subsequently, sulfasalazine (Salazotyrin, Pharmacia; Azulfidine, Pfizer) was added and gradually increased to 2 g daily. Despite six months of combination therapy, she had 10 swollen and tender joints and an elevated erythrocyte sedimentation rate (54 mm per hour). Twelve months after onset, we were asked to evaluate her for possible tumor necrosis factor (TNF) inhibitor therapy.

RESEARCH FRONTIER:
Camps M, Ruckle T, Ji H, et al.
Blockade of PI3Kγ suppresses joint inflammation and damage in mouse models of rheumatoid arthritis.
Nat Med 2005;11:936-43.
Phosphoinositide 3-kinases (PI3K) have long been considered promising drug targets for the treatment of inflammatory and autoimmune disorders as well as cancer and cardiovascular diseases. But the lack of specificity, isoform selectivity and poor biopharmaceutical profile of PI3K inhibitors have so far hampered rigorous disease-relevant target validation. Here we describe the identification and development of specific, selective and orally active smallmolecule inhibitors of PI3Kgamma (encoded by Pik3cg). We show that Pik3cg(-/-) mice are largely protected in mouse models of rheumatoid arthritis; this protection correlates with defective neutrophil migration, further validating PI3Kgamma as a therapeutic target. We also describe that oral treatment with a PI3Kgamma inhibitor suppresses the progression of joint inflammation and damage in two distinct mouse models of rheumatoid arthritis, reproducing the protective effects

shown by Pik3cg(-/-) mice. Our results identify selective PI3Kgamma inhibitors as potential therapeutic molecules for the treatment of chronic inflammatory disorders such as rheumatoid arthritis.

RESEARCH FRONTIER:
Albana S, Prakken B
T Cell Epitope–Specific Immune Therapy for Rheumatic Diseases
Arthritis Rheum 2006; 54:19–25
The dramatic progress gained in molecular immunology has enabled the evolution from traditional pharmacologic strategies of aggressive immune suppression to biologic-based therapies aimed at addressing the pathophysiologic process more directly. So far, the greatest progress has been achieved in the area of controlling individual cytokine pathways that contribute to rheumatoid inflammation. In particular, biologic agents aimed at interfering with tumor necrosis factor (TNF), interleukin-1 (IL-1), and, more recently, IL-6 have been very successful in various clinical settings None of those strategies, however, induces a sustained remission, and therefore none can fully restore homeostasis to the immune system. Consequently, lifelong treatment with such agents is necessary, which entails considerable costs and increases the risk of long-term side effects. Rising awareness of these problems has created a consensus on the need for a therapeutic strategy that will capitalize more comprehensively on our understanding of the immunopathology of rheumatic diseases. In particular, pathways leading to adaptive autoimmunity need to be better exploited. Ideally, such approaches should be crafted so that they are complementary to the current cytokine-directed therapies. We will discuss herein the current status of therapeutic strategies aimed at correcting T cell–mediated inflammation. In particular, we will discuss our perspective regarding a T cell epitope– specific approach to restoration of naturally occurring mechanisms that modulate inflammation.

REVIEW:
Cope AP
T cells in rheumatoid arthritis
Arthritis Res Ther. 2008;10 Suppl 1:S1. Epub 2008 Oct 15
Over the past decade and a half, advances in our understanding of the pathogenesis of immune-mediated diseases such as rheumatoid arthritis (RA) have translated directly into benefit for patients. Much of this benefit has arisen through the introduction of targeted biological therapies. At the same time, technological advances have made it possible to define, at the cellular and molecular levels, the key pathways that influence the initiation and persistence of chronic inflammatory autoimmune reactions. As our understanding grows, it is likely that this knowledge will be translated into a second generation of biological therapies that are tailor-made for the patient. This review summarizes current perspectives on RA disease pathogenesis, with particular emphasis on what RA T cells look like, what they are likely to see, and how they contribute to persistence of the chronic inflammatory response.

REVIEW:
Hügle T, van Laar JM.
Stem cell transplantation for rheumatic autoimmune diseases.
Arthritis Res Ther. 2008;10(5):217. Epub 2008 Oct 10.

Immunoablative therapy and hematopoietic stem cell transplantation (HSCT) is an intensive treatment modality aimed at 'resetting' the dysregulated immune system of a patient with immunoablative therapy and allow outgrowth of a nonautogressive immune system from reinfused hematopoietic stem cells, either from the patient (autologous HSCT) or a healthy donor (allogeneic HSCT). HSCT has been shown to induce profound alterations of the immune system affecting B and T cells, monocytes, and natural killer and dendritic cells, resulting in elimination of autoantibody-producing plasma cells and in induction of regulatory T cells. Most of the available data have been collected through retrospective cohort analyses of autologous HSCT, case series, and translational studies in patients with refractory autoimmune diseases. Long-term and marked improvements of disease activity have been observed, notably in systemic sclerosis, systemic lupus erythematosus, and juvenile idiopathic arthritis, and treatment-related morbidity and mortality have improved due to better patient selection and modifications of transplant regimens. Treatment-related mortality has decreased to approximately 7%. Prospective, randomised, controlled clinical trials are ongoing or planned in systemic sclerosis, systemic lupus erythematosus, and several non-rheumatological conditions.

REVIEW:
Rhodes B, Vyse TJ.
The genetics of SLE: an update in the light of genome-wide association studies.
Rheumatology (Oxford). 2008 Nov;47(11):1603-11. Epub 2008 Jul 8.
Understanding the pathogenesis of SLE remains a considerable challenge. Multiple abnormalities of both the innate and adaptive immune system have been described and, furthermore, immunological dysfunction precedes clinical presentation by many years. There is a strong genetic basis to SLE, which means that genetic studies can play a key role in furthering our understanding of this disease. Since susceptibility variants are present from birth and are unaffected by the course of the disease, or by its treatment, genetic analysis is, perhaps uniquely, capable of identifying fundamental, causative, disease mechanisms. Over the last 12 months, there has been a staggering increase in our understanding of SLE genetics. We have seen the identification of new and important SLE susceptibility genes through candidate gene studies, and we have seen the publication of two whole-genome association analyses. The 'hypothesis free' whole-genome studies have provided additional evidence in support of a number of existing susceptibility genes and have identified novel gene candidates. In this article, we review the current SLE genetics literature in the light of these recent advances and we discuss our current understanding of the functional role of the key susceptibility genes. By considering how these genes fall into clusters with shared function we can begin to understand how dysregulation at a number of key immunological steps may predispose to the development of SLE.

3. Immune renal disorders

REVIEW:
Nangaku M, Mouser WG.
Mechanisms of immune-deposit formation and the mediation of immune renal injury.
Clin Exp Nephrology 2005;9:183-91
The passive trapping of preformed immune complexes is responsible for some forms of glomerulonephritis that are associated with mesangial or subendothelial deposits. The biochemical characteristics of circulating antigens play important roles in determining the biologic activity of immune complexes in these cases. Examples of circulating immune complex diseases include the

classic acute and chronic serum sickness models in rabbits, and human lupus nephritis. Immune deposits also form "in situ". In situ immune deposit formation may occur at subepithelial, subendothelial, and mesangial sites. In situ immune-complex formation has been most frequently studied in the Heymann nephritis models of membranous nephropathy with subepithelial immune deposits. While the autoantigenic target in Heymann nephritis has been identified as megalin, the pathogenic antigenic target in human membranous nephropathy had been unknown until the recent identification of neutral endopeptidase as one target. It is likely that there is no universal antigen in human membranous nephropathy. Immune complexes can damage glomerular structures by attracting circulating inflammatory cells or activating resident glomerular cells to release vasoactive substances, cytokines, and activators of coagulation. However, the principal mediator of immune complex mediated glomerular injury is the complement system, especially C5b-9 membrane attack complex formation. C5b-9 inserts in sublytic quantities into the membranes of glomerular cells, where it produces cell activation, converting normal cells into resident inflammatory effector cells that cause injury. Excessive activation of the complement system is normally prevented by a series of circulating and cell-bound complement regulatory proteins. Genetic deficiencies or mutations of these proteins can lead to the spontaneous development of glomerular disease. The identification of specific antigens in human disease may lead to the development of fundamental therapies. Particularly promising future therapeutic approaches include selective immunosuppression and interference in complement activation and C5b-9-mediated cell injury.

RESEARCH FRONTIER:

Gomez-Guerrero C, Lopez-Franco O, Sanjuan G et al.

Suppressors of cytokine signaling regulate Fc receptor signaling and cell activation during immune renal injury.

J Immunol 2004;172:6969-77.

Suppressors of cytokine signaling (SOCS) are cytokine-inducible proteins that modulate receptor signaling via tyrosine kinase pathways. We investigate the role of SOCS in renal disease, analyzing whether SOCS regulate IgG receptor (FcgammaR) signal pathways. In experimental models of immune complex (IC) glomerulonephritis, the renal expression of SOCS family genes, mainly SOCS-3, significantly increased, in parallel with proteinuria and renal lesions, and the proteins were localized in glomeruli and tubulointerstitium. Induction of nephritis in mice with a deficiency in the FcgammaR gamma-chain (gamma(-/-) mice) resulted in a decrease in the renal expression of SOCS-3 and SOCS-1. Moreover, blockade of FcgammaR by Fc fragment administration in rats with ongoing nephritis selectively inhibited SOCS-3 and SOCS-1, without affecting cytokine-inducible Src homology 2- containing protein and SOCS-2. In cultured human mesangial cells (MC) and monocytes, IC caused a rapid and transient induction of SOCS-3 expression. Similar kinetics was observed for SOCS-1, whereas SOCS-2 expression was very low. MC from gamma(-/-) mice failed to respond to IC activation, confirming the participation of FcgammaR. Interestingly, IC induced tyrosine phosphorylation of SOCS-3 and Tec tyrosine kinase, and both proteins coprecipitated in lysates from IC-stimulated MC, suggesting intracellular association. IC also activated STAT pathway in MC, which was suppressed by SOCS overexpression, mainly SOCS-3. In SOCS-3 knockdown studies, specific antisense oligonucleotides inhibited mesangial SOCS-3 expression, leading to an increase in the ICinduced STAT activation. Our results indicate that SOCS may play a regulatory role in FcgammaR

signaling, and implicate SOCS as important modulators of cell activation during renal inflammation.

4. Immune endocrine and reproductive disorders

REVIEW:

Klein JR.

The immune system as regulator of thyroid hormone activity.

Exp Biology and Medicine 2006;231:229-36.

It has been known for decades that the neuroendocrine system can both directly and indirectly influence the developmental and functional activity of the immune system. In contrast, far less is known about the extent to which the immune system collaborates in the regulation of endocrine activity. This is particularly true for immune-endocrine interactions of the hypothalamuspituitarythyroid axis. Although thyroid-stimulating hormone (TSH) can be produced by man types of extrapituitary cells--including T cells, B cells, splenic dendritic cells, bone marrow hematopoietic cells, intestinal epithelial cells, and lymphocytes--the functional significance of those TSH pathways remains elusive and historically has been largely ignored from a research perspective. There is now, however, evidence linking cells of the immune system to the regulation of thyroid hormone activity in normal physiological conditions as well as during times of immunological stress. Although the mechanisms behind this are poorly understood, they appear to reflect a process of local intrathyroidal synthesis of TSH mediated by a population of bone marrow cells that traffic to the thyroid. This hitherto undescribed cell population has the potential to microregulate thyroid hormone secretion leading to critical alterations in metabolic activity independent of pituitary TSH output, and it has expansive implications for understanding mechanisms by which the immune system may act to modulate neuroendocrine function during times of host stress. In this article, the basic underpinnings of the hematopoietic-thyroid connection are described, and a model is presented in which the immune system participates in the regulation of thyroid hormone activity during acute infection.

RESEARCH FRONTIER:

Tsuchida K.

Activins, myostatin and related TGF-beta family members as novel therapeutic targets for endocrine, metabolic and immune disorders.

Current Drug Targets-Immune Endocrine and Metabolic Disorders 2004;4:157-66.

Activins and inhibins were first identified by virtue of their ability to regulate follicle-stimulating hormone (FSH) secretion from the anterior pituitary. Activins are also powerful regulators of gonadal functions. However, the physiological functions of activins are not restricted to reproductive tissues. Activins are involved in apoptosis of hepatocytes and B cells, fibrosis, inflammation and neurogenesis. Activins are regarded as novel drug targets since blocking activins would provide benefits by preventing apoptosis, fibrosis, inflammation and growth of several cancers. Activins are members of the transforming growth factor-beta (TGF-beta) family, which has numerous peptide growth and differentiation factors including activins, bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and TGF-betas. Among them, GDF8 is also known as myostatin and is structurally related to activins. Myostatin is specifically expressed in the skeletal muscle lineage and is a candidate for muscle chalone negatively regulating the growth of myoblasts. Myostatin is regarded as a good drug target since therapeutics that modulate skeletal muscle growth would be useful for disease conditions such as muscular

dystrophy, sarcopenia, cachexia and even diabetes. Recent studies have revealed that activins and myostatin signal through activin type II receptors (ActRIIA and ActRIIB) and their activities are regulated by extracellular binding proteins, follistatins and follistatin-related gene (FLRG). Furthermore, signaling of activins, myostatin and related ligands is also controlled by intracellular receptor-interacting proteins by novel mechanisms. In this review, I would like to show the current progress in the field emphasizing the importance of activins and myostatin as novel drug targets for immune, endocrine and metabolic disorders.

REVIEW:
A. Fischer, O. Goulet, and C. Bodemer, et al
Cutaneous manifestations of immune dysregulation,
polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome
British Journal of Dermatology epub 2008 Sep 15
BACKGROUND: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare disorder characterized by neonatal autoimmune enteropathy, diabetes and thyroiditis, food allergies and skin rash. IPEX syndrome is caused by mutations in FOXP3, a master control gene of regulatory T cells (Tregs), resulting in absent or dysfunctional Tregs. Data in the literature are scarce and the cutaneous manifestations are rarely depicted.
Objectives: To evaluate the frequency and characteristics of cutaneous manifestations found in IPEX. METHODS: Retrospective single-centre study of a case series of IPEX. Patients' data were retrieved from medical files and numerous parameters concerning general and cutaneous characteristics of the disease were recorded. RESULTS: Ten children with IPEX were studied. Cutaneous involvement was present in seven of 10 chidren; age at onset was 0–4 months, median 1Æ5. All patients presented with atopic dermatitis (AD). Three presented more psoriasiform lesions. Eczema was severe; most affected areas were lower limbs, trunk and face. Pruritus was present in four of seven, and painful fissurary cheilitis in four of seven. Hyper-IgE was found in seven of 10 and hypereosinophilia in five of 10. Skin biopsies showed eczematiform or psoriasiform features. Affected patients were improved by dermocorticoids; no clear improvement was obtained with immunosuppressive regimens. Other features were urticaria secondary to food allergies and staphylococcal sepsis, mostly Staphylococcus aureus and catheter related.
CONCLUSION: AD seems to be a frequent finding in IPEX syndrome, which is characterized by Treg anomalies. This hints to a possible role of Tregs in AD, which is then discussed in this study.

Eisenbarth GS and Gottlieb PA
Autoimmune Polyendocrine Syndromes
N Engl J Med 2004;350:2068-79.
The autoimmune polyendocrine syndromes are diverse, and their diversity is a characteristic that is both clinically important and instructive when their basic immunologic features are considered (Table 1). These syndromes include monogenic disorders (such as autoimmune polyendocrine syndrome type I, which has classic and characteristic disease associations and complex genetic disorders (such as autoimmune polyendocrine syndrome type II, in which the component diseases are more variable Some of the component disorders are common (e.g., thyroid autoimmunity and celiac disease), whereas others are rare (e.g., Addison's disease and myasthenia gravis). Some of the disorders are usually asymptomatic (e.g., celiac disease); others are symptomatic but typically diagnosed after years of illness (Addison's disease, which features severe fatigue and nausea, and pernicious anemia, which causes neuropathic symptoms); and still others are clinically dramatic at

the time of diagnosis (type 1A diabetes, also known as immune-mediated diabetes and formerly called insulin-dependent diabetes). The term "polyendocrine" itself is a misnomer, in that not all patients have multiple endocrine disorders, and many have nonendocrine autoimmune diseases. Nevertheless, the recognition that patients in whom multiple autoimmune disorders are diagnosed may have a specific genetic syndrome, may be at increased risk for multiple autoimmune disorders, and may have relatives who have an increased risk should spur clinicians toward early diagnosis and treatment. A general question concerning the autoimmune polyendocrine disorders relates to the shared "antigen" that can result in the targeting of multiple tissues. In fact, it is likely that the affected organs and tissues do not share any specific molecule but rather have different molecules that are more or less likely to be targets when the immune system fails to maintain self-tolerance to a variety of molecules, in particular specific peptides within target organs (Fig. 1). In addition, specific genetic polymorphisms influence which specific diseases develop; for example, a polymorphism of the insulin gene related to the thymic expression of insulin alters the risk of type 1A diabetes but not the risk of other autoimmune disorders.

REVIEW:
Owen CJ, Jennings CF, Imrie H, et al
Mutational Analysis of the *FOXP3* Gene and Evidence for Genetic Heterogeneity in the Immunodysregulation, Polyendocrinopathy, Enteropathy Syndrome
J Clin Endocrinol Metab 88: 6034–6039, 2003
The immunodysregulation, polyendocrinopathy, enteropathy syndrome (IPEX), is a rare disorder of immune regulation resulting in multiple autoimmune disorders, which demonstrates X-linked recessive inheritance. The disease gene, *FOXP3*, was identified in 2001, and several mutations within this gene have since been described in patients with IPEX. We used linkage analysis, mutational screening of the *FOXP3* gene, human leukocyte antigen typing, and analysis of X-chromosome inactivation to investigate 2 kindreds (21 subjects in total) with 4 male infants (3 now deceased) and 1 girl affected by IPEX. In 1 family a novel *FOXP3* mutation was identified in the proband, with a single base deletion at codon 76 of exon 2, leading to a frameshift, which predicted a truncated protein product (108 residues *vs.* 431 in wild type). In the second family, the *FOXP3* locus was excluded by recombination, and mutational analysis of the gene was negative. The affected girl from this family was shown to have human leukocyte antigen DR2 and DR6 alleles and random X-chromosome inactivation in peripheral blood mononuclear cells. Our analysis has elucidated the molecular basis of IPEX in one family and has, for the first time, provided evidence for an autosomal locus, suggesting genetic heterogeneity in this syndrome.

5. Immune pulmonary disorders

REVIEW:
Demedts IK, Bracke KR, Maes T et al.
Different roles for human lung dendritic cell subsets in pulmonary immune defense mechanisms.
Am J Resp Cell Mol Biol 2006;35:387-93.
Dendritic cells (DC) have a central role in the initiation of adequate immune responses. They recognize pathogens by means of Toll-like receptors (TLR) and link innate to adaptive immune responses by releasing proinflammatory cytokines and inducing T cell proliferation. We conducted this study to evaluate the expression and function of TLR on human lung DC subsets and to study

their T cell stimulatory capacity. TLR gene expression by human pulmonary DC was evaluated by RT-PCR, while protein expression was analyzed by flow cytometry. We investigated cytokine release by DC in response to different TLR ligands. T cell stimulatory capacity was evaluated by mixed leukocyte reactions of purified lung DC with allogeneic T cells. Myeloid dendritic cells type 1 (mDC1) and myeloid dendritic cells type 2 (mDC2) express mRNA transcripts for TLR1, TLR2, TLR3, TLR4, TLR6, and TLR8. Flow cytometric analysis demonstrated high TLR2 protein expression for mDC1 and moderate TLR4 expression for mDC2. mDC1 and mDC2 release proinflammatory cytokines (TNF-alpha, IL-1beta, IL-6, and IL-8) in response to TLR2 and TLR4 ligands. TLR3 ligands induce cytokine release in mDC1, but not in mDC2. Plasmacytoid DC (pDC) express TLR7 and TLR9 and release proinflammatory cytokines in response to imiquimod and IFN-alpha in response to CpG oligonucleotides. mDC1 are strong inducers of T cell proliferation, while pDC hardly induce any T cell proliferation. mDC2 have an intermediate T cellstimulatory capacity. Our results show divergent roles for the different human lung DC subsets, both in innate and adaptive immune responses.

RESEARCH FRONTIER:

Zhang-Hoover J, Stein-Streilein J. Tolerogenic
APC generate CD8+ T regulatory cells that modulate pulmonary interstitial fibrosis.
J Immunol 2004;172:178-85.

Transforming growth factor-beta2-treated Ag-pulsed APC mimic APC from the immune privileged eye, and provide signals that generate regulatory T (Tr) cells and mediate peripheral tolerance. We postulated that TGF-beta2-treated Ag-pulsed APC (tolerogenic APC (tol-APC)) might also orchestrate regulation of immune mediated pathogenesis in nonimmune privileged tissues such as the lung. We used an adoptive transfer model of autoimmune pulmonary interstitial fibrosis called hapten immune pulmonary interstitial fibrosis (ADT-HIPIF) in this study. Mice that received 2,4,6-trinitrobenzene sulfonic acid-sensitized cells and challenged (intratracheally) with the hapten developed pulmonary interstitial fibrosis. However, transfer (i.v.) of TGF-beta2-treated 2,4,6-trinitrobenzene sulfonic acidpulsed bone marrow-derived APC (tol-APC) to experimental mice 1 day after intratracheal challenge reduced the collagen deposition in the interstitium of the lung that usually follows challenge. Furthermore, ADT-HIPIF mice that received tol-APC developed Ag-specific efferent CD8+ T cells. Adoptive transfer of the Tr cells to another set of presensitized mice mediated suppression of the efferent phase of Th1 immune response and the subsequent immune dependent pulmonary interstitial fibrosis. Thus, tol-APC induced efferent CD8+ Tr cells in immune mice, and the regulation of the immune response limited the development of autoimmune pulmonary fibrosis in sensitized and pulmonary-challenged mice. Because ADT-HIPIF shares etiological and pathological characteristics with a variety of human immune inflammatory conditions in the lung that eventuate into interstitial fibrosis, these studies provide insight into potential therapy to alter the course of pulmonary fibrosis in humans.

REVIEW:

M Aydogan, AO Eifan, I Gocmen, C Ozdemir, NN Bahceciler, IB Barlan
Clinical and Immunologic Features of Pediatric Patients With Common Variable Immunodeficiency and Respiratory Complications
J Investig Allergol Clin Immunol 2008; Vol. 18(4): 260-265

BACKGROUND: Common variable immunodefi ciency (CVID) is the term used to describe a heterogeneous group of B-cell defi ciency syndromes characterized by hypogammaglobulinemia,

impaired antibody production, and recurrent bacterial infections. OBJECTIVE: To determine the clinical manifestations and perform an immunological analysis of pediatric CVID patients suffering from respiratory complications. METHODS: The records of 10 patients with CVID who were followed up from 1992 to 2005 (6 males and 4 females) with a median (interquartile range) age of 13.9 (10.4-19.4) years were reviewed. All patients met the standard criteria set for CVID. RESULTS: Median total serum levels of immunoglobulin (Ig) G, IgM, and IgA in mg/dL were 383.5 (239.2-574.5), 32.5 (17.0-117.0), and 12.5 (5.0-30.7), respectively. Median age at the onset of symptoms, at CVID diagnosis, and on starting intravenous Ig therapy was 4.0 (0.8-6.2), 9.4 (6.7-11.3), and 9.1 (7.0-11.6) years, respectively. Associated disorders were recurrent infections (100%), bronchiectasis (90%), and growth failure (80%), whereas malabsorption, malignant neoplasm, infl ammatory bowel disease, and autoimmune disorders were less common. All bronchiectatic patients had a low percentage of B cells, with an average of 4% (range, 1%-7%). The characteristic computed tomography fi nding in patients with CVID was a multilobar pattern. Malignant neoplasm developed an average of 11.5 (range, 6.5-20.2) years after the diagnosis of CVID was made. CONCLUSION: Recurrent respiratory infection should be evaluated to rule out CVID. Early diagnosis and intravenous Ig replacement therapy may reduce the frequency of respiratory infection. Low levels of serum Ig and percentage of B lymphocytes at diagnosis are important parameters for identifying patients at risk of structural lung damage.

6. Immune gastrointestinal and hepatobiliary disorders

REVIEW:
Terjung B, Spengler U.
Role of auto-antibodies for the diagnosis of chronic cholestatic liver diseases.
Clin Reviews in Allergy and Immunol 2005;28:115-33.

Auto-antibodies are an integral part of the diagnostic armentarium in chronic cholestatic liver disorders, such as primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), autoimmune cholangitis, or overlap syndromes among these disorders. However, care should be taken not to overestimate the diagnostic specificity. Auto-antibodies to mitochondrial antigens (AMAs) with reactivity to the E2 subunit of the pyruvate dehydrogenase complex represent the hallmark antibody for the diagnosis of PBC, whereas antinuclear antibodies (ANAs) with low disease specificity are found in up to 50% of these sera. Antibodies that recognize nuclear envelope proteins exert a similarly high diagnostic specificity as AMA in PBC but occur at a rather low prevalence. The role of auto-antibodies is less well-studied for patients with PSC, but there is growing evidence that only antineutrophil cytoplasmic antibodies(ANCAs) are of relevant diagnostic significance. In contrast, auto-antibodiesparticularlyAMAs-do not contribute to the diagnosis of auto-immune cholangitis, whereas ANCAs,ANAs, smooth muscle antibodies, and AMAs are of varying significance in PBC-autoimmune hepatitis (AIH) or PSC-AIH overlap syndromes. It has been widely accepted that the course of the auto-antibody serum end point titers are not suited for the clinical management of patients with chronic cholestatic liver disorders. Additionally, autoantibodies in these disorders usually do not contribute to the immunopathogenesis of the disease.

REVIEW:
Farrell RJ, Kelly CP.
Celiac sprue.
N Engl J Med 2002;346:180-88.

Celiac sprue, also known as celiac disease and gluten-sensitive enteropathy, is characterized by malabsorption resulting from inflammatory injury to the mucosa of the small intestine after the ingestion of wheat gluten or related rye and barley proteins. There is clinical and histologic improvement on a strict gluten-free diet, and relapse when dietary gluten is reintroduced. Accounts of celiac sprue date back to the first century A.D. It was not until the 1940s, however, that the link to gluten ingestion was established; Dicke, a Dutch pediatrician, observed that the condition of children with celiac sprue improved during the food shortages of World War II, only to relapse after cereal supplies were restored. Until fairly recently, celiac sprue was considered uncommon in the United States, with an estimated prevalence of 1 per 3000 population. However, greater awareness of its presentations and the availability of new, accurate serologic tests have led to the realization that celiac sprue is relatively common, affecting 1 of every 120 to 300 persons in both Europe and North America.

REVIEW:
Xavier R.J., Podolsky D.K.
Unravelling the pathogenesis of inflammatory bowel disease
Nature. 448:427-34, 2007
Recently, substantial advances in the understanding of the molecular pathogenesis of inflammatory bowel disease (IBD) have been made owing to three related lines of investigation. First, IBD has been found to be the most tractable of complex disorders for discovering susceptibility genes, and these have shown the importance of epithelial barrier function, and innate and adaptive immunity in disease pathogenesis. Second, efforts directed towards the identification of environmental factors implicate commensal bacteria (or their products), rather than conventional pathogens, as drivers of dysregulated immunity and IBD. Third, murine models, which exhibit many of the features of ulcerative colitis and seem to be bacteria-driven, have helped unravel the pathogenesis/mucosal immunopathology of IBD.

REVIEW:
Targan SR. Karp LC.
Inflammatory bowel disease diagnosis, evaluation and classification: state-of-the art approach.
Current Opinion in Gastroenterology. 23:390-4, 2007 Jul.
Progress in inflammatory bowel disease, aided by use of animal models, and focused on pathways leading to inflammation and the relationship between the innate and adaptive immune systems, is identifying target pathogenic mechanisms for therapeutic intervention. This review will describe the most recent advances and discuss promising pathways for therapeutic discovery. RECENT FINDINGS: Identification and testing of immune and genetic markers to distinguish subgroups of patients with inflammatory bowel disease have surged over the last decade. What was limited to a few serum antibodies is now complemented with a number of genetic associations. Recent years have seen renewed interest, with additional evidence on the relationship between intestinal commensal bacteria and the inflammatory process in Inflammatory Bowel Disease. SUMMARY: There is emerging evidence that discriminating pathogenic abnormalities are present in certain clusters of patients, defined by selected immune responses. These traits have been used to identify correlates between relevant mouse models and immunophenotypic clusters of patients. Such approaches will not only help us to more easily define groups of patients for study, but will also

enhance our understanding of the interface between various pathways and disease expression, and ultimately, identify the primal therapeutic targets in the appropriate subgroups of patients.

7. Immune neurologic and neuromuscular disorders

REVIEW:
Lutterotti A. Martin R.
Getting specific: monoclonal antibodies in multiple sclerosis.
Lancet Neurology. 7:538-47, 2008

For more than a decade the only therapies that were available for multiple sclerosis (MS) were two immunomodulatory drugs-interferon beta and glatiramer acetate-and the immunosuppressant mitoxantrone. Natalizumab, a monoclonal antibody against alpha4 integrin, has been approved by the US Food and Drug Administration and the European Medicines Agency on the basis of its higher efficacy than the available treatments and its good safety profile. Monoclonal antibodies that are already licensed to treat other diseases, such as cancer and autoimmune diseases, are being tested for the treatment of MS. Additionally, novel targets are currently being investigated for MS. The therapeutic use of monoclonal antibodies was initially viewed with great scepticism owing to the high rates of sensitisation against mouse proteins, their pharmacokinetic properties, and the difficulties in their production. However, most of these problems have been overcome, and monoclonal antibodies are now among the most promising therapies for MS.

REVIEW:
Skeie GO, Apostolski S, Evoli A et al.
Guidelines for the treatment of autoimmune neuromuscular tansmission disorders.
Eur J Neuro 2006;13:691-9.

Important progress has been made in our understanding of the cellular and molecular processes underlying the autoimmune neuromuscular transmission (NMT) disorders; myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS) and neuromyotonia (peripheral nerve hyperexcitability; Isaacs syndrome). To prepare consensus guidelines for the treatment of the autoimmune NMT disorders. References retrieved from MEDLINE, EMBASE and the Cochrane Library were considered and statements prepared and agreed on by disease experts and a patient representative. The proposed practical treatment guidelines are agreed upon by the Task Force: (i) Anticholinesterase drugs should be the first drug to be given in the management of MG (good practice point). (ii) Plasma exchange is recommended as a short-term treatment in MG, especially in severe cases to induce remission and in preparation for surgery (level B recommendation). (iii) Intravenous immunoglobulin (IvIg) and plasma exchange are equally effective for the treatment of MG exacerbations (level A Recommendation). (iv) For patients with non-thymomatous autoimmune MG, thymectomy (TE) is recommended as an option to increase the probability of remission or improvement (level B recommendation). (v) Once thymoma is diagnosed TE is indicated irrespective of the severity of MG (level A recommendation). (vi) Oral corticosteroids is a first choice drug when immunosuppressive drugs are necessary in MG (good practice point). (vii) In patients where long-term immunosuppression is necessary, azathioprine is recommended together with steroids to allow tapering the steroids to the lowest possible dose whilst maintaining azathioprine (level A recommendation). (viii) 3,4-diaminopyridine is recommended as symptomatic treatment and IvIg has a positive short-term effect in LEMS (good practice point). (ix) All neuromyotonia patients should be treated symptomatically with an anti-epileptic drug that reduces peripheral nerve hyperexcitability (good practice point). (x) Definitive management of

paraneoplastic neuromyotonia and LEMS is treatment of the underlying tumour (good practice point). (xi) For immunosuppressive treatment of LEMS and NMT it is reasonable to adopt treatment procedures by analogy with MG (good practice point).

REVIEW:
Mimori T. Imura Y. Nakashima R. Yoshifuji H.
Autoantibodies in idiopathic inflammatory myopathy: an update on clinical and pathophysiological significance.
Current Opinion in Rheumatology. 19:523-9, 2007
Idiopathic inflammatory myopathy is characterized by the production of autoantibodies to various cellular constituents. These autoantibodies closely correlate with certain clinical conditions and prognosis of disease. This review examines recent progress in myositis-specific autoantibodies, particularly in their clinical significance and pathophysiological roles. RECENT FINDINGS: During the 1-year review period, novel myositis-specific autoantibodies were identified in clinically amyopathic dermatomyositis (anti-CADM-140 antibody) and malignancy-associated myositis (anti-p155 and anti-p155/p140 antibodies). These new autoantibodies are extremely important because it is thought that myositis-specific autoantibodies are negative in these subgroups, and may enable a new classification of idiopathic inflammatory myopathy. New clinical aspects of other myositis-specific autoantibodies (anti-aminoacyl-tRNA synthetases, anti-signal recognition particles and anti-Mi-2) are also described. The possibility was raised that the high expression of myositis-specific autoantigens in regenerating muscle cells and certain cancers may be involved in initiating and perpetuating the autoimmune response in myositis. SUMMARY: Myositis-specific autoantibodies are useful markers for clinical diagnosis, classification and predicting prognosis of idiopathic inflammatory myopathy. To understand the etiopathogenic mechanisms of the disease it is particularly important to elucidate the nature of target autoantigens recognized by these myositis-specific autoantibodies.

8. Immune hematologic disorders

HISTORIC REVIEW:
Kormoczi GF, Mayr WL. Milestones in immunohaematology. Transpl Immunol. 2005 Aug;14(3-4):155-7.
The milestones in immunohematology, as seen by immunogeneticists, are described.

REVIEW:
Zola H, Swart B, Nicholson I et al. Blood.2005 Nov 1;106(9):3123-6. Epub 2005 Jul 14.
The immune system works through leukocytes interacting with each other, with other cells, with tissue matrices, with infectious agents, and with other antigens. These interactions are mediated by cell-surface glycoproteins and glycolipids. Antibodies against these leukocyte molecules have provided powerful tools for analysis of their structure, function, and distribution. Antibodies have been used widely in hematology, immunology, and pathology, and in research, diagnosis, and therapy. The associated CD nomenclature is commonly used when referring to leukocyte surface molecules and antibodies against them. It provides an essential classification for diagnostic and therapeutic purposes. The most recent (8th) Workshop and Conference on Human Leukocyte Differentiation Antigens (HLDA), held in Adelaide, Australia, in December 2004, allocated 95 new CD designations and made radical changes to its aims and future operational strategy in order to maintain its relevance to modern human biology and clinical practice.

FRONTIER:

Elstrom RL, Martin P, Leonard JP. New biologic agents and immunologic strategies. Hematol Oncol Clin North Am. 2008 Oct;22(5):1037-49, x-xi.

The treatment of non-Hodgkin lymphoma has traditionally consisted of cytotoxic chemotherapy, which can frequently induce remissions but less reliably delivers long-term disease-free survival. The last two decades have heralded an era of increasing exploration of therapies derived from improved biologic understanding of tumors and tumor-host interactions, including the development of therapeutic tactics that take advantage of immune mechanisms to target and kill tumors. Foremost among these has been the development of monoclonal antibodies. Currently, an array of novel therapeutics in development may improve outcomes further, including novel monoclonals and other agents that take advantage of or optimize immune system function in the treatment of lymphoma or that provide other mechanisms of antitumor activity.

9. Immune ocular disorders

REVIEW:

Lim L, Suhler EB, Smith JR.

Biologic therapies for inflammatory eye disease.

Clin Exp Ophthamol 2006;34:365-74.

The era of biologic medical therapies provides new options for patients with treatment-resistant inflammatory eye disease. In this review, the authors summarize current published experience in a rapidly progressing clinical field, including the use of biologics, such as the tumour necrosis factor blockers, daclizumab and rituximab, and related agents, interferons and intravenous immunoglobulin, for the treatment of uveitis, scleritis and orbital inflammation. Reports of dramatic recoveries in patients with recalcitrant ocular inflammation who have received such therapies must be balanced against the high cost of biologics and the potential for serious, and at times unanticipated, complications of this treatment

10. Immune skin disorders

HISTORIC REVIEW:

Blank M, Gisondi P, Mimouni D, Peserico A, Piaserico s, Shoenfeld Y, Reunala T., Zambruno G, Di Zenzo G, Girolomoni G. New insights into the autoantibody-mediated mechanisms of autoimmune bullous diseases and urticaria. Clin Exp Rheumatol. 2006 Jan-Feb;24(1 Suppl 40):S20-5.

The skin is a common target of cellular and/or antibody mediated pathological immune responses. Pemphigoids, pemphigus vulgaris and dermatitis herpetiformis are bullous disease due to autoantibodies targeting specific proteins of the skin. The pemphigoid autoantigens are the BP180 and the BP230 antigens, two components of the epithelial basement membrane zone. Additional antigenic targets reported in a portion of patients are laminin 5, the alpha6 subunit of the hemidesmosomal integrin alpha6beta4 and a glycoprotein termed p200. The epidermal and mucosal epithelial cells detachment (acantholysis) characteristic of pemphigus vulgaris is induced by autoantibodies directed against the desmoglein 3 and 1. The desmogleins are desmosomal cadherins, which play a major role in the cell-to-cell adhesion. Dermatitis herpetiformis is regarded as cutaneous phenotype of coeliac disease. A novel autoimmune hypothesis of coeliac disease links wheat gliadin and tissue transglutaminase (TG2) in the gut, which leads to T cell response and IgA autoantibody formation. In dermatitis herpetiformis skin the target for IgA

deposition seems to be epidermal TG3. Urticaria is a complex syndrome caused by both immune and non-immune mechanisms. In a subsets of patients with chronic urticaria mast cell degranulation is induced by autoantibodies directed against the a-subunit of the high-affinity IgE receptor, and/or the IgE.

REVIEW:

Sidonia Mihai, Cassian Sitaru. Immunopathology and molecular diagnosis of autoimmune bullous diseases. J Cell Mol Med. 2007 May-Jun;11(3):462-81.

Autoimmune bullous diseases are associated with autoimmunity against structural components maintaining cell–cell and cell–matrix adhesion in the skin and mucous membranes. Pemphigus diseases are characterized by autoantibodiesagainst the intercellular junctions and intraepithelial blisters. In pemphigoid diseases and epidermolysis bullosaacquisita, sub-epidermal blistering is associated with autoantibodies targeting proteins of the hemidesmosomalanchoring complex. The autoantigens in autoimmune blistering diseases have been extensively characterized overthe past three decades. In general, the pathogenicity of autoantibodies, already suggested by clinical observations,has been conclusively demonstrated experimentally. Detection of tissue-bound and circulating serum autoantibodieand characterization of their molecular specificity is mandatory for the diagnosis of autoimmune blistering diseases. For this purpose, various immunofluorescence methods as well as immunoassays, including immunoblotting,enzyme-linked immunosorbent assay and immunoprecipitation have been developed. This review article describes the immunopathological features of autoimmune bullous diseases and the immunological and molecular tests usedfor their diagnosis and monitoring.

FRONTIER:

O'Regan GM, Sandilands, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. J Allergy Clin Immunol. 2008 Oct;122(4):689-93.

The recent identification of loss-of-function mutations in the structural protein filaggrin as a widely replicated major risk factor for eczema sheds new light on disease mechanisms in eczema, a disease that had heretofore largely been considered to have a primarily immunologic etiopathogenesis. The filaggrin gene (FLG) mutation findings are consistent with a recently proposed unifying hypothesis that offers a mechanistic understanding of eczema pathogenesis synthesizing a heritable epithelial barrier defect and resultant diminished epidermal defense mechanisms to allergens and microbes, followed by polarized T(H)2 lymphocyte responses with resultant chronic inflammation, including autoimmune mechanisms. Although compelling evidence from genetic studies on FLG implicates perturbed barrier function as a key player in the pathogenesis of eczema in many patients, much is still unknown about the sequence of biologic, physicochemical, and aberrant regulatory events that constitute the transition from an inherited barrier defect to clinical manifestations of inflammatory eczematous lesions and susceptibility to related atopic disorders. The exact contribution of FLG to the wider atopic story, factors modifying FLG expression, and the role of other barrier proteins remain to be delineated. In this review we highlight recent advances in our understanding of the FLG genetics in the cause of eczema and related complex diseases.

D. Transplantation Medicine

1. Recognition of alloantigens

REVIEW:

Robert I. Lechler, Oliver A. Garden, Laurence A. Turka

The complementary roles of deletion and regulation in transplantation tolerance

Nature Reviews Immunology 3, 147 - 158 (01 Feb 2003)

Neonatal tolerance of alloantigens was described in mice nearly half a century ago, but unfortunately, the translation of these early findings into the clinical arena proved to be much more challenging than was first anticipated. However, the past decade has seen considerable progress in our understanding of the mechanisms that contribute to transplantation tolerance in experimental models. This review outlines our current understanding of the mechanisms of allograft tolerance, emphasizing the complementary roles of deletion and regulation of alloreactive T cells.

2. Alloreactive T cell activation

REVIEW:

Patrick T. Walsh 1, Terry B. Strom 2 and Laurence A. Turka

Routes to Transplant Tolerance versus Rejection

The Role of Cytokines

Immunity. 2004 Feb;20(2):121-31

Abstract

The alloimmune response can be divided into specific junctures where critical decisions between tolerance and immunity are made which define the outcome of the transplant. At these "decision nodes" various cytokines direct alloresponsive T cells to develop either a proinflammatory response aimed at graft destruction or an immunoregulatory response facilitating graft acceptance. This review will focus on the role of these cytokines in influencing the progression of an alloimmune response leading ultimately to either allograft survival or rejection.

3. Allograft rejection

RESEARCH FRONTIER:

Heidt S, San D, Chadha, R, et al

The impact of Th17 cells on transplant rejection and the induction of tolerance

Curr Opin Organ Transplant. 2010 15:456-461

This review aims to provide an overview of the latest evidence for the involvement of Th17 cells in the rejection of solid organ allografts. It will also consider the implications of the relationship between the differentiation pathways of Th17 and regulatory T cells (Tregs), as well as their plasticity in the context of transplantation tolerance. Recent findings: In the absence of the Th1 lineage in vivo, Th17 cells are capable of rejecting cardiac allografts, showing the capacity of Th17 cells to cause allograft rejection, at least in experimental models. Th17 cells are relatively unsusceptible to suppression by Tregs, although this may be context dependent. Furthermore, addition of inflammatory signals to a Treg-inducing environment leads to Th17 development and established Tregs can be converted to Th17 cells under inflammatory conditions. SUMMARY: The capacity of Th17 cells to cause allograft rejection is becoming increasingly clear. However,

the role and contribution of Th17 cells in allograft rejection in the presence of the full orchestra of T helper cells remains elusive. The apparent resistance of Th17 to be suppressed by Tregs may pose a hurdle for effective immunosuppression and tolerance inducing protocols. Furthermore, the close developmental pathways of Th17 and Tregs and the ability of Tregs to convert into Th17 cells in the presence of inflammatory signals may impede the establishment of specific unresponsiveness to donor alloantigens in vivo.

a. Hyperacute

REVIEW:

Rowshani AT, Bemelman FJ, Lardy NM, et al

Humoral immunity in renal transplantation: clinical significance and therapeutic approach

Clin Transplant 2008: 22: 689–699.

Donor-specific antibodies (DSA) form a significant barrier in solid organ transplantation of highly pre-sensitized candidates. Although avoiding transplantation over a positive cross-match test can largely prevent the occurrence of hyperacute antibody-mediated rejection, transplantation of highly pre-sensitized candidates is often complicated by the occurrence of acute and chronic antibody-mediated graft rejection leading to diminished graft function and survival. The pre-existent HLA and/or non-HLA-specific antibodies are without any doubt important contributing factors underlying humoral-mediated graft injury. Furthermore, increasing evidence underlines the association of newly formed de novo DSA after transplantation with poor graft function and survival. There is still a need to further develop desensitizing therapies not only to make transplantation of highly presensitized candidates feasible, but also to reduce the new formation of alloantibodies. Here, we summarize current views on desensitization therapies and the impact of the presence of DSA on the fate of the kidney graft.

b. Acute

REVIEW:

Singh N, Pirsch J, Sarmaniego M

Antibody-mediated rejection: treatment alternatives and outcomes.

Transplant Rev (Orlando). 2009;23:34-46

Over the past 10 years, thanks to the development of sensitive methods of antibody detection and markers of antibody injury such as C4d staining, the role of anti-human leukocyte antigen (HLA) and non-HLA alloantibodies as effectors of acute and chronic immune allograft injury has been revisited. Antibody-mediated rejection (AMR) defines all allograft rejection caused by antibodies directed against donor-specific HLA molecules, blood group antigen (ABO)-isoagglutinins, or endothelial cell antigens. Antibody-mediated rejection can be a recalcitrant process, resistant to therapy and carries an ominous prognosis to the graft. In concordance with these views, treatment protocols for AMR use permutations of a multiple-prong approach that include (1) the suppression of the T-cell dependent antibody response, (2) the removal of donor reactive antibody, (3) the blockade of the residual alloantibody, and (4) the depletion of naive and memory B-cells. Although all published protocols report a variable rate of success, a major weakness of all current protocols is the lack of effective anti-plasma cell agents. In comparison to acute AMR, the treatment for chronic AMR (CAMR) is not well characterized. Although in acute AMR large titers of pre-existent alloantibodies result in massive activation of the complement system and lytic injury of the graft endothelium, thereby requiring aggressive and fast removal of the offending agents, in CAMR, complement activation results in sublytic endothelial cell injury and activation.

Although this type of injury results in chronic graft failure, its slow progression likely renders it amenable of suppression by heightening of maintenance immunosuppression and anti-idiotypic blockade of the circulating alloantibody without the need of plasma exchange. In this review, we will discuss the rationale behind the design of treatment protocols for acute AMR and CAMR as well as their reported results and complications.

c. Chronic

REVIEW:
Inguilli E.
Mechanisms of cellular rejection in transplantation
Pediatr Nephrol 2010 25:61–74
The explosion of new discoveries in the field of immunology has provided new insights into mechanisms that promote an immune response directed against a transplanted organ. Central to the allograft response are T lymphocytes. This review summarizes the current literature on allorecognition, costimulation,memory Tcells, Tcellmigration, and their role in both acute and chronic graft destruction. An in depth understanding of the cellular mechanisms that result in both acute and chronic allograft rejection will provide new strategies and targeted therapeutics capable of inducing long-lasting, allograft-specific tolerance

REVIEW:
Tejani A ,Emmett L .
Acute and chronic rejection.
Semin Nephrol. 2001 Sep;21(5):498-507.
The major histocompatibility complex molecules are the primary antigens responsible for causing graft rejection, and T-cell recognition of alloantigens is the cardinal event initiating cellular rejection. Current concepts suggest that direct allorecognition mediates acute rejection, whereas indirect allorecognition mediates chronic rejection. In biopsy tissue of rejecting human renal allografts, several cytotoxic T-lymphocyte molecules are upregulated. The net result of cytokine release and the acquisition of cell surface receptors is the emergence of antigen-specific and graft-destructive T cells. Acute rejection is more frequent in children than in adults. By the end of the first year posttransplantation, 45% of living donor recipients and 60% of cadaver donor recipients will have an episode of rejection. In recent years, with improved immunosuppressive therapy, the incidence of acute rejection is decreasing at a rate of about 8% each year, however, chronic rejection graft loss has increased to 41% of all graft losses in the last 2 years. The mechanisms leading to chronic rejection and attempts to reduce acute rejections should provide a better half-life to children postrenal transplantation.

REVIEW:
Peter Libby and Jordan S. Pober
Chronic Rejection
Immunity. 2001 Apr;14(4):387-97

REVIEW:
Peter J. Nelson, Alan M. Krensky
Chemokines, Chemokine Receptors, and Allograft Rejection
Immunity. 2001 Apr;14(4):387-97

4. Prevention and treatment of allograft rejection

REVIEW:

Robert I Lechler1, Megan Sykes2, Angus W Thomson3 & Laurence A Turka4

Organ transplantation—how much of the promise has been realized?

Nature Medicine 11, 605 - 613 (2005)

Since the introduction of organ transplantation into medical practice, progress and optimism have been abundant. Improvements in immunosuppressive drugs and ancillary care have led to outstanding short-term (1-3-year) patient and graft survival rates. This success is mitigated by several problems, including poor long-term (>5-year) graft survival rates, the need for continual immunosuppressive medication and the discrepancy between the demand for organs and the supply. Developing methods to induce transplant tolerance, as a means to improve graft outcomes and eliminate the requirement for immunosuppression, and expanding the pool of organs for transplantation are the major challenges of the field.

a. Immunosupression

REVIEW:

Durrbach A, Francois H, Beaudreuil S, et al.

Advances in immunosuppression for renal transplantation

Nat Rev Nephrol 2010; 6:160-167

The development of immunosuppressants with minimal adverse and nephrotoxic effects is important to improve outcomes, such as acute and chronic antibody-mediated rejection, after organ transplantation. In addition, the application of expanded criteria for donors and transplantation in immunized patients necessitates the development of new therapies. Drug development over the past 10 years has generally been disappointing, but several new promising compounds have been or are being developed to prevent acute and chronic transplant rejection. In this Review, we report on several compounds that have been developed to remove allogenic T cells and/or to inhibit T-cell activation. We also discuss compounds that interfere with antibody-mediated rejection.

Duncan MD, Wilkes DS

Transplant-related immunosuppression: a review of immunosuppression and pulmonary infections.

Proc Am Thorac Soc. 2005;2(5):449-55.

Solid organ and hematopoietic stem cell transplantation are definitive therapies for a variety of end-stage diseases. Immunosuppression has improved graft survival but leaves the patient susceptible to infectious complications. Of these, pulmonary infections are the leading cause of morbidity and mortality in the transplant recipient. Allograft rejection is mediated primarily by T cells, with B cells playing a role via antibody production. Depending on the transplant type, rejection can be hyperacute, acute, or chronic. Hyperacute rejection occurs as an immediate response to preformed antibodies to donor human leukocyte antigens. Acute cellular rejection involves recipient T-cell recognition of human leukocyte antigen molecules expressed on donor-derived, antigen-presenting cells (direct allorecognition) or presentation of donor-derived peptides by recipient antigen-presenting cells to recipient T cells (indirect allorecognition). Once the alloantigens are recognized as foreign, the activation, proliferation, and production of cytokines by T lymphocytes and other immune cells lead to the amplification of the alloimmune response. This complex process involves the generation of effector T cells, antibody production by activated B

cells, and macrophage activation. Alloimmunity is facilitated by the production of many cytokines, chemokines, and other effector molecules, such as complement. The immunosuppressants involve many classes of drugs, including antibody therapies that eliminate specific groups of cells or alter signaling pathways used by effector cells. The article reviews the agents and associated infections.

b. Methods to reduce allograft immunogenicity

REVIEW:

Martins PN, Chandraker A ,Tullius SG .

Modifying graft immunogenicity and immune response prior to transplantation: potential clinical applications of donor and graft treatment. Transpl Int. 2006;19:351-9.

Many studies have shown a strong association between initial graft injury and poor longterm graft outcome. Events initiated by unspecific immune-activating processes including brain death and ischemia/reperfusion injury occurring prior to transplantation reduce graft functionality and amplify the host immune response. These events may be particularly relevant for less than optimal grafts with reduced resistance to unspecific injuries. Several approaches to ameliorate immune activation of the graft by treating the donor or the graft have been studied. While various substances have been shown to have protective effects in experimental transplantation, only a few drugs have been tested clinically and have demonstrated beneficial effects. We review the results of experimental and clinical studies on donor or graft immunomodulation prior to transplantation and analyze the evidence tosupport clinical application of these strategies.

c. Methods to induce allograft host tolerance

RESEARCH FRONTIER:

Battaglia M

Potential T regulatory cell therapy in transplantation:how far have we come and how far can we go?

Transpl Int. 2010;23:761-70

Graft survival has been lately improved by the introduction of efficient immunosuppressive drugs. However, late graft loss caused by chronic rejection and the side effects of long-term immunosuppression remain major obstacles for successful transplantation. Operational tolerance, which is defined by the lack of acute and chronic rejection and indefinite graft survival with normal graft function in the absence of continuous immunosuppression, represents an attractive alternative. Nevertheless, tolerance after allogeneic transplantation is commonly considered the ‘mission impossible’ for both immunologists and clinicians. One of the mechanisms involved in tolerance is the suppression of graft-specific alloreactive T cells, which largely mediate graft rejection, by regulatory T cells (Tregs) or by soluble factors produced by Treg cells. With this review, I will make an effort to collect and describe the significant studies performed in transplanted patients, and not in animal models or in in vitro systems, with the attempt to: (i) understand how tolerance is achieved, (ii) define whether and how Treg cells influence transplant tolerance, (iii) describe the first clinical trials with Treg cells in humans (i.e. how far have we come) and (iv) predict the futureof Treg cell-based therapy in humans (i.e. how far can we go).

REVIEW:

Jeffrey A. Bluestone

Regulatory T-cell therapy: is it ready for the clinic?

Nature Reviews Immunology 5, 343 - 349 (18 Mar 2005)

The identification of suppressor T cells as important regulators of basic processes that are designed to maintain tolerance has opened an important area of potential clinical investigation in autoimmunity, graft-versus-host disease and transplantation. However, the field has been limited by an inability to define the antigenic specificities of these cells and by the small numbers of circulating regulatory T cells. Recently, new methods for expanding polyclonal and antigen-specific regulatory T cells have emerged. This article summarizes efforts to exploit regulatory T-cell therapy for the treatment of immunological diseases and poses the question of when and where regulatory T cells will first impact on clinical diseases.

5. GVHD: Acute and Chronic

REVIEW GVHD:
Ferrara JLM, Levine JE, Reddy P, Holler E
Graft-versus-host disease
Lancet 2009; 373: 1550–61

Haemopoietic-cell transplantation (HCT) is an intensive therapy used to treat high-risk haematological malignant disorders and other life-threatening haematological and genetic diseases. The main complication of HCT is graftversus- host disease (GVHD), an immunological disorder that aff ects many organ systems, including the gastrointestinal tract, liver, skin, and lungs. The number of patients with this complication continues to grow, and many return home from transplant centres after HCT requiring continued treatment with immunosuppressive drugs that increases their risks for serious infections and other complications. In this Seminar, we review our understanding of the risk factors and causes of GHVD, the cellular and cytokine networks implicated in its pathophysiology, and current strategies to prevent and treat the disease. We also summarise supportive-care measures that are essential for management of this medically fragile population.

RESEARCH FRONTIER:
Ford ML, Larsen CP
Overcoming the memory barrier in tolerance induction: molecular mimicry and functional heterogeneity among pathogen-specific T-cell populations
Curr Opin Organ Transpl 2010, 15:405–410

This review highlights recent advances in our understanding of the frequency and nature of alloreactivity among memory T-cell populations, and discusses recent successes in experimentally targeting these populations in order to prolong graft survival. Recent findings Recent studies suggest that not only is alloreactivity present within peripheral T-cell compartments of normal healthy individuals, but cross-reactivity between viral-specific T cells and allotropes may in fact be a very common occurrence. Furthermore, this crossreactivity functions at the level of molecular mimicry of T-cell receptor recognition. Therapeutics that specifically target cell surface molecules or effector pathways used by memory T cells to mediate graft rejection will likely be required in order to attenuate the donor-reactive memory T-cell response during transplantation. A major challenge facing the field over the next decade is to define the heterogeneity that exists within memory T-cell populations that impacts graft survival. Understanding the functional and phenotypic differences that modify the memory T-cell barrier to tolerance induction might allow a strategy in which strength of immunosuppression could be tailored to fit the immunological history

of a given transplant recipient in order to minimize nonimmune toxicities, maximize protective immunity, and prolong graft survival.

REVIEW ACUTE GVHD:
Couriel D. Caldera H. Champlin R. Komanduri K
Acute graft-versus-host disease: pathophysiology, clinical manifestations, and management.
Cancer. 2004;101:1936-46
Hematopoietic stem cell transplantation has evolved as a central treatment modality in the management of different hematologic malignancies. Despite adequate posttransplantation immunosuppressive therapy, acute graft-versus-host disease (GVHD) remains a major cause of morbidity and mortality in the hematopoietic stem cell transplantation setting, even in patients who receive human leukemic antigen (HLA) identical sibling grafts. Up to 30% of the recipients of stem cells or bone marrow transplantation from HLA-identical related donors and most patients who receive cells from other sources (matched-unrelated, non-HLA-identical siblings, cord blood) will develop > Grade 2 acute GVHD despite immunosuppressive prophylaxis. Thus, GVHD continues to be a major limitation to successful hematopoietic stem cell transplantation. In this review, the authors summarize the most current knowledge on the pathophysiology, clinical manifestations, and management of this potentially life-threatening transplantation complication.

REVIEW CHRONIC GVHD:
Cutler C, Antin JH.
Chronic graft-versus-host disease.
Curr Opin Oncol. 2006;18:126-131.
Chronic graft-versus-host disease is an important cause of late morbidity and mortality after allogeneic stem cell transplantation. With the renewed interest in its pathophysiology and treatment, this review discusses recent clinical and laboratory advances in this disease. Advances in pathophysiology, the relationship between chronic graft-versus-host disease and relapse incidence, and recent developments in the prophylaxis, initial therapy, and therapy for refractory disease are discussed. RECENT FINDINGS: A better understanding of the pathophysiology of chronic graft-versushost disease, including the potential role of a coordinated B-cell and T-cell response, is demonstrated. Corticosteroids and cyclosporine or tacrolimus remain the standard as initial therapy. This combination is effective in the majority of affected patients, although therapy is often required for longer than 1 year. Although no strategy has been demonstrated to be effective in specifically preventing chronic graft-versus-host disease, several drugs have recently been demonstrated to be effective therapeutic agents for steroid-refractory disease. Agents such as mycophenolate mofetil, sirolimus, and rituximab have demonstrated response rates of greater than 60% in patients with steroid-refractory disease. SUMMARY: Renewed interest and understanding of chronic graft-versus-host disease have led to novel treatment strategies for steroid-refractory disease. A focus on the initial therapy and prophylaxis against chronic graftversus-host disease is now warranted.

RESEARCH FRONTIER:
Rieger K , Loddenkemper C, Maul J, et al
Mucosal FOXP3+ regulatory T cells are numerically deficient in acute and chronic GvHD
Blood 2006;103:2758-2763.

CD4+CD25+ regulatory T cells (Tregs) control immune responses to self- and foreign antigens and play a pivotal role in autoimmune diseases, infectious and noninfectious inflammation, and graft rejection. Since recent experimental studies have indicated that Tregs were able to ameliorate graft-versus-host disease (GvHD), we analyzed the number of infiltrating Tregs in the intestinal mucosa as one site of GvH reactivity using immunoenzymatic labeling to enumerate FOXP3+ T cells in 95 intestinal biopsies from 49 allografted patients in comparison with healthy controls and patients with infectious inflammation. While patients with cytomegalovirus (CMV)-colitis or diverticulitis showed a concomitant increase of CD8+ effectors and Tregs, acute and chronic GvHD were characterized by the complete lack of a counter-regulation indicated by a FOXP3+/CD8+ T-cell ratio identical to healthy controls. In contrast, specimens without histologic signs of GvHD demonstrated increased numbers of FOXP3+ per CD8+ T cells, indicating that the potential for Treg expansion is principally maintained in allografted patients. Our findings provide evidence that GvHD is associated with an insufficient up-regulation of Tregs in intestinal GvHD lesions. The determination of FOXP3+/CD8+ ratio can be a helpful tool to discriminate GvHD from infectious inflammation after allogeneic stem cell transplantation.

LANDMARK ARTICLE:
Martin PJ , Hansen JA, Buckner CD, et al.
Effects of in vitro depletion of T cells in HLA-identical allogeneic marrow grafts
Blood 1985;66:664-672
We report results of a pilot study designed to evaluate the effects of in vitro depletion of T lymphocytes from donor marrow in patients receiving HLA-identical marrow grafts for treatmentof hematologic malignancies. Twenty patients aged 31 to 50 years were prepared fortransplantation with cyclophosphamide (120 mg/kg) and fractionated total body irradiation (12.0or 15.75 Gy). All received cyclosporine after grafting. The donor marrows were treated with a mixture of eight murine monoclonal antibodies and rabbit serum complement in a manner that achieved a 2- to 3-log depletion of T cells in most patients. Initial engraftment occurred promptly in 19 of the patients, and only three had clinically significant acute graft-versus-host disease. Depletion of donor T cells, however, was associated with an increased incidence of graft failure, which occurred as late as 244 days after transplantation. Graft failure was transient in one patient but apparently was irreversible in seven others. Three of the seven patients had cytogenetic but not morphological evidence of leukemic relapse at the time of graft failure. All seven patients with irreversible graft failure have died, six after receiving second bone marrow transplants. Seven of the eight cases of graft failure occurred among the 11 patients prepared for transplantation with 12.0 Gy of total-body irradiation, and only one occurred among the nine patients with advanced malignancies who received 15.75 Gy of total-body irradiation. This association with irradiation dose suggests that host factors were partly responsible for the graft failures. Because graft failure seldom occurs in irradiated recipients of unmodified HLA identicalallogeneic marrow transplants, it appears that T cells in the donor marrow may serve a beneficial function in helping to maintain sustained engraftment possibly by eliminating host cells that can cause graft failure. Optimal application of in vitro manipulation of donor marrow asa method for preventing graft-versus-host disease will require more effective immunosuppression of the recipient in order to assure sustained engraftment and function of donor stem cells.

a. Prevention

REVIEW PREVENTION OF ACUTE GVHD:

Messina C, Faraci M, de Fazio V, et al.
Prevention and treatment of acute GvHD
Bone Marrow Transplant. 2008;4:S65-70
GvHD remains a source of significant morbidity and mortality in the setting of allogeneic haematopoietic SCT.\ Improving outcomes in stem cell transplant recipients requires additionaltherapeuti c modalities for GvHD, especially for patients who fail to respond to initial therapy with steroids. Moreover, while the absence of acute GvHD (aGvHD) is associated with a higher risk of relapse of the underlying malignant disease, severe\ aGvHD usually induces the occurrence of life-threatening complications such as severe infections. This article summarizes the current state of aGvHD prophylaxis and treatment.

BRIEF REVIEW PREVENTION AND TREATMENT OF CHRONIC GVHD:
Soiffer R.
Immune modulation and chronic graft-versus-host disease.
Bone Marrow Transpl 2008;42:S66-69
As more and more patients undergoing allogeneic hematopoietic SCT (HSCT) survive the early post-transplant period, the number of individuals at risk for chronic GVHD has grown. Treatment for established cGVHD remains unsatisfactory. No experimental agent has demonstrated superiority to steroids alone in a randomized clinical trial. Distinguishing chronic from acute graft-versus-host disease is a major issue. The importance of achieving clarity in cGVHD diagnosis is critical as efforts are undertaken to understand its pathogenesis and to design definitive trials that can target prevention and/or treatment. Immune tolerance to self-antigens may be broken in cGVHD, giving rise to the autoimmune manifestations of the disorder. Recent attention has focused on CD4+CD25 regulatory T cells and their relationship to cGVHD. Significant enthusiasm has emerged for manipulating Treg either ex vivo or in vivo for clinical benefit. Another immunomodulatory approach to cGVHD might be the targeting of B lymphocytes and the antibodies they produce. As efforts continue to devise strategies to treat and prevent chronic GVHD, it is important to acknowledge the link between cGVHD and freedom from relapse, at least for certain malignancies.

REVIEW Prevention ACUTE GVHD:
Chao NJ, Chen BJ.
Prophylaxis and Treatment of Acute Graft-Versus-Host Disease
Semin Hematol. 2006;44:32-41.
Acute graft-versus-host disease (GVHD) remains a major obstacle to successful allogeneic hematopoietic stem cell transplantation (HSCT). The ability to prevent GVHD--the application of successful prophylaxis--is crucial as treatment when prophylaxis fails or remains suboptimal. A calcineurin inhibitor in combination with methotrexate is still the mainstream regimen for prophylaxis of GVHD. Despite a steady increase in the repertoire of available drugs, corticosteroids remain the first-line therapy for patients who fail prevention and develop GVHD. Pan T-cell depletion studies suggest that success in prophylaxis and treatment of GVHD will depend on whether GVHD can be prevented without losing anti-malignancy and anti-infectious effects. Better understanding of the allogeneic response that is responsible for GVHD will facilitate the development of such an approach.

REVIEW PREVENTION OF CHRONIC GVHD:

Lee SJ.
New approaches for preventing and treating chronic graft-versus-host disease.
Blood 2005;105:4200-6
Despite improvements in the practice of allogeneic hematopoietic stem cell transplantation (HCT) over the last 25 years, chronic graft-versus-host disease (GVHD) remains a substantial problem with little change in the incidence, morbidity, and mortality of this complication. In fact, with increased use of peripheral blood, transplantation of older patients, and less immediate transplantation-related mortality, the prevalence of chronic GVHD may increase. One of the difficulties in combating chronic GVHD is a lack of understanding about the pathophysiology of the syndrome. Inherent difficulties in conducting human clinical trials also contribute to the lack of meaningful progress. This review covers potential new approaches to the prevention andtreatment of chronic GVHD.

b. Treatment

REVIEW TREATMENT OF ACUTE GVHD:
Paczesny S, Choi SW, Ferrara JLM
Acute graft-versus-host disease: new treatment strategies
Curr Opin Hematol 2009,16:427–436
Graft-versus-host disease (GVHD) remains a major cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT), despite improvements in our understanding of its pathophysiology as well as the generation of new monoclonal antibodies, immunomodulatory chemotherapy, cellular therapeutics and supportive care. Herein, we review therapies that have proven effective as well as newer agents that have recently improved GVHD response rates and survival following HCT. Recent findings: Novel approaches to prevent or treat GVHD are often based on evidence from experimental models. Our understanding of the pathophysiology of GVHD may lead to the development of innovative strategies that target both soluble and cellular effectors. Among such agents are sirolimus, anti-tumor necrosis factor antibodies, anti-LFA-3– IgG fusion protein, extracorporeal photopheresis, mesenchymal stem cells and regulatory T cells. Obstacles to the improvement of HCT include the tight linkage between GVHD toxicity and the beneficial graft-versus-leukemia (GVL) effect, as well as the impairment of immune reconstitution by immunomodulatory drugs leading to life-threatening infections. The design of newer phase I/II clinical trials are underway. Future therapies are likely to include modulation of cell types that play key roles in the GVH process, including regulatory T cells, dendritic cells, natural killer T cells and B cells.

REVIEW TREATMENT OF CHRONIC GVHD:
Jacobsohn D
Optimal management of chronic graft-versus-host disease in children
Br J Haematol 2010;150:278–292
Summary: Chronic graft-versus-host disease (GVHD) is a major complication after allogeneic haematopoietic stem cell transplantation (HSCT). Not only is it the major cause of late mortality in HSCT patients, but it also accounts for significant morbidity. Much of the literature on chronic GVHD has focused on adults. Chronic GVHD is of major importance in children, especially since they have years to live following the complications of chronic GVHD and its therapy. The goal is to review incidence, manifestations, and therapies, especially when applicable to the paediatric population.

REVIEW Treatment of Acute GVHD:
Bolanos-Meade J
Update on the management of acute graft-versus-host disease.
Curr Opin Oncol. 2006;18:120-5
Acute graft-versus-host disease is one of the commonest complications after allogeneic stem cell transplantation. Recent advances in its prevention and therapy are giving new hope to patients with this disease. This review covers the major advances in prophylaxis and therapy for this problem. RECENT FINDINGS: The use of novel approaches for prophylaxis such as posttransplant cyclophosphamide and non-methotrexate-containing regimens is discussed. The results of therapy with new agents such as pentostatin, pulse cyclophosphamide, longwavelength ultraviolet A phototherapy, and monoclonal antibodies such as denileukin diftitox or etanercept are reviewed. SUMMARY: Without question, outcome in patients who develop graftversus- host disease is improving. With better supportive care, and more effective prophylaxis and therapy, these patients have an improved chance for full recovery. Patients should be enrolled, when possible, in studies aimed to prevent and treat graft-versus-host disease.

REVIEW Treatment of Chronic GVHD:
Bhushan V, Collins RH
CLINICIAN'S CORNER - Chronic Graft-vs-Host Disease
JAMA. 2003;290:2599-2603
Allogeneic hematopoietic cell transplantation (HCT) is a treatment used increasingly for a variety of malignant and nonmalignant diseases of the bone marrow and immune system.1 Although the procedure cures many patients with otherwise incurable diseases, it is often associated with serious immunological complications, particularly graft-vs-host disease (GVHD).2 A chronic form of GVHD afflicts many allogeneic HCT recipients, resulting in dysfunction of numerous organ systems and an oftentimes profound state of immunodeficiency.3-5 Chronic GVHD is the most frequent cause of poor long-term outcome and quality of life after allogeneic HCT. The syndrome typically develops several months after transplantation, when the patient may no longer be under the direct care of the transplant team. The patient's primary physician plays an important role in diagnosis and treatment of the patient with chronic GVHD.

E. Immune System Related Malignancies and Cellular Disorders

1. B cell and plasma cell neoplasms

REVIEW:
Jumaa H, Hendriks RW, Reth M.
B cell signaling and tumorigenesis.
Annu Rev Immunol. 2005;23:415-45
The proliferation and differentiation of lymphocytes are regulated by receptors localized on the cell surface. Engagement of these receptors induces the activation of intracellular signaling proteins that transmit the receptor signals to distinct targets and control the cellular responses. The first signaling proteins to be discovered in higher organisms were the products of oncogenes. For example, the kinases Src and Abelson (Abl) were originally identified as oncogenes and were later characterized as important proteins for signal transduction in various cell types, including ymphocytes. Now, as many cellular signaling molecules have been discovered and ordered into

certain pathways, we can better understand why particular signaling proteins are associated with tumorigenesis. In this review, we discuss recent progress in unraveling the molecular mechanisms of signaling pathways that control the proliferation and differentiation of early B cells. We point out the concepts of auto-inhibition and subcellular localization as crucial aspects in the regulation of B cell signaling.

Jaglowski SM, Byrd JC.
Rituximab in chronic lymphocytic leukemia.
Semin Hematol. 2010 Apr;47(2):156-69.
Rituximab is a class I chimeric anti-CD20 antibody that has shown efficacy in chronic lymphocytic leukemia (CLL), both as a single agent and in combination with traditional chemotherapies. The modest activity demonstrated in early studies evaluating rituximab in relapsed CLL was improved with higher doses or more dose-intensive regimens that overcame the unfavorable pharmacokinetic features commonly found in CLL. These studies led to a variety of combination trials of rituximab with chemotherapy, where both phase II and later phase III studies have shown great promise for the advancement of CLL therapy. Despite the therapeutic success of rituximab in CLL, studies demonstrating the definitive relative mechanism of tumor clearance are still lacking and this requires further investigation. In addition to being used as a therapy for CLL, rituximab is an effective treatment for autoimmune CLL complications such as hemolytic anemia and immune thrombocytopenia (ITP). Patients with CLL may experience early infusion-related side effects that can be diminished with corticosteroid pretreatment and stepped-up dosing. Risk factors for infusion-related toxicity may relate to atypical CLL expressing bright CD20 antigen expression, although several different studies have not clearly implicated elevated white blood cell count as a risk factor. Other adverse events, including delayed cytopenias, reactivation of hepatitis B, and development of progressive multifocal leukoencephalopathy, are rare. Future efforts focusing on novel combination-based strategies will be required to fully appreciate the benefit of this therapy in CLL.

Wolach O, Bairey O, Lahav M.
Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature.
Medicine (Baltimore). 2010 Sep;89(5):308-18.
Rituximab is a chimeric monoclonal antibody against CD20 that is used mainly for the treatment of CD20-positive lymphoma. Recently, its use has been expanded to include treatment of other nonmalignant diseases such as rheumatologic diseases and autoimmune cytopenia. Correlating with the increased use of rituximab has been an increased number of reports of its late adverse effects. One of these is late-onset neutropenia (LON). Most investigators define LON as grade III-IV neutropenia occurring 3-4 weeks after the last treatment with rituximab, in the absence of an alternative explanation for the neutropenia.We report 6 cases of LON identified in our institution. Four patients were treated for diffuse large B-cell lymphoma, and 2 patients for follicular lymphoma. Median patient age was 68 years (range, 33-83 yr); LON appeared after a median interval of 77 days (range, 42-153 d) and lasted for a median of 5 days (range, 1-45 d). Five of the 6 patients presented with infectious complications, and 4 patients experienced recurrent episodes of neutropenia. One patient presented with LON and concomitant subacute pulmonary disease that was attributed to rituximab therapy.In addition to our own case series we present a systematic review of the literature, which we performed to compile data to describe better the syndrome of

LON. Systematic studies, case series, and case reports were extracted. Most studies dealing with LON are retrospective by design and are limited by the heterogeneous populations included in the analysis. The incidence of LON is generally reported to be in the range of 3%-27%. Data regarding populations at risk are not consistent, and in some instances are conflicting.Patients considered at increased risk of LON include patients after autologous stem cell transplantation, patients treated for acquired immunodeficiency syndrome (AIDS)-related lymphoma, and patients treated with purine analogues. Patients who received previous cytotoxic treatment as well as those treated with more intensive chemotherapy or with chemotherapy in combination with radiotherapy are also considered to be at risk of LON. In addition, advanced stages of disease and having received multiple doses of rituximab are risk factors for LON.The mechanism of LON is poorly understood. Direct toxicity is very unlikely. Some speculate that there may be an infectious etiology involved, as well as an antibody-mediated process, but these ideas have not been substantiated. The concept of a lymphocyte subpopulation imbalance leading to LON has been presented based on the demonstration of T-LGL in peripheral blood and bone marrow of patients with LON. Perturbations in stromal-derived factor-1 and in the BAFF cytokine have also been discussed as potential players in the pathogenesis of LON. A recent study correlated specific polymorphism in the immunoglobulin G Fc receptor FCγRIIIa 158 V/F with increased rates of LON.The clinical significance of LON is important because it may affect treatment strategies. Of note, infectious complications are not very frequent and not very severe. Pooling data from the major retrospective studies reveals an infection rate of 16.9%. Most infections were mild and resolved promptly. One death occurred from infection during neutropenia. Repeated episodes of LON are not uncommon, but it is so far impossible to identify those patients at risk of these relapsing episodes of LON. Re-treatment with rituximab after LON may result in recurrent episodes, but the implications and risks are uncertain at the present time. The role of growth factors once LON appears is ill defined, and the decision to use them should be made on a case-by-case basis.

RESEARCH FRONTIER:
Richardson PG ,Sonneveld P,Schuster MW, et al
Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma
N Engl J Med 2005;352:2487-2498
BACKGROUND: This study compared bortezomib with high-dose dexamethasone in patients With relapsed multiple myeloma who had received one to three previous therapies. METHODS: We randomly assigned 669 patients with relapsed myeloma to receive either an intravenous bolus of bortezomib (1.3 mg per square meter of body-surface area) on days 1, 4, 8, and 11 for eight Three-week cycles, followed by treatment on days 1, 8, 15, and 22 for three fiveweek cycles, or high-dose dexamethasone (40 mg orally) on days 1 through 4, 9 through 12, and 17 through 20 for four five-week cycles, followed by treatment on days 1 through 4 for five fourweek cycles. Patients who were assigned to receive dexamethasone were permitted to cross over to receive bortezomib in a companion study after disease progression. RESULTS: Patients treated with bortezomib had higher response rates, a longer time to progression (the primary end point), and a longer survival than patients treated with dexamethasone. The combined complete and partial response rates were 38 percent for bortezomib and 18 percent for dexamethasone ($P<0.001$), and the complete response rates were 6 percent and less than 1 percent, respectively ($P<0.001$). Median times to progression in the bortezomib and dexamethasone groups were 6.22 months (189 days) and 3.49 months (106 days), respectively (hazard ratio, 0.55; $P<0.001$). The one-year survival rate was 80 percent among patients taking bortezomib and 66 percent among patients taking

dexamethasone (P=0.003), and the hazard ratio for overall survival with bortezomib was 0.57 (P=0.001). Grade 3 or 4 adverse events were reported in 75 percent of patients treated with bortezomib and in 60 percent of those treated with dexamethasone. CONCLUSIONS: Bortezomib is superior to high-dose dexamethasone for the treatment of patients with multiple myeloma who have had a relapse after one to three previous therapies.

LANDMARK ARTICLE:
Miller RA, Maloney DG, Warnke R, Levy R.
Treatment of B-cell lymphoma with monoclonal anti-idiotype antibody
N Engl J Med. 1982;306:517-22

2. T cell neoplasms

REVIEW:
Ho K, Valdez F, Garcia R, Tirado CA.
JAK2 Translocations in hematological malignancies: Review of the literature.
J Assoc Genet Technol. 2010;36(3):107-9.
JAK2 is a cytoplasmic tyrosine kinase whose gene is located on chromosome 9p24. It is involved in the regulation of different cytokines and growth factors and plays an important role in the diagnosis and treatment of myeloproliferative neoplasms (Smith et al., 2008). Translocations involving the JAK2 locus are uncommon with just a few cases described in the literature, and they usually lead to a fusion protein with JAK2 (Patnaik et al., 2010). Chromosome 9p24 abnormalities have been described in myeloid and lymphoid neoplasms including chronic myelogenous leukemia (CML), acute megakaryoblastic leukemia, CD10+ B-cell acute lymphoblastic leukemia, T-cell ALL and chronic myeloproliferative disorders (CMD) (Smith et al., 2008; Lacronique et al., 1997). Although the breakpoints of each translocation are known, characterization of the partner gene has not been done in many of the cases reported due to insufficient sample or other factors. In the present study we review all translocations involving JAK2 that have been reported in the literature.

REVIEW
Rizvi MA. Evens AM. Tallman MS. Nelson BP. Rosen ST.
T-cell non-Hodgkin lymphoma
Blood. 2006:107;1255-64
T-cell non-Hodgkin lymphomas (NHLs) are uncommon malignancies. The current WHO/EORTC classification recognizes 9 distinct clinicopathologic peripheral T-cell NHLs. These disorders have unique characteristics and require individualized diagnostic and therapeutic strategies. Tremendous progress has been made in recent years in the understanding of the pathogenesis of these disorders. Specific chromosomal translocations and viral infections are now known to be associated with certain lymphomas. In this review, we describe their clinical and pathologic features. We also discuss the use of molecular studies in the diagnostic work-up of T-cell lymphomas. Because of the rarity of these disorders and the lack of well-designed clinical trials, the treatment of peripheral T-cell NHLs is often challenging. Additional studies are required to learn more about the biology of these diseases, which may lead to more optimal and possibly targeted therapies.

REVIEW:
Willemze R, Jaffe ES, Burg G, et al.
WHOEORTC classification for cutaneous lymphomas.

Blood. 2005; 105:3768-3785.
Primary cutaneous lymphomas are currently classified by the European Organization for Research and Treatment of Cancer (EORTC) classification or the World Health Organization (WHO) classification, but both systems have shortcomings. In particular, differences in the classification of cutaneous T-cell lymphomas other than mycosis fungoides, Sezary syndrome, and the group of primary cutaneous CD30+ lymphoproliferative disorders and the classification and terminology of different types of cutaneous B-cell lymphomas have resulted in considerable debate and confusion. During recent consensus meetings representatives of both systems reached agreement on a new classification, which is now called the WHO-EORTC classification. In this paper we describe the characteristic features of the different primary cutaneous lymphomas and other hematologic neoplasms frequently presenting in the skin, and discuss differences with the previous classification schemes. In addition, the relative frequency and survival data of 1905 patients with primary cutaneous lymphomas derived from Dutch and Austrian registries for primary cutaneous lymphomas are presented to illustrate the clinical significance of this new classification.

RESEARCH FRONTIER:
Buttgereit P, Schakowski F, Marten A, et al.
Effects of adenoviral wild-type p53 gene transfer in p53-mutated lymphoma cells.
Cancer Gene Ther. 2001;8:430-439.
The present study assessed the role of adenoviral vector-mediated wild-type p53 gene transfer in B lymphoma cells. Deficiency of p53-mediated cell death is common in human cancer contributing to both tumorigenesis and chemoresistance. Lymphoma cells are being considered as suitable targets for gene therapy protocols. Recently, we reported an adenoviral protocol leading to highly efficient gene transfer to B lymphoma cells. All lymphoma cell lines (n=5) tested here showed mutations in the p53 gene locus. The aim of this work was to transduce lymphoma cells with the wild-type p53 gene. Using this protocol, 88% of Raji, 75% of Daudi, and 45% of OCI-Ly8-LAM53 cells were transfected with the reporter gene green fluorescent protein at a multiplicity of infection of 200. The expression of green fluorescent protein in CA46 and BL41 cells was 27% and 42%, respectively. At this multiplicity of infection, growth characteristics of lymphoma cell lines were not changed significantly. In contrast, cells transduced with wild-type p53 gene showed an inhibition of proliferation as well as an increase in apoptosis. Cell loss by apoptosis after p53 gene transfer was up to 40% as compared to transduction with an irrelevant vector. In addition, we determined the effects of DNA damage produced by the DNA topoisomerase II inhibitor etoposide on wild-type p53 transfected lymphoma cells. In Ad-p53-transfected Raji cells, treatment with the drug resulted in a marked increase of cell loss in comparison to Ad-beta-Gal-transfected cells (45% vs. 77%). Interestingly, performing cytotoxicity studies, we could show an increased sensitivity of Raji and Daudi cells against immunological effector cells. In conclusion, transduction of wild-type p53 into lymphoma cells expressing mutated p53 was efficient and led to inhibition of proliferation and increase in apoptotic rate in some cell lines dependent on p53 mutation. This protocol should have an impact on the use of lymphoma cells in cancer gene therapy protocols.

LANDMARK ARTICLE:
Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC.
Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-celllymphoma.

Proc Natl Acad Sci 1980;77:7415.
Retrovirus particles with type C morphology were found in two T-cell lymphoblastoid cell lines, HUT 102 and CTCL-3, and in fresh peripheral blood lymphocytes obtained from a patient with a cutaneous T-cell lymphoma (mycosis fungoides). The cell lines continuously produce these viruses, which are collectively referred to as HTLV, strain CR(HTLVCR). Originally, the production of virus from HUT 102 cells required induction with 5-iodo-2′-deoxyuridine, but the cell line became a constitutive producer of virus at its 56th passage. Cell line CTCL-3 has been a constitutive producer of virus from its second passage in culture. Both mature and immature extracellular virus particles were seen in thin-section electron micrographs of fixed, pelleted cellular material; on occasion, typical type C budding virus particles were seen. No form of intracellular virus particle has been seen. Mature particles were 100-110 nm in diameter, consisted of an electron-dense core surrounded by an outer membrane separated by an electronlucent region, banded at a density of 1.16 g/ml on a continuous 25-65% sucrose gradient, and contained 70S RNA and a DNA polymerase activity typical of viral reverse transcriptase (RT; RNA-dependent DNA nucleotidyltransferase). Under certain conditions of assay, HTLVCR RT showed cation preference for Mg2+ over Mn2+, distinct from the characteristics of cellular DNA 317 polymerases purified from human lymphocytes and the RT from most type C viruses. Antibodies to cellular DNA polymerase γ and anti-bodies against RT purified from several animal retroviruses failed to detectably interact with HTLVCR RT under conditions that were positive for the respective homologous DNA polymerase, demonstrating a lack of close relationship of HTLVCR RT to cellular DNA polymerases γ or RT of these viruses. Six major proteins, with sizes of approximately 10,000, 13,000, 19,000, 24,000, 42,000, and 52,000 daltons, were apparent when doubly banded, disrupted HTLVCR particles were chromatographed on a NaDodSO4/polyacrylamide gel. The number of these particle-associated proteins is consistent with the expected proteins of a retrovirus, but the sizes of some are distinct from those of most known retroviruses of the primate subgroups.

3. Monocyte/macrophage neoplasms

REVIEW:

Tallman MS, Kim HT.; Paietta E, et al.

Acute Monocytic Leukemia Does Not Have a Worse Prognosis Than Other Subtypes of AML: A Report From the Eastern Cooperative Oncology Group

J Clin Oncol 2004;22:1276

PURPOSE: Acute monocytic leukemia is a distinct subtype of acute myeloid leukemia (AML) with characteristic biologic and clinical features. This study was designed to compare the outcome of patients with M5 to that of other subtypes of AML, and to identify differences in M5a and M5b. PATIENTS and METHODS: Methods: We reviewed all patients with AML M5 entered in three clinical trials for newly diagnosed AML conducted by the Eastern Cooperative Oncology Group between 1989 and 1998. Eighty-one patients, 21 with M5a and 60 with M5b, were identified. RESULTS: The complete remission rate was 62% for all patients with M5; 52% for patients with M5a and 65% for patients with M5b (P = .3), and 60% for the 1,122 patients with non-M5 AML entered on the same clinical trials (P = .8 for M5 v non-M5). The 3-year disease-free survival was 26% for all M5 patients; 18% for M5a and 28% for M5b (P = .31), and 33% for non-M5 patients (P = .13 for M5 v non-M5). The 3-year overall survival was 31% for all M5 patients; 33% for M5a and 30% for M5b (P = .65), and 30% for non-M5 (P = .74 for M5 v non-M5). The karyotypes of patients with AML M5 were heterogeneous. CD11b was the only leukemic cell antigen expressed

differently in M5a (53%) compared to M5b (77%) to a significant degree (P =.02). CONCLUSION: AML M5 represents an immunologically heterogeneous population similar to non-M5 AML with a prognosis that is not dependent on morphology. The disease-free survival and overall survival of patients with M5a, M5b, and non-M5 appear not to differ with currently available therapy.

Biswas SK, Mantovani A.
Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm.
Nat Immunol. 2010 Oct;11(10):889-96.
Plasticity is a hallmark of cells of the myelomonocytic lineage. In response to innate recognition or signals from lymphocyte subsets, mononuclear phagocytes undergo adaptive responses. Shaping of monocyte-macrophage function is an essential component of resistance to pathogens, tissue damage and repair. The orchestration of myelomonocytic cell function is a key element that links inflammation and cancer and provides a paradigm for macrophage plasticity and function. A better understanding of the molecular basis of myelomonocytic cell plasticity will open new vistas in immunopathology and therapeutic intervention.

Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, Moiraghi B, Shen Z, Mayer J, Pasquini R, Nakamae H, Huguet F, Boqué C, Chuah C, Bleickardt E, Bradley-Garelik MB, Zhu C, Szatrowski T, Shapiro D, Baccarani M.
Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia.
N Engl J Med. 2010 Jun 17;362(24):2260-70.
BACKGROUND: Treatment with dasatinib, a highly potent BCR-ABL kinase inhibitor, has resulted in high rates of complete cytogenetic response and progression-free survival among patients with chronic myeloid leukemia (CML) in the chronic phase, after failure of imatinib treatment. We assessed the efficacy and safety of dasatinib, as compared with imatinib, for the first-line treatment of chronic-phase CML.METHODS: In a multinational study, 519 patients with newly diagnosed chronic-phase CML were randomly assigned to receive dasatinib at a dose of 100 mg once daily (259 patients) or imatinib at a dose of 400 mg once daily (260 patients). The primary end point was complete cytogenetic response by 12 months, confirmed on two consecutive assessments at least 28 days apart. Secondary end points, including major molecular response, were tested at a significance level of 0.0001 to adjust for multiple comparisons. RESULTS: After a minimum follow-up of 12 months, the rate of confirmed complete cytogenetic response was higher with dasatinib than with imatinib (77% vs. 66%, P=0.007), as was the rate of complete cytogenetic response observed on at least one assessment (83% vs. 72%, P=0.001). The rate of major molecular response was higher with dasatinib than with imatinib (46% vs. 28%, P<0.0001), and responses were achieved in a shorter time with dasatinib (P<0.0001). Progression to the accelerated or blastic phase of CML occurred in 5 patients who were receiving dasatinib (1.9%) and in 9 patients who were receiving imatinib (3.5%). The safety profiles of the two treatments were similar. CONCLUSIONS: Dasatinib, administered once daily, as compared with imatinib, administered once daily, induced significantly higher and faster rates of complete cytogenetic response and major molecular response. Since achieving complete cytogenetic response within 12 months has been associated with better long-term, progression-free survival, dasatinib may improve the long-term outcomes among patients with newly diagnosed chronic-phase CML. (ClinicalTrials.gov number, NCT00481247.)

Barrett AJ, Le Blanc K.
Immunotherapy prospects for acute myeloid leukaemia.
Clin Exp Immunol. 2010 Aug;161(2):223-32.
While chemotherapy is successful at inducing remission of acute myeloid leukaemia (AML), the disease has a high probability of relapse. Strategies to prevent relapse involve consolidation chemotherapy, stem cell transplantation and immunotherapy. Evidence for immunosurveillance of AML and susceptibility of leukaemia cells to both T cell and natural killer (NK) cell attack and justifies the application of immune strategies to control residual AML persisting after remission induction. Immune therapy for AML includes allogeneic stem cell transplantation, adoptive transfer of allogeneic or autologous T cells or NK cells, vaccination with leukaemia cells, dendritic cells, cell lysates, peptides and DNA vaccines and treatment with cytokines, antibodies and immunomodulatory agents. Here we describe what is known about the immunological features of AML at presentation and in remission, the current status of immunotherapy and strategies combining treatment approaches with a view to achieving leukaemia cure.

Greer JP, Mosse CA.
Natural killer-cell neoplasms.
Curr Hematol Malig Rep. 2009 Oct;4(4):245-52.
The natural killer (NK)-cell neoplasms are rare, representing less than 1% of non-Hodgkin lymphoma, except in Asia and Latin America, where they represent 3% to 6%. NK-cell neoplasms include immature acute leukemias; a blastic NK-cell lymphoma, which is obsolete because of its plasmacytoid dendritic-cell origin; and mature NK neoplasms, comprising extranodal NK/T-cell lymphoma (ENKL), nasal-type; aggressive NK-cell leukemia; and chronic NK-cell lymphoproliferative disorders, which are often reactive. Epstein-Barr virus is usually detected in tumor cells of ENKL and aggressive NK-cell leukemia. The latter two mature NK neoplasms are relatively chemoresistant because of the frequent expression of P-glycoprotein. Early radiation is advocated for localized nasal ENKL. Stem cell transplantation is recommended for advanced disease, owing to a poor prognosis. Novel agents, including chemotherapy, inhibitors of molecular pathways, and monoclonal antibodies, are under investigation.

Maniati E, Soper R, Hagemann T.
Up for Mischief? IL-17/Th17 in the tumour microenvironment.
Oncogene. 2010 Oct 21;29(42):5653-62.
The role of interleukin (IL)-17 and the IL-17-producing T helper (Th)17 cells in cancer has recently become the focus of extensive investigation. An expanding body of literature implicates Th17 cells and their hallmark cytokine in both pro- and anti-tumourigenic processes. In this review we describe their biological activities and outline the reciprocal interactions between Th17 cells and other cells of the immune system. We also discuss the evidence regarding their dual role in the tumour microenvironment. An understanding of the processes that regulate the pro- or anti-tumour activities of Th17 cell and IL-17 will allow the development of more effective means for cancer immunotherapy.

4. Mast Cell Dyscrasias

REVIEW ARTICLES
Noack F. Sotlar K. Notter M. Thiel E. Valent P. Horny HP.
Aleukemic mast cell leukemia with abnormal immunophenotype and c-kit mutation D816V.

Leukemia & Lymphoma. 45(11):2295-302, 2004 Nov.
ABSTRACT: Mastocytosis comprises a heterogeneous group of disorders characterized by proliferation and accumulation of mast cells in 1 or more organ systems. Mast cell leukemia (MCL) is an extremely rare subtype of mastocytosis in which a leukemic spread of mast cells and a rapid progression of disease is seen. In typical cases, mast cells are found in the peripheral blood. However, an aleukemic variant of MCL (formerly termed malignant mastocytosis) has also been described. We here report a case of aleukemic MCL with abnormal immunophenotype of mast cells and the classical c-kit point mutation Asp-816-Val (=D816V). The 75-year-old male patient had a short history of weight loss and lymphadenopathy. There were no urticaria pigmentosa-like skin lesions. The bone marrow was diffusely infiltrated with atypical mast cells that comprised more than 80% of all nucleated cells on a bone marrow smears. As assessed by immunohistochemistry, neoplastic mast cells expressed tryptase, chymase, CD2, CD25, CD68, and the KIT protein (CD117). Mutation analysis revealed the c-kit mutation D816V. Since circulating mast cells could not be detected in the peripheral blood, the diagnosis of aleukemic MCL was established in accordance to the updated WHO consensus classification. This case further supports the notion that the pathogenesis (c-kit mutation D816V) in MCL is closely related to that found in indolent mast cell disorders. However, additional (but yet unknown) molecular (genetic) defects have to be considered to explain the extremely heterogenous clinical course in these patients.

Alvarez-Twose I. Gonzalez de Olano D. Sanchez-Munoz L. Matito A. Esteban-Lopez MI. Vega A. Mateo MB. Alonso Diaz de Durana MD. de la Hoz B. Del Pozo Gil MD. Caballero T. Rosado A. Sanchez Matas I. Teodosio C. Jara-Acevedo M. Mollejo M. Garcia-Montero A. Orfao A. Escribano L.
Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms.
Journal of Allergy & Clinical Immunology. 125(6):1269-1278.e2, 2010 Jun
ABSTRACT BACKGROUND: Systemic mast cell activation disorders (MCADs) are characterized by severe and systemic mast cell (MC) mediators-related symptoms frequently associated with increased serum baseline tryptase (sBt). OBJECTIVE: To analyze the clinical, biological, and molecular characteristics of adult patients presenting with systemic MC activation symptoms/anaphylaxis in the absence of skin mastocytosis who showed clonal (c) versus nonclonal (nc) MCs and to provide indication criteria for bone marrow (BM) studies. METHODS: Eighty-three patients were studied. Patients showing clonal BM MCs were grouped into indolent systemic mastocytosis without skin lesions (ISMs(-); n = 48) and other c-MCADs (n = 3)-both with CD25(++) BM MCs and either positive mast/stem cell growth factor receptor gene (KIT) mutation or clonal human androgen receptor assay (HUMARA) tests-and nc-MCAD (CD25-negative BM MCs in the absence of KIT mutation; n = 32) and compared for their clinical, biological, and molecular characteristics. RESULTS: Most clonal patients (48/51; 94%) met the World Health Organization criteria for systemic mastocytosis and were classified as ISMs(-), whereas the other 3 c-MCAD and all nc-MCAD patients did not. In addition, although both patients with ISMs(-) and patients with nc-MCAD presented with idiopathic and allergen-induced anaphylaxis, the former showed a higher frequency of men, cardiovascular symptoms, and insect bite as a trigger, together with greater sBt. Based on a multivariate analysis, a highly efficient model to predict clonality before BM sampling was built that includes male sex (P = .01), presyncopal and/or syncopal episodes (P = .009) in the absence of urticaria and angioedema (P = .003), and sBt >25 microg/L (P = .006) as independent predictive factors. CONCLUSIONS:

Patients with c-MCAD and ISMs(-) display unique clinical and laboratory features different from nc-MCAD patients. A significant percentage of c-MCAD patients can be considered as true ISMs(-) diagnosed at early phases of the disease.

RESEARCH FRONTIER:
Pardanani A. Tefferi A.
Proposal for a revised classification of systemic mastocytosis
Blood. 115(13):2720-1, 2010 Apr 1.

Karlberg M. Ekoff M. Huang DC. Mustonen P. Harvima IT. Nilsson G.
The BH3-mimetic ABT-737 induces mast cell apoptosis in vitro and in vivo: potential for therapeutics
Journal of Immunology. 185(4):2555-62, 2010 Aug 15.
ABSTRACT: Mast cells and their mediators are implicated in the pathogenesis of many different diseases. One possible therapeutic intervention in mast cell-associated diseases can be to reduce the number of tissue mast cells by inducing mast cell apoptosis. In this study, we demonstrate that mast cells exhibit a high sensitivity to ABT-737, a BH3-only mimetic molecule that induces apoptosis through high-affinity binding to the prosurvival proteins, Bcl-2, Bcl-XL, and Bcl-w. Primary mast cells as well as mast cell lines tested succumbed to apoptosis in response to the inhibitor at varying but seemingly low concentrations compared with other leukocytes investigated. I.p. injections of ABT-737 in mice resulted in a total abolishment of mast cells in the peritoneum. Confocal microscopy analysis of peritoneal cells revealed apoptotic bodies of mast cells being phagocytosed by macrophages. In addition, ex vivo treatment of human skin biopsies with ABT-737 demonstrated increased mast cell apoptosis. The data we present in this article show exceptional mast cell sensitivity to ABT-737, a selective inhibitor of antiapoptotic proteins, rendering a possible application for BH3-only mimetic compounds like ABT-737 in mast cell-associated diseases, such as mastocytosis, allergy, asthma, and other chronic inflammations.

REVIEW:
Akin C. Metcalfe DD.
Systemic mastocytosis
Annu Rev Med. 2004;55:419-32
Systemic mastocytosis is a clonal disorder of the mast cell and its progenitor. The symptoms of systemic mastocytosis are due to the pathologic accumulation and activation of mast cells in various tissues such as bone marrow, skin, gastrointestinal tract, liver, and spleen. Recent studies revealed striking differences between the molecular and cellular biology of mast cells in patients with mastocytosis and those of healthy individuals. These findings are being used in formulating diagnostic criteria as well as designing novel treatment approaches to the disease.

REVIEW:
Brockow K.
Urticaria pigmentosa
Immunol Allergy Clin North Am 2004;24:287-316.
Urticaria pigmentosa (UP), resulting from the accumulation of excessive numbers of mast cells in the skin, is the most common form of cutaneous mastocytosis. Observations highlight the diversity of this disease. Clonal expansion of early hematopoietic progenitor cells carrying

activating mutations in KIT seems to be the basis of adult-onset UP. New pathogenetic findings are leading to the development of new diagnostic surrogate markers of disease and therapeutic approaches targeting neoplastic mast cells. Promising strategies may arise from an increased understanding about the cause of mastocytosis and the signaling pathways initiated by kit activation.

RESEARCH FRONTIER:
Akin C, Metcalfe D
The biology of Kit in disease and the application of pharmacogenetics
J Allergy Clin Immunol 2004:114;13-19.
C-kit encodes a transmembrane protein with intrinsic tyrosine kinase activity, which functions as the receptor for stem cell factor. It is expressed on a variety of cell types, including mast cells, hematopoietic progenitor cells, melanocytes, germ cells, and gastrointestinal pacemaker cells. Mutations resulting in alteration of Kit function are associated with diseases involving each of these cells. Recent development of tyrosine kinase inhibitors led to their evaluation as novel therapies for diseases associated with Kit activation. This review will discuss the pathobiology of Kit in human disease, with a particular emphasis on implications for potential targeted treatment strategies in mast cell disease.

LANDMARK ARTICLE:
Schwartz LB, Metcalf DD,Miller JS, et al.
Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis
N Engl J Med 1987 316:1622-1626
Better methods are needed to assess mast-cell activation in vivo and to distinguish the activation Better methods are needed to assess mast-cell activation in vivo and to distinguish the activation of mast cells from that of basophils. Tryptase, a neutral protease selectively concentrated in the secretory granules of human mast cells (but not basophils), is released by mast cells together with histamine and serves as a marker of mast-cell activation. In 17 patients with systemic mastocytosis, concentrations of tryptase in plasma were linearly related to those of histamine (P less than 0.01). Eleven of the 17 patients had tryptase levels of 4 to 88 ng per milliliter, indicating ongoing mast-cell activation. In each of six patients who experienced corresponding anaphylactic reactions after penicillin, aspirin, or melon ingestion, a wasp sting, exercise, or antilymphocyte globulin injection, tryptase levels in serum ranged from 9 to 75 ng per milliliter, indicating mast-cell activation during each of these events. In contrast, serum tryptase levels were less than 5 ng per milliliter in all patients presenting with myocardial disease (n = 8, 6 with hypotension) or sepsis (n = 6, 3 with hypotension) and in the controls (n = 20). One patient had a myocardial infarction after anaphylaxis in response to a wasp sting and an elevated tryptase level of 25 ng per milliliter. Thus, the plasma or serum tryptase level is a diagnostic correlate of mast cell related events.

IMAGES IN CLINICAL MEDICINE:
Systemic Mastocytosis
Deb A., Tefferi A.
N Engl J Med 2003; 349:e7 and
Asmis L. M., Girardet C.

N Engl J Med 2002; 346:174

5. Eosinophilic Disorders

REVIEW:

Simon D. Wardlaw A. Rothenberg ME.

Organ-specific eosinophilic disorders of the skin, lung, and gastrointestinal tract

Journal of Allergy & Clinical Immunology. 126(1):3-13, 2010

ABSTRACT: Eosinophils are multifunctional leukocytes that increase in various tissues in patients with a variety of disorders. Locally, they can be involved in the initiation and propagation of diverse inflammatory responses. In this review the clinical association of eosinophils with diseases of the skin, lung, and gastrointestinal tract is summarized. An approach to determining the causal role of eosinophils in these diseases is presented. Recent findings concerning molecular diagnosis, cause, and treatment are discussed.

Tefferi A. Gotlib J. Pardanani A.

Hypereosinophilic syndrome and clonal eosinophilia: point-of-care diagnostic algorithm and treatment update.

Mayo Clinic Proceedings. 85(2):158-64, 2010 Feb

ABSTRACT: Acquired eosinophilia is operationally categorized into secondary, clonal, and idiopathic types. Causes of secondary eosinophilia include parasite infections, allergic or vasculitis conditions, drugs, and lymphoma. Clonal eosinophilia is distinguished from idiopathic eosinophilia by the presence of histologic, cytogenetic, or molecular evidence of an underlying myeloid malignancy. The World Health Organization classification system for hematologic malignancies recognizes 2 distinct subcategories of clonal eosinophilia: chronic eosinophilic leukemia, not otherwise specified and myeloid/lymphoid neoplasms with eosinophilia and mutations involving platelet-derived growth factor receptor alpha/beta or fibroblast growth factor receptor 1. Clonal eosinophilia might also accompany other World Health Organization-defined myeloid malignancies, including chronic myelogenous leukemia, myelodysplastic syndromes, chronic myelomonocytic leukemia, and systemic mastocytosis. Hypereosinophilic syndrome, a subcategory of idiopathic eosinophilia, is defined by the presence of a peripheral blood eosinophil count of 1.5 x 10(9)/L or greater for at least 6 months (a shorter duration is acceptable in the presence of symptoms that require eosinophil-lowering therapy), exclusion of both secondary and clonal eosinophilia, evidence of organ involvement, and absence of phenotypically abnormal and/or clonal T lymphocytes. The presence of the latter defines lymphocytic variant hyper eosinophilia, which is best classified under secondary eosinophilia. In the current review, we provide a simplified algorithm for distinguishing the various causes of clonal and idiopathic eosinophilia and discuss current therapy, including new drugs (imatinib mesylate, alemtuzumab, and mepolizumab).

RESEARCH FRONTIER:

Busse WW. Ring J. Huss-Marp J. Kahn JE.

A review of treatment with mepolizumab, an anti-IL-5 mAb, in hypereosinophilic syndromes and asthma

Journal of Allergy & Clinical Immunology. 125(4):803-13, 2010 Apr.

ABSTRACT: The hypereosinophilic syndromes (HESs) are a heterogeneous group of diseases characterized by peripheral blood eosinophilia with end-organ damage and varying in severity

from nonspecific symptoms to life-threatening. Treatment objectives are a safe reduction of blood and tissue eosinophil levels and prevention of eosinophil-mediated tissue damage. Current treatment of patients with HESs, who lack the FIP-1-like 1-platelet-derived growth factor receptor alpha (FIP1L1-PDGFRA) fusion gene, is mainly systemic corticosteroid therapy. Eosinophil development from hematopoietic progenitor cells is regulated by IL-5, which influences maturation, differentiation, mobilization, activation, and survival. Consequently, inhibiting IL-5 is a logical therapeutic objective for patients with HESs or selected patients with asthma. Mepolizumab is a fully humanized anti-IL-5 monoclonal IgG(1) antibody that binds to free IL-5 with high affinity and specificity to prevent IL-5 from associating with the IL-5 receptor complex alpha-chain on the surface of eosinophils. In clinical trials with patients with HESs, mepolizumab reduced blood eosinophil counts and the maintenance corticosteroid dose and had no major safety concerns. Mepolizumab reduced airway and blood eosinophils and prevented asthma exacerbations. Thus, mepolizumab may be effective for long-term treatment of patients with selected eosinophilic disorders. A review of treatment with mepolizumab, an anti-IL-5 mAb, in hypereosinophilic syndromes and asthma

Rothenberg ME. Klion AD. Roufosse FE. Kahn JE. Weller PF. Simon HU. Schwartz LB. Rosenwasser LJ. Ring J. Griffin EF. Haig AE. Frewer PI. Parkin JM. Gleich GJ
Treatment of patients with the hypereosinophilic syndrome with mepolizumab.[Erratum appears in N Engl J Med. 2008 Jun 5;358(23): 2530]
ABSTRACT BACKGROUND: The hypereosinophilic syndrome is a group of diseases characterized by persistent blood eosinophilia, defined as more than 1500 cells per microliter with end-organ involvement and no recognized secondary cause. Although most patients have a response to corticosteroids, side effects are common and can lead to considerable morbidity. METHODS: We conducted an international, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of an anti-interleukin-5 monoclonal antibody, mepolizumab, in patients with the hypereosinophilic syndrome. Patients were negative for the FIP1L1-PDGFRA fusion gene and required prednisone monotherapy, 20 to 60 mg per day, to maintain a stable clinical status and a blood eosinophil count of less than 1000 per microliter. Patients received either intravenous mepolizumab or placebo while the prednisone dose was tapered. The primary end point was the reduction of the prednisone dose to 10 mg or less per day for 8 or more consecutive weeks. RESULTS: The primary end point was reached in 84% of patients in the mepolizumab group, as compared with 43% of patients in the placebo group (hazard ratio, 2.90; 95% confidence interval [CI], 1.59 to 5.26; P<0.001) with no increase in clinical activity of the hypereosinophilic syndrome. A blood eosinophil count of less than 600 per microliter for 8 or more consecutive weeks was achieved in 95% of patients receiving mepolizumab, as compared with 45% of patients receiving placebo (hazard ratio, 3.53; 95% CI, 1.94 to 6.45; P<0.001). Serious adverse events occurred in seven patients receiving mepolizumab (14 events, including one death; mean [+/-SD] duration of exposure, 6.7+/-1.9 months) and in five patients receiving placebo (7 events; mean duration of exposure, 4.3+/-2.6 months). CONCLUSIONS: Our study shows that treatment with mepolizumab, an agent designed to target eosinophils, can result in corticosteroid-sparing for patients negative for FIP1L1-PDGFRA who have the hypereosinophilic syndrome

REVIEW:
Roufosse F, Cogan E, Goldman M

Recent advances in pathogenesis and management of hypereosinophilic syndromes.
Allergy. 2004;59:673-89
Idiopathic hypereosinophilic syndrome is a largely heterogeneous disorder defined until now as persistent marked hypereosinophilia of unknown origin generally complicated by end-organ damage. Recent studies clearly indicate that many patients fulfilling the diagnostic criteria of this syndrome can now be classified as presenting one of two major disease variants: the myeloproliferative or the lymphocytic variant. Research in cellular and molecular biology has provided .rm evidence for the existence of discrete hematological disorders underlying these variants, questioning the pertinence of continued reference to idiopathic hypereosinophilic syndrome in such patients. Furthermore, identication of these variants has a number of prognostic and therapeutic implications thatmust be taken into consideration for adequate management of these patients.

REVIEW:
Klion, AD, Bochner, BS, Gleich GJ, et al
Approaches to the treatment of hypereosinophilic syndromes: A workshop summary report
J Allergy Clin Immunol 2006;117:1292-302.
Hypereosinophilic syndromes are a heterogeneous group ofuncommon disorders characterized by the presence of markedperipheral blood eosinophilia, tissue eosinophilia, or both, resulting in a wide variety of clinical manifestations. Although corticosteroids are the first-line therapy for many of these disorders, approaches to the treatment of patients who do not tolerate or are unresponsive to corticosteroids are poorly standardized. A multidisciplinary group of 37 clinicians and scientists participated in a workshop held in May 2005 in Bern, Switzerland to discuss current and future approaches to therapy for 3 eosinophilmediated disorders: hypereosinophilic syndrome, Churg-Strauss syndrome, and eosinophil-associated gastrointestinal disease. The goal of the workshop was to summarize available data regarding treatment of these disorders to identify the most promising therapies and approaches for further study. There was consensus among all of the participants that the identification of markers of disease progression to assess treatment responses is a research priority for all 3 disorders. Furthermore, the need for newer therapeutic strategies and novel drugs, as well as multicenter trials to assess all treatment modalities, was emphasized.

LANDMARK PAPER:
Cools J. DeAngelo DJ. Gotlib J. Stover EH. Legare RD. Cortes J. Kutok J. Clark J. Galinsky I. Griffin JD. Cross NC. Tefferi A. Malone J. Alam R. Schrier SL. Schmid J. Rose M. Vandenberghe P. Verhoef G. Boogaerts M. Wlodarska I. Kantarjian H. Marynen P. Coutre SE. Stone R. Gilliland DG.
A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome
ABSTRACT BACKGROUND: Idiopathic hypereosinophilic syndrome involves a prolonged state of eosinophilia associated with organ dysfunction. It is of unknown cause. Recent reports of responses to imatinib in patients with the syndrome suggested that an activated kinase such as ABL, platelet-derived growth factor receptor (PDGFR), or KIT, all of which are inhibited by imatinib, might be the cause. METHODS: We treated 11 patients with the hypereosinophilic syndrome with imatinib and identified the molecular basis for the response. RESULTS: Nine of the 11 patients treated with imatinib had responses lasting more than three months in which the

eosinophil count returned to normal. One such patient had a complex chromosomal abnormality, leading to the identification of a fusion of the Fip1-like 1 (FIP1L1) gene to the PDGFRalpha (PDGFRA) gene generated by an interstitial deletion on chromosome 4q12. FIP1L1-PDGFRalpha is a constitutively activated tyrosine kinase that transforms hematopoietic cells and is inhibited by imatinib (50 percent inhibitory concentration, 3.2 nM). The FIP1L1-PDGFRA fusion gene was subsequently detected in 9 of 16 patients with the syndrome and in 5 of the 9 patients with responses to imatinib that lasted more than three months. Relapse in one patient correlated with the appearance of a T674I mutation in PDGFRA that confers resistance to imatinib. CONCLUSIONS: The hypereosinophilic syndrome may result from a novel fusion tyrosine kinase - FIP1L1-PDGFRalpha - that is a consequence of an interstitial chromosomal deletion. The acquisition of a T674I resistance mutation at the time of relapse demonstrates that FIP1L1-PDGFRalpha is the target of imatinib. Our data indicate that the deletion of genetic material may result in gain-of-function fusion proteins.

RESEARCH FRONTIER:
Kim YJ, Prussin C, Martin B, et al
Rebound eosinophilia after treatment of hypereosinophilic syndrome and eosinophilic gastroenteritis with monoclonal anti-IL-5 antibody SCH55700
J Allergy Clin Immunol. 2004;114:1449-55.
BACKGROUND: Hypereosinophilic syndrome and eosinophilic gastroenteritis with peripheral eosinophilia are characterized by sustained eosinophilia and eosinophil-mediated tissue damage. Although treatment with the humanized monoclonal anti-IL-5 antibody SCH55700 resulted in improvement of eosinophilia and clinical symptoms in 6 of 8 of patients with hypereosinophilic syndrome or eosinophilic gastroenteritis with peripheral eosinophilia for as long as 12 weeks, eosinophil counts subsequently rose above baseline levels, accompanied by an exacerbation of symptoms. OBJECTIVE: To identify the mechanism underlying this rebound eosinophilia. METHODS: Purified eosinophils from patients or normal donors were cultured with IL-5, patient serum, and/or anticytokine antibodies, and eosinophil survival was assessed by flow cytometry. Serum and intracellular cytokine levels were measured by multiplex sandwich ELISA and flow cytometry, respectively. RESULTS: Before treatment with SCH55700, in vitro eosinophil survival in media and in response to recombinant IL-5 was similar in patients and normal donors. At 1 month posttreatment, the eosinophil survival curves were unchanged in 4 of 5 patients in media and in all 5 patients in response to recombinant IL-5. Normal eosinophil survival was prolonged in cultures containing posttreatment but not pretreatment sera (pretreatment vs posttreatment, 10.74% vs 73.02% live cells; P = .01). This posttreatment serum effect on eosinophil survival was reversed by the addition of the monoclonal anti-IL-5 antibody TRFK5. Although increased levels of serum IL-5 were observed at 1 month compared with 2 to 3 days posttreatment in 5 of 6 patients (P = .04), intracellular cytokine analysis did not reveal increased production of IL-5 by peripheral blood mononuclear cells. CONCLUSIONS: The rebound eosinophilia after SCH55700 treatment is a result of a serum factor that enhances eosinophil survival. Reversal of this effect by the addition of antibody to IL-5 suggests that this factor may be IL-5 itself.

LANDMARK ARTICLE:
Schrezenmeier H,Thome SD, Tewald F, et al.
Interleukin-5 is the predominant eosinophilopoietin produced by cloned T lymphocytes in

hypereosinophilic syndrome.
Exp Hematol. 1993;21:358-65
oned T lymphocytes (TLC) of the CD4+CD8- phenotype established from peripheral blood of a patient with idiopathic hypereosinophilic syndrome (HES) were found to release a lineagespecific eosinophilic colony-stimulating factor (Eo-CSF). The present study was undertaken to identify the lymphokine accounting for this Eo-CSF activity. Comparison of TLC-derived Eo-CSF with recombinant human interleukin-5 (rhIL-5), recombinant human granulocytemacrophage colony-stimulating factor (rhGM-CSF) and recombinant human interleukin-3 (rhIL-3) by in vitro clonogenic assays revealed similar bioactivity of HES-derived Eo-CSF and IL-5. Neutralization studies using specific antibodies against IL-5, GM-CSF and IL-3 confirmed that IL-5 mainly accounts for the Eo-CSF activity in all 9 HES-derived TLC tested. Eosinophilic colony (CFU-Eo) formation supported by conditioned media of the TLC was significantly inhibited in all clones by addition of anti-IL-5 monoclonal antibody (MAB) to the conditioned media. Inhibition by anti-IL-5 MAB was specific and dose-dependent. In 2 of the 9 clones, anti-GM-CSF antibodies could partially neutralize the Eo-CSF activity in the conditioned media. In 4 clones, addition of a combination of anti-IL-5 MAB and anti-GM-CSF antiserum to the conditioned media reduced CFU-Eo formation significantly more than addition of anti-IL-5 MAB alone. In none of the TLC could a significant role for IL-3 in eosinophilic colony formation be shown. These results were confirmed at the mRNA level. Cytokine transcripts were detected by reverse transcription (RT) and subsequent polymerase chain reaction (PCR). Under the same experimental conditions, all HES-derived TLC, but only one third of tested TLC from healthy donors, expressed IL-5 mRNA 5 days after stimulation. In control TLC with inducible IL-5 mRNA expression, IL-5 transcripts were found for only 3 days after stimulation. In contrast, HES-derived TLC contained IL-5 mRNA at least until day 18 after restimulation. All HES clones expressed GM-CSF mRNA upon stimulation. Two HES-derived TLC were found to lack IL-3 mRNA even after stimulation. Whereas IL-5 was expressed abundantly in all HESclones, the intensity of PCR products for GM-CSF and IL-3 showed striking differences. Our in vitro results suggest that IL-5 produced by activated CD4+ T lymphocytes plays a crucial role in the induction of eosinophilia in HES. In addition, GM-CSF but not IL-3 seems to contribute partially to the increased eosinophil production in HES.

6. Cryopathies and Amyloid

REVIEW:
Grateau G. Duruoz MT.
Autoinflammatory conditions; When to suspect? How to treat?
Best Practice & Research in Clinical Rheumatology. 24(3):401-11, 2010 Jun.
ABSTRACT: The term 'autoinflammatory disease' encompasses an enlarging group of inflammatory disorders defined as Mendelian genetic diseases of the innate immune system. This group is growing considering the fact that diseases sharing strong similarities with this core group can be defined as autoinflammatory. The core group consists now of six disorders also known as hereditary recurrent fever syndromes. The most common is familial Mediterranean fever, an autosomal recessive disease affecting mainly populations of Mediterranean ancestry. All these six diseases are characterised by inflammatory attacks both at the clinical and at the biological level. The diagnosis of each of these diseases relies first on clinical features and second on genetic testing, which is guided by the clinical results. Deciphering the role of interleukin-1 in the regulation of the inflammatory response through the inflammasome represents a major advance in

the knowledge of the mechanisms of these diseases with, as a main consequence, treatment with interleukin-1 inhibitors. Copyright 2009 Elsevier Ltd. All rights reserved

Chee CE. Lacy MQ. Dogan A. Zeldenrust SR. Gertz MA.
Pitfalls in the diagnosis of primary amyloidosis
Clinical lymphoma, myeloma & leukemia. 10(3):177-80, 2010 Jun.
ABSTRACT: Primary (AL) amyloidosis is the most prevalent type of systemic amyloidosis, and management of this disease has evolved through the years from supportive care to aggressive treatments that include immunomodulatory agents and high-dose chemotherapy with hematopoietic stem cell transplantation. However, other types of amyloidosis are increasingly recognized, such as familial amyloidosis and senile cardiac amyloidosis, and management of these conditions is different from that of AL amyloidosis. Congo red staining with exhibition of an apple-green birefringence is diagnostic of amyloid. Immunohistochemistry can detect amyloid deposits but has limitations, and newer molecular techniques such as mass spectrometry show promise in determining types of amyloidosis. Physicians need to be aware of clinical scenarios that can mimic AL amyloidosis to avoid misdiagnosis and harm to the patient.

Pettersson T. Konttinen YT.
Amyloidosis-recent developments.
Seminars in Arthritis & Rheumatism. 39(5):356-68, 2010 Apr
ABSTRACT OBJECTIVES: To describe the clinical presentation, diagnosis, classification, grading, evaluation of prognosis, and treatment of amyloidosis against the background of its pathomechanisms. METHODS: PubMed and MEDLINE databases (1990 to October 2007) and internet were searched for the key word amyloidosis and evaluated on the basis of the authors' own clinical experience and work on the topic. RESULTS: A clinical suspicion of amyloidosis arises when a patient with a chronic inflammatory disease, plasma cell dyscrasia, or a family history of hereditary amyloidosis develops "an amyloid syndrome" or more rare but specific signs. Microscopy of Congo red stained tissue specimens under polarized light shows birefringent amyloid, which is typed by identification of the amyloid precursor by immunohistochemistry, amino acid sequencing, or proteomics. The diagnosis can be supported by genetic tests. Amyloidosis now covers biochemically and clinically 27 distinct types in man and 9 in animals. Grading to mild, moderate, and severe disease based on laboratory tests and radiology is introduced. Prognosis is affected by the rate of synthesis and the concentration of the circulating precursor. Accurate diagnosis of the underlying disease is mandatory as the treatment is based on disease control and inhibition of amyloid precursor production. Organ-specific treatment, such as transplantation, hemodialysis, treatment of heart failure, pacemakers, and substitution to prevent nutritional deficiencies, is often needed. CONCLUSIONS: As our knowledge of the pathogenesis of amyloidosis and the structure-function relationship of amyloid proteins increases, new therapies will be developed to prevent protein misfolding and aggregation, inhibit fibrillogenesis, and enhance clearance of amyloid. Copyright

RESEARCH FRONTIER:
Kerchner GA. Boxer AL.
Bapineuzumab
Expert Opinion on Biological Therapy. 10(7):1121-30, 2010 Jul.

ABSTRACT: IMPORTANCE OF THE FIELD: Alzheimer's disease is the leading cause of dementia in the elderly, and there is no disease-modifying therapy yet available. Immunotherapy directed against the beta-amyloid peptide may be capable of slowing the rate of disease progression. Bapineuzumab, an anti-beta-amyloid monoclonal antibody, will be the first such agent to emerge from Phase III clinical trials. AREAS COVERED IN THIS review The primary literature on bapineuzumab from 2009 and 2010 is reviewed in its entirety, along with the literature on AN1792, a first-generation anti-beta-amyloid vaccine, from 2003 to 2009. Other Alzheimer's disease immunotherapeutics currently in development, according to www.clinicaltrials.gov , are also discussed. WHAT THE READER WILL GAIN: In addition to a critical appraisal of the Phase II trial results for bapineuzumab, this review considers the broader field of immunotherapy for Alzheimer's disease as a whole, including the challenges ahead. TAKE HOME MESSAGE: Bapineuzumab appears capable of reducing the cerebral beta-amyloid peptide burden in patients with Alzheimer's disease. However, particularly in APOE 4 carriers, its ability to slow disease progression remains uncertain, and vasogenic edema - a dose-limiting and potentially severe adverse reaction - may limit its clinical applicability

Kastritis E. Wechalekar AD. Dimopoulos MA. Merlini G. Hawkins PN. Perfetti V. Gillmore JD. Palladini G.
Journal of Clinical Oncology. 28(6):1031-7, 2010 Feb 20
Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis
ABSTRACT: PURPOSE: To assess the efficacy and tolerability of bortezomib with or without dexamethasone and to define prognostic factors for patients with primary systemic light chain (AL) amyloidosis treated with bortezomib or both. PATIENTS AND METHODS Ninety-four patients from three centers were analyzed: 19% received the combination as first-line treatment, 81% had a median of two previous therapies, and 69% had refractory disease, while most patients had symptomatic heart involvement or elevated serum N-terminal pro-brain natriuretic peptide (NT-proBNP). Results A hematologic response was achieved in 71% within a median of 52 days, including 25% complete responses (CRs). Previously untreated patients had a 47% CR rate. Age 65 years or younger (P = .043) and twice weekly administration of bortezomib (P = .041) were associated with higher response rates. A cardiac response was documented in 29% of patients, in most as sustained improvement of functional class and less often as a decrease in wall thickness. Hematologic responses were associated with a cardiac response and NT-proBNP reduction. After a median follow-up of 12 months, 29% of patients had organ progression and 27% had hematologic progression. Median survival has not been reached and the 1-year survival rate is 76%. Baseline NT-proBNP was independently associated with survival (P = .001), while in a landmark analysis, survival was associated with NT-proBNP reduction of > or = 30% (P = .006) and achievement of hematologic response (P = .001). Toxicity was manageable and mostly consisted of neuropathy, orthostasis, peripheral edema, and constipation or diarrhea. CONCLUSION Bortezomib with or without dexamethasone is active in AL amyloidosis and induces rapid responses and high rates of hematologic and organ responses. Serial measurement of cardiac biomarkers is a powerful predictor of outcome

REVIEW:
Ferri C, Mascia MT
Cryoglobulinemic vasculitis
Curr Opin Rheumatol 2006;18:54–63.

Cryoglobulinemic vasculitis is an immune-complexmediated systemic vasculitis involving small–medium-sized vessels. A causative role of hepatitis C virus in over 80% patients has been definitively established, with heterogeneous geographical distribution. This review focuses on recent etiopathogenetic, clinico-diagnostic, and therapeutic studies.

REVIEW:
Mark B. Pepys
Amyloidosis
Ann Rev Med 2006; 57: 223-241
Amyloidosis is a clinical disorder caused by extracellular deposition of insoluble abnormal fibrils, derived from aggregation of misfolded, normally soluble, protein. About 23 different unrelated proteins are known to form amyloid fibrils in vivo, which share a pathognomonic structure although they are associated with clinically distinct conditions. Systemic amyloidosis, with amyloid deposits in the viscera, blood vessel walls, and connective tissue, is usually fatal and is the cause of about one per thousand deaths in developed countries. This rarity and the variable involvement of different organs and tissues are often responsible for missed or delayed diagnosis, and amyloidosis remains a considerable clinical challenge. However, recent elucidation of important aspects of pathogenesis, as well as developments in diagnosis, monitoring, and treatment, have greatly improved outcomes, especially when patients are managed in specialist centers.

RESEARCH FRONTIER:
Mazzaro C, Zorat F, Caizzi M, et al.
Treatment with peg-interferon alfa-2b and ribavirin of hepatitis C virus-associated mixed cryoglobulinemia: a pilot study.
J Hepatol. 2005;42:632-8
BACKGROUND/AIMS: The aim of this study is to verify the efficacy and safety of peginterferon alfa-2b in combination with ribavirin for initial treatment of HCV-associated mixed cryoglobulinemia. METHODS: Eighteen patients (7 women and 11 men) affected by mixed cryoglobulinemia were included in the study and treated with peg-interferon alfa-2b 1.0 microg/kg once a week plus ribavirin (1000 mg daily) for 48 weeks, regardless of the HCV genotype. RESULTS: At the end of the treatment HCV-RNA became undetectable in 15 patients (83%) and most patients improved clinically. One subject suspended treatment at 13th week due to depression. A large fraction of the patients (8 cases: 44%) relapsed both virologically and clinically a few weeks after the end of therapy. At the end of follow-up, only eight patients (44%) obtained a sustained virological response. CONCLUSIONS: Peg-interferon alfa-2b in combination with ribavirin seems safe and useful for patients affected by mixed cryoglobulinemia, but not as effective as in patients with HCV-positive chronic hepatitis without cryoglobulinemia.

LANDMARK ARTICLE:
Levo Y , Gorevic PD , Kassab HJ,et al
Association between hepatitis B virus and essential mixed cryoglobulinemia
N Engl J Med 1977;296:1501-1504
In view of a high frequency of liver involvement in patients with essential mixed cryoglubulinemia, we looked for evidence for hepatitis B virus infection in 25 serum specimens and 19 cryoprecipitates obtained from 30 patients. Three of the 25 serum specimens contained

Hbs Ag, and 12 had antibody. The frequency of positive results was increased to six and 11 of 19 respectively when cryoprecipitates were examined, and 14 of 19 (74 per cent) of the cryoprecipitates were positive for either HBs Ag or its antibody. Electron microscopy of four cryoprecipitates showed structures resembling the 20-nm and 27-nm spheres, tubules, as well as the Dane particles characteristic of hepatitis B virus infection. Since such infection appears to be involved in the pathogenesis of the syndrome, the term "essential mixed cryoglobulinemia" should be replaced by "mixed cryoglobulinemia secondary to hepatitis B virus" or perhaps to other viral infections.

7. Clinical skills: Physical findings associated with neoplasms, interpretation of serum protein electrophoresis and immunoelectrophoresis, interpretation of serum immunoglobulin levels, and interpretation of lymphocyte subset data.

Velez NF. Saavedra-Lauzon AP.
Toxic exanthems in the adult population
American Journal of Medicine. 123(4):296-303, 2010 Apr.
ABSTRACT: Frequently the internist is confronted with the nonspecific exanthematous eruption. While often a sign of a benign and self-limiting process, an exanthem also might herald the development of a more severe systemic syndrome. Infections, immune-mediated processes, drug reactions, a neoplasm, and familial syndromes with poor prognoses might all manifest initially with an exanthem. A thorough history and complete physical examination should be performed on all patients who present with an exanthem. Characterization of the exanthem morphology, other physical examination findings, and review of systems can help guide laboratory testing and ensure prompt diagnosis and early treatment of potentially life-threatening conditions. This article provides a brief overview of the conditions that must be considered in the evaluation of an ill patient with an exanthem.

Salzman BE. Lamb K. Olszewski RF. Tully A. Studdiford J.
Diagnosing cancer in the symptomatic patient
Primary Care; Clinics in Office Practice. 36(4):651-70; 2009 Dec
ABSTRACT: Finding cancer at its earliest, most treatable stage gives patients the greatest chance of survival. For a number of cancers, screening tests allow for early detection and treatment, and thereby, reduce cancer-related mortality. However, many cancers are discovered by symptomatic presentation rather than screening. This article addresses several symptoms commonly reported in the primary care setting, including rectal bleeding, a breast lump, cough, lymphadenopathy, and weight loss, and offers an evidence-based approach to the consideration and possibly the diagnosis of cancer.

REVIEW (Paraneoplastic findings):
Thomas I. Schwartz RA.
Cutaneous paraneoplastic syndromes: uncommon presentations.
Clin Dermatol. 2005;23:593-600, 2005
Paraneoplastic syndromes are a group of clinical manifestations associated with a malignancy, but not directly related to the primary tumor itself or to its metastases. Characteristically, they follow a course parallel to the tumor, resolve with successful treatment of the primary tumor, and tend to recur with its relapse or the onset of metastases. The mechanism by which they occur is not well understood, but may be related to the production of bioactive substances by or in response to the

tumor, such as polypeptide hormones, hormone-like peptides, antibodies or immune complexes, cytokines, or growth factors.

REVIEW (Immunoelectophoresis):
Keren, D
Procedures for the Evaluation of Monoclonal Immunoglobulins
Arch Pathol Lab Med. 1999;123:126–132)
A wide variety of techniques are available for the screening, characterization, and quantification of monoclonal proteins. These techniques vary in regard to the expense, skill and intensity of labor involved, and sensitivity for detection of low levels of monoclonal proteins or of those with unusual migration. Detection of monoclonal proteins requires the use of high-resolution electrophoresis (either gel-based or capillary) and immunofixation (or immunosubtraction). Immunoelectrophoresis is not recommended. Urine for detection of monoclonal free light chains should be from 24-hour samples, and the aliquot should be concentrated at least 100-fold prior to electrophoresis and immunofixation. Dipstick and sulfosalicylic acid techniques are not sensitive enough to detect small quantities ofmonoclonal free light chains and should not be used as screening tests for this purpose**.**

REVIEW (SPEP):
O'Connell TX, Horita, TJ. Kasravi B
Understanding and Interpreting Serum
Protein Electrophoresis
Am Fam Physician 2005;71:105-12.
Serum protein electrophoresis is used to identify patients with multiple myeloma and other serum protein disorders. Electrophoresis separates proteins based on their physical properties, and the subsets of these proteins are used in interpreting the results. Plasma protein levels display reasonably predictable changes in response to acute inflammation, malignancy, trauma, necrosis, infarction, burns, and chemical injury. A homogeneous spike-like peak in a focal region of the gamma-globulin zone indicates a monoclonal gammopathy. Monoclonal gammopathies are associated with a clonal process that is malignant or potentially malignant, including multiple myeloma, Waldenström's macroglobulinemia, solitary plasmacytoma, smoldering multiple myeloma, monoclonal gammopathy of undetermined significance, plasma cell leukemia, heavy chain disease, and amyloidosis. The quantity of M protein, the results of bone marrow biopsy, and other characteristics can help differentiate multiple myeloma from the other causes of monoclonal gammopathy. In contrast, polyclonal gammopathies may be caused by any reactive or inflammatory process.

REVIEW (immunoglobulin interpretation):
Ballow M.
Primary immunodeficiency disorders: Antibody deficiency
JAllergy Clin Immunol 2002;109:581-91.
As a group, antibody deficiencies represent the most common types of primary immune deficiencies in human subjects. Often symptoms do not appear until the latter part of the first year of life, as passively acquired IgG from the mother decreases to below protective levels. As with the T-cell immune deficiencies, the spectrum of antibody deficiencies is broad, ranging from the most severe type of antibody deficiency with totally absent B cells and serum Igs to patients who have a

selective antibody deficiency with normal serum Ig. In addition to the increased susceptibility to infections, a number of other disease processes (eg, autoimmunity and malignancies) can be involved in the clinical presentation. Fortunately, the availability of intravenous immune serum globulin has made the management of these patients more complete. Recently, molecular immunology has led to identification of the gene or genes involved in many of these antibody deficiencies. As discussed in this review, this has led to a better elucidation of the B-cell development and differentiation pathways and a more complete understanding of the pathogenesis of many of these antibody deficiencies.

REVIEW (lymphocyte subsets):
Backteman K. Ernerudh J
Biological and methodological variation of lymphocyte subsets in blood of human adults
Journal of Immunological Methods. 322(1-2):20-7, 2007 Apr 30
ABSTRACT: Although lymphocyte populations are often monitored over time, information about the biological variation over time is limited. Three-colour-flow cytometry was used to investigate the biological and methodological variation of lymphocyte populations in blood. Fifteen healthy individuals (11 females and 4 males) were longitudinally monitored for 2-8 years. Blood samples were drawn monthly when possible. In total, 493 observations were included. Absolute counts and proportions were determined for T-cells (CD3(+)), T-helper cells (CD3(+) CD4(+)), cytolytic T-cells (CD3(+) CD8(+)), B-cells (CD3(-) CD19(+)) and NK-cells (CD3(-) CD16(+)/56(+)). As to variation over the year, ANOVA testing showed only a minor monthly variation for absolute counts of the CD8(+) population ($p<0.05$) for October compared with June and July, whereas no significant differences were found for the other populations or in the proportions of lymphocyte subsets. Although lower than the longitudinal variation, the methodological variation, expressed as coefficient of variation (CV %), was in a similar range as the variation over time, indicating that the normal biological variation should not be overestimated, while the methodological inter-assay should be taken into consideration

REVIEW (lymphocyte subsets):
Blom B. Spits H
Development of human lymphoid cells
Ann Rev Immunol. 2006;24:287-320
The lymphocytes, T, B, and NK cells, and a proportion of dendritic cells (DCs) have a common developmental origin. Lymphocytes develop from hematopoietic stem cells via common lymphocyte and various lineage-restricted precursors. This review discusses the current knowledge of human lymphocyte development and the phenotypes and functions of the rare intermediate populations that together form the pathways of development into T, B, and NK cells and DCs. Clearly, development of hematopoietic cells is supported by cytokines. The studies of patients with genetic deficiencies in cytokine receptors that are discussed here have illuminated the importance of cytokines in lymphoid development. Lineage decisions are under control of transcription factors, and studies performed in the past decade have provided insight into transcriptional control of human lymphoid development, the results of which are summarized and discussed in this review.

GUIDELINE PRACTICE PARAMETER:
Bonilla, FA, Bernstein IL, Khan D, et al.

Practice Parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol. 2005;94:S1-63

A principal aim of this Practice Parameter is to organize current knowledge and practice in the diagnosis and management of primary immunodeficiency diseases. Preparation of this Practice Parameter included a review of the medical literature, mainly via the PubMed database. Published clinical studies or reports were rated by category of evidence and used to establish the strength of a clinical recommendation. There are few randomized trials in the diagnosis and management of primary immunodeficiency. Thus, most of these recommendations represent evidence from published case series or reports or the opinions of experts in the field.

RESEARCH FRONTIER:
Schenkein JG. Park S. Nahm MH.
Pneumococcal vaccination in older adults induces antibodies with low opsonic capacity and reduced antibody potency.
Vaccine. 26(43):5521-6, 2008 Oct 9

ABSTRACT: The primary mode of prevention of adult disease from Streptococcus pneumoniae is vaccination with anti-capsular polysaccharide vaccine; however, its effects are less in the targeted older population than in young persons. Few studies have examined the mechanism behind this limited effectiveness. We have measured antibody concentrations and opsonization titers for multiple serotypes amongst both old adults and young, healthy controls. To avoid specificity problems associated with pneumococcal antibody ELISA, we absorbed the serum samples with c-polysaccharide and capsular polysaccharide of 22F type. Antibody concentrations were found to be similar for six out of the seven tested serotypes, while opsonization titers were significantly higher in six out of seven serotypes in the younger population. Antibody potency, as measured by the ratio of opsonization titer to antibody concentration, was found to be significantly higher for the younger subjects for all serotypes. We conclude that, while all ages of adults make similar concentrations of antibodies in response to pneumococcal vaccine, the effectiveness of those antibodies is significantly reduced in the older adult population.

F. Established and Evolving Immune-based Treatment Modalities

1. Glucocorticoids and Immunosuppressants (also see Section III.A.)

REVIEW:
Barnes PJ. "Mechanisms and resistance in glucocorticoid control of inflammation," J Steroid Biochem Mol Biol. 2010 May 31;120(2-3):76-85. Epub 2010 Feb 25.

Glucocorticoids are the most effective anti-inflammatory therapy for many chronic inflammatory and immune diseases, such as asthma, but are relatively ineffective in other diseases such as chronic obstructive pulmonary disease (COPD). Glucocorticoids suppress inflammation by several mechanisms. Glucocorticoids suppress the multiple inflammatory genes that are activated in chronic inflammatory diseases, such as asthma, by reversing histone acetylation of activated inflammatory genes through binding of liganded glucocorticoid receptors (GR) to coactivator molecules and recruitment of histone deacetylase-2 (HDAC2) to the activated transcription complex. At higher concentrations of glucocorticoids GR homodimers interact with DNA recognition sites to activate transcription through increased histone acetylation of anti-inflammatory genes and transcription of several genes linked to glucocorticoid side effects. Decreased glucocorticoid responsiveness is found in patients with severe asthma and asthmatics

who smoke, as well as in all patients with COPD and cystic fibrosis. Several molecular mechanisms of glucocorticoid resistance have now been identified. HDAC2 is markedly reduced in activity and expression as a result of oxidative/nitrative stress so that inflammation becomes resistant to the anti-inflammatory actions of glucocorticoids. Dissociated glucocorticoids have been developed to reduce side effects but so far it has been difficult to dissociate anti-inflammatory effects from adverse effects. In patients with glucocorticoid resistance alternative anti-inflammatory treatments are being investigated as well as drugs that may reverse the molecular mechanism of glucocorticoid resistance.

RESEARCH FRONTIER:

Li LB, Leung DY, Martin RJ, Goleva E. "Inhibition of histone deacetylase 2 expression by elevated glucocorticoid receptor beta in steroid-resistant asthma," Am J Respir Crit Care Med. 2010 Oct 1;182(7):877-83. Epub 2010 Jun 10.

RATIONALE: Cross-talk between glucocorticoid receptors and histone deacetylases (HDACs) under steroid-insensitive conditions has not been explored. OBJECTIVES: To evaluate expression and interaction of HDACs with glucocorticoid receptor isoforms in bronchoalveolar lavage and peripheral blood mononuclear cells from steroid-resistant versus steroid-sensitive patients with asthma. METHODS: Expression of HDACs 1 through 11 was measured by real-time polymerase chain reaction in primary cells and in the DO11.10 cell line, designed to overexpress glucocorticoid receptor β. Glucocorticoid receptor β expression was inhibited in bronchoalveolar lavage cells by small interfering RNA. Human HDAC2 promoter fragments were cloned into a luciferase reporter vector, and transiently transfected with glucocorticoid receptor α- and β-encoding plasmids into the cells. Luciferase activity was then assayed in response to glucocorticoids. MEASUREMENTS AND MAIN RESULTS: Levels of HDAC2 mRNA, but not other histone deacetylases, were significantly decreased in bronchoalveolar lavage cells but not in peripheral blood mononuclear cells from steroid-resistant patients with asthma. Overexpression of glucocorticoid receptor β in DO11.10 cells selectively reduced HDAC2 mRNA and protein levels. Silencing of glucocorticoid receptor β in bronchoalveolar lavage cells from patients with asthma significantly increased HDAC2 mRNA. Luciferase activity assays with HDAC2 promoter reporter constructs identified two glucocorticoid-inducible regions in the HDAC2 promoter. Promoter activity was increased more than fourfold in dexamethasone-treated cells cotransfected with glucocorticoid receptor α. Cotransfection of glucocorticoid receptor β abolished this effect in a dose-dependent manner. CONCLUSIONS: Glucocorticoid receptor β controls expression of histone deacetylase 2 by inhibiting glucocorticoid response elements in its promoter. This highlights a novel mechanism by which glucocorticoid receptor β promotes steroid insensitivity

REVIEW:

Ito K, Chung KF, Adcock IM.

Update on glucocorticoid actionand resistance.

J Allergy Clin Immunol 2006 Mar;117(3):522-43.

Extensive development of inhaled and oral glucocorticoids has resulted in highly potent molecules that have been optimized to target activity to the lung and minimize systemic exposure. These have proved highly effective for most asthmatic subjects, but despite these developments, there are a number of subjects with asthma who fail to respond to even high doses of inhaled or even oral glucocorticoids. Advances in delineating the fundamental mechanisms of glucocorticoid pharmacology, especially the concepts of transactivation and transrepression and cofactor

recruitment, have resulted in better understanding of the molecular mechanisms whereby glucocorticoids suppress inflammation. The existence of multiple mechanisms underlying glucocorticoid insensitivity raises the possibility that this might indeed reflect different diseases with a common phenotype, and studies examining the efficacy of potential new agents should be targeted toward subgroups of patients with severe corticosteroid-resistant asthma who clearly require effective new drugs and other approaches to improved asthma control.

REVIEW:
Niven AS, Argyros G.
Alternate treatments in asthma.
Chest 2003;123:1254-1265.
Asthma is a disease that is characterized by airway inflammation and is manifested by pulmonary symptoms, reversible airway obstruction, and evidence of bronchial hyperreactivity. Standard asthma therapy, as defined by the management guidelines issued in 1999 by the National Heart, Lung, and Blood Institute, includes oral and inhaled corticosteroids, leukotriene antagonists, short-acting and long-acting β-agonists, cromolyn, and nedocromil. Although these agents are generally successful at controlling asthma symptoms, there remains a small but significant number of patients with persistent symptoms, frequent exacerbations, and objective pulmonary abnormalities despite maximum standard therapy. The long-term use of oral and high-dose inhaled corticosteroids can be associated with significant side effects, prompting research efforts to identify alternate agents that are effective in the treatment of asthma. The purpose of this review is to characterize the type of patient who may benefit from alternate, nonsteroidal agents and to examine the current evidence behind their use. Although the use of a variety of alternate agents has been reported, we will focus in this article on agents that have been evaluated in prospective, randomized trials or have novel mechanisms of action. Anti-IgE and soluble interleukin (IL)-4 receptor therapy have been the subject of several reviews, and therefore will not be included in this discussion.

REVIEW:
Nelson RP, Ballow M.
Immunomodulation and immunotherapy:
Drugs, cytokines, cytokine receptors and antibodies.
J Allergy ClinImmunol 2003; 111:S720-32.
The preceding chapters in this primer have provided an overview of the immune response that serves as a background for understanding potential sites for immune modulation and immunotherapy. A number of soluble growth and activation factors are released from various cell populations involved in the immune response. They play vital roles in the initiation, propagation, and regulation of immunologic responses. Pharmacologic immunomodulators include suppressive and stimulatory agents. Immunosuppressive therapies include antimetabolites, cytotoxic drugs, radiation, adrenocortical glucocorticosteroids, immunophilins, and therapeutic antibodies. The field of clinical immunostimulation is emerging as an important therapeutic modality for a number of immunodeficiency diseases, chronic viral infections, and cancer. These compounds will be discussed in terms of general principles, molecular targets, major indications, and adverse effects.

COCHRANE REVIEW:

Choo KJ, Simons E, Sheikh A. "Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review," Allergy. 2010 Oct;65(10):1205-11. Epub 2010 Jun 18.

BACKGROUND: Anaphylaxis is a serious hypersensitivity reaction that is rapid in onset and may result in death. A number of guidelines recommend glucocorticoids for the treatment of people experiencing anaphylaxis. OBJECTIVES: We sought to assess the benefits and harms of glucocorticoid treatment during episodes of anaphylaxis. METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, Issue 3), MEDLINE (Ovid) (1966 to September 2009), EMBASE (Ovid) (1988 to September 2009), CINAHL (EBSCOhost) (to September 2009) and The Science Citation Index Expanded (SCI-EXPANDED) (1945 to September 2009). We also searched the UK National Research Register and websites listing ongoing trials and contacted international experts in anaphylaxis in an attempt to locate unpublished material. We sought to include randomized and quasi-randomized controlled trials comparing glucocorticoids with any control (either placebo, adrenaline (epinephrine), an antihistamine, or any combination of these). Two authors independently assessed articles for inclusion. RESULTS: None of the 2496 reports identified satisfied the inclusion criteria. CONCLUSIONS: We conclude that there is no evidence from high-quality studies for the use of steroids in the emergency management of anaphylaxis. Therefore, we can neither support nor refute the use of these drugs for this purpose.

RESEARCH FRONTIER:

Dente FL, Bacci E, Bartoli ML, et al. "Effects of oral prednisone on sputum eosinophils and cytokines in patients with severe refractory asthma," Ann Allergy Asthma Immunol. 2010 Jun;104(6):464-70.

BACKGROUND: Severe asthma occurs in a heterogeneous group of patients in whom symptoms and airway inflammation persist despite maximal antiasthma treatment. OBJECTIVE: To verify whether a short-term course of oral steroids would modify sputum inflammatory cytokine and sputum eosinophil concentrations and whether this effect is related to the presence of sputum eosinophilia. METHODS: In 59 patients with severe refractory asthma, we measured pulmonary function and inflammatory markers in hypertonic saline-induced sputum before and after 2 weeks of treatment with 0.5 mg/kg of oral prednisone (n = 39) or placebo (n = 20) daily. Selected sputum portions were assayed for total and differential cell counts and supernatant interleukin (IL) 5 and IL-8 concentrations. RESULTS: At baseline, no statistical differences were found among placebo- and prednisone-treated patients in terms of sputum inflammatory cell percentages and IL-5 and IL-8 concentrations. After treatment, forced expiratory volume in 1 second significantly increased and sputum eosinophil percentages and IL-5 and IL-8 concentrations significantly decreased in the prednisone group, whereas no changes were observed in the placebo group. The positive effect of prednisone treatment was observed only in patients with baseline sputum eosinophilia, whereas in noneosinophilic patients with severe asthma prednisone induced only a significant decrease of sputum IL-8. CONCLUSIONS: Additional high-dose oral corticosteroids improve pulmonary function and reduce not only sputum eosinophil but also sputum proinflammatory cytokine concentrations in patients with severe refractory asthma.

LANDMARK ARTICLE:

Hench PS, Kendall EC, Slocumb CH, Polley HF.

Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions: A study in clinical physiology.

Arch Intern Med. 1950;85:546–666.

LANDMARK ARTICLE:
Boardley JE, Carey RA, Harvey AM.
Preliminary observations on the effect of adrenocorticotropic hormone in allergic diseases. Bull. Johns. Hopkins. Hosp. 1949; 85, 396–410.
The Nobel Prize for Medicine was awarded in 1950 to Hench for the discovery of synthesized ACTH and cortisol where it was efficaciously used in rheumatoid arthritis. This study was published around the time documenting efficacy in 5 asthmatic patients with eosinophilic sputums who improved and had resolution of sputum eosinophilia after a 3 week period of ACTH injections. It was later confirmed that oral cortisol had the same beneficial effects.

RESEARCH FRONTIER:
Rosen J, Miner J.
The search for safer glucocorticoid receptor ligands.
Endocrine Reviews 2005;26(3): 452-64.
The search for novel glucocorticoids with reduced side effects has been intensified by the discovery of new molecular details regarding the function of the glucocorticoid receptor. These new insights may pave the way for novel, safer therapies that retain the efficacy of currently prescribed steroids.

2. Modified Allergen Immunotherapy

RESEARCH FRONTIER:
J. L. Ceuppens, D. Bullens, H. Kleinjans, J. van der Werf and the PURETHAL Birch Efficacy Study Group. "Immunotherapy with a modified birch pollen extract in allergic rhinoconjunctivitis: clinical and immunological effects," Clinical & Experimental Allergy 2009; 39, 1903-1909.
BACKGROUND: Modification of allergens by glutaraldehyde in extracts used for immunotherapy reduces the risk for side-effects, but the therapeutic efficacy of such extracts still requires further evaluation. The aim of this study was to show the efficacy and safety of immunotherapy with a single-strength glutaraldehyde-modified aluminium hydroxideadsorbed extract of birch pollen. METHODS: In a multi-centre, randomized, placebo-controlled double-blind setting, starting in 2001 between 1 August and 15 December, birch pollen-allergic subjects (n = 62) were injected subcutaneously with increasing doses of the allergen extract or placebo at weekly intervals over a 6-week period (or longer if adverse reactions occurred). Maintenance dose was given monthly for at least 18 months till June 2003. Efficacy was evaluated on the basis of the clinical index score (CIS), a combined symptom and medication score. RESULTS: Fifty-eight patients could be evaluated for clinical efficacy. Treatment with the birch pollen extract resulted in a lower CIS for the eye and nose during the peak birch pollen season of 2003, compared with placebo (reductions of 42% and 31%, respectively) (P = 0.017 and 0.039). Active treatment induced IgG and IgG4 antibodies reacting with Bet v 1 (Po0.001). Sera from treated patients had a blocking effect on Bet v 1-induced basophil activation (Po0.04). No major adverse reactions occurred, and local Reactions, if occurring, were mild. Conclusion Immunotherapy with a modified slow-release birch pollen extract, administered in a single-strength preparation with a rapid dose increase, is safe and efficacious. IgG and IgG4 antibodies against native Bet v 1 are induced, which block basophil activation.

RESEARCH FRONTIER:
T. Ball, B. Linhart, K. Sonneck et al
"Reducing allergenicity by altering allergen fold: a mosaic protein of Phl p 1 for allergy vaccination,"
Allergy 2009: 64: 569–580.
BACKGROUND: The major timothy grass pollen allergen, Phl p 1, resembles the allergenic epitopes of natural group I grass pollen allergens and is recognized by more than 95% of grass-pollen-allergic patients. Our objective was the construction, purification and immunologic characterization of a genetically modified derivative of the major timothy grass pollen allergen, Phl p 1 for immunotherapy of grass pollen allergy. METHODS: A mosaic protein was generated by PCR-based re-assembly and expression of four cDNAs coding for Phl p 1 fragments and compared to the Phl p 1 wild-type by circular dichroism analysis, immunoglobulin E (IgE)-binding capacity, basophil activation assays and enzyme-linked immunosorbent assay competition assays. Immune responses to the derivative were studied in BALB/c mice. RESULTS: Grass-pollen-allergic patients exhibited greater than an 85% reduction in IgE reactivity to the mosaic as compared with the Phl p 1 allergen and basophil activation experiments confirmed the reduced allergenic activity of the mosaic. It also induced less Phl p 1-specific IgE antibodies than Phl p 1 upon immunization of mice. However, immunization of mice and rabbits with the mosaic induced IgG antibodies that inhibited patients' IgE-binding to the wild-type allergen and Phl p 1-induced degranulation of basophils. CONCLUSION: We have developed a strategy based on rational molecular reassembly to convert one of the clinically most relevant allergens into a hypoallergenic derivative for allergy vaccination.

RESEARCH FRONTIER:
Soili A. Saarelainen, Tuure T. Kinnunen, et al
"Immunotherapeutic potential of the immunodominant T-cell epitope of lipocalin allergen Bos d 2 and its analogues,"
Immunology 2007; 123, 358-366.
Lipocalin allergens, which contain most of the important animal-derived respiratory sensitizers, induce T helper type 2 (Th2) deviation, but the reasons for this are not clear. To explore the prospects for peptide-based allergen immunotherapy and to elucidate the characteristics of the immunodominant epitope of Bos d 2, BALB/c mice were immunized with a peptide containing the epitope, peptides containing its analogues, peptides from the corresponding regions of other lipocalin proteins, and peptides with a homologous sequence. We observed that murine spleen cells recognized the immunodominant epitope of Bos d 2, p127–142, in almost the same way as human Bos d 2-specific T cells did. Enzyme-linked immunosorbent spot-forming cell assay (ELISPOT) analyses showed that p127–142 and a corresponding peptide from horse Equ c 1 induced a Th2-deviated cellular response, whereas a homologous bacterial peptide from Spiroplasma citri induced a Th0-type response. Interestingly, the spleen cell response to the bacterial peptide and p127–142 was cross-reactive, that is, able to induce reciprocally the proliferation and cytokine production of primed spleen cells in vitro. More importantly, the peptides were able to skew the phenotype of T cells primed with the other peptide. Our results suggest that modified peptides can be useful in allergen immunotherapy.

REVIEW:

L. Cox.
"Accelerated immunotherapy schedules: review of efficacy and safety,"
Ann Allergy Asthma Immunol. 2006;97:126–138.
OBJECTIVE: To provide a comprehensive evaluation of accelerated immunotherapy build-up schedules in terms of adversereactions and clinical efficacy. DATA SOURCES: Peer-reviewed studies and review articles were selected from the PubMed database for articles published in the years 1976 to 2006 using the following keywords: rush, cluster immunotherapy in combination with allergic rhinitis, asthma, Hymenoptera, and imported fire ant. STUDY SELECTION: Studies were selected if they provided safety and efficacy information on accelerated allergen immunotherapy schedules. Most of the studies reviewed were double-blind, placebo controlled, but some open-observational studies were included if they provided immunotherapy safety or other information the author thought was relevant. RESULTS: A wide range of systemic reactions were reported in the literature with inhalant allergens: ranging from 27% to 100% of the patients in rush immunotherapy studies and 0% to 79% of patients in the cluster studies. Predictors of systemic reactions with rush immunotherapy were forced expiratory volume in 1 second less than 80% of predicted and a high degree of skin test reactivity. Premedication clearly reduces the risk of systemic reactions with rush immunotherapy, but the effect on cluster schedules was not as clear. CONCLUSION: Accelerated immunotherapy build-up schedules in selected patients may provide a rapid alternative to conventional build-up schedules without a significant increase in risk.

REVIEW:
Wilson, D. R., M. T. Lima, et al.
Sublingual immunotherapy for allergic rhinitis: systematic REVIEW: and meta-analysis.
Allergy 2005;60: 4-12.
Allergic rhinitis is a common condition which, at its most severe, can significantly impair quality of life despite optimal treatment with antihistamines and topical nasal corticosteroids. Allergen injection immunotherapy significantly reduces symptoms and medication requirements in allergic rhinitis but its use is limited by the possibility of severe systemic reactions. There has therefore been considerable interest in alternative routes for delivery of allergen immunotherapy, particularly the sublingual route. The objective was to evaluate the efficacy of sublingual immunotherapy (SLIT), compared with placebo, for reductions in symptoms and medication requirements. The Cochrane Controlled Clinical Trials Register, MEDLINE (1966-2002), EMBASE (1974-2002) and Scisearch were searched, up to September 2002, using the terms (Rhin* OR hay fever) AND (immunotherap* OR desensiti*ation) AND (sublingual). All studies identified by the searches were assessed by the reviewers to identify Randomized Controlled Trials involving participants with symptoms of allergic rhinitis and proven allergen sensitivity, treated with SLIT or corresponding placebo. Data from identified studies was abstracted onto a standard extraction sheet and subsequently entered into RevMan 4.1. Analysis was performed by the method of standardized mean differences (SMD) using a random effects model. P-values < 0.05 were considered statistically significant. Subgroup analyses were performed according to the type of allergen administered, the age of participants and the duration of treatment. Twentytwo trials involving 979 patients, were included. There were six trials of SLIT for house dust mite allergy, five for grass pollen, five for parietaria, two for olive and one each for, ragweed, cat, tree and cupressus. Five studies enrolled exclusively children. Seventeen studies administered the allergen by sublingual drops subsequently swallowed, three by drops subsequently spat out and two by sublingual tablets. Eight studies involved treatment for less

than 6 months, 10 studies for 6-12 months and four studies for greater than 12 months. All included studies were double-blind placebo-controlled trials of parallel group design. Concealment of treatment allocation was considered adequate in all studies and the use of identical placebo preparations was almost universal. There was significant heterogeneity, most likely due to widely differing scoring systems between studies, for most comparisons. Overall there was a significant reduction in both symptoms (SMD -0.42, 95% confidence interval -0.69 to -0.15; P = 0.002) and medication requirements [SMD -0.43 (-0.63, -0.23); P = 0.00003] following immunotherapy. Subgroup analyses failed to identify a disproportionate benefit of treatment according to the allergen administered. There was no significant reduction in symptoms and medication scores in those studies involving only children but total numbers of participants was too small to make this a reliable conclusion. Increasing duration of treatment does not clearly increase efficacy. The total dose of allergen administered may be important but insufficient data was available to analyze this factor.

REVIEW PEPTIDE IMMUNOTHERAPY:
Larche M
Peptide Immunotherapy
Immunol Allergy Clin North Am. 2006 May;26(2):321-32
Synthetic peptides representing T-cell epitopes of allergens and autoantigens have been employed to induce antigen-specific tolerance in vivo in experimental models and the clinical setting. delivery of peptides orally or by injection leads to reduced reactivity to antigen accompanied by the induction of T cells with a regulatory phenotype. Peptide therapy may provide a safe, effective, and economically viable approach for disease-modifying therapy in autoimmune and allergic diseases.

RESEARCH FRONTIER:
Creticos P. S., Schroeder J. T., Hamilton R. G
Immunotherapy with a Ragweed–Toll-Like Receptor 9 Agonist Vaccine for Allergic Rhinitis
N Engl J Med 2006; 355:1445-1455
BACKGROUND: Conjugating immunostimulatory sequences of DNA to specific allergens offers a new approach to allergen immunotherapy that reduces acute allergic responses. METHODS: We conducted a randomized, double-blind, placebo-controlled phase 2 trial of a vaccine consisting of Amb a 1, a ragweed-pollen antigen, conjugated to a phosphorothioate oligodeoxyribonucleotide immunostimulatory sequence of DNA (AIC) in 25 adults who were allergic to ragweed. Patients received six weekly injections of the AIC or placebo vaccine before the first ragweed season and were monitored during the next two ragweed seasons. RESULTS: There was no pattern of vaccine-associated systemic reactions or clinically significant laboratory abnormalities. AIC did not alter the primary end point, the vascular permeability response (measured by the albumin level in nasal-lavage fluid) to nasal provocation. During the first ragweed season, the AIC group had better peak-season rhinitis scores on the visual-analogue scale (P=0.006), peak-season daily nasal symptom diary scores (P=0.02), and midseason overall quality-of-life scores (P=0.05) than the placebo group. AIC induced a transient increase in Amb a 1–specific IgG antibody but suppressed the seasonal increase in Amb a 1–specific IgE antibody. A reduction in the number of interleukin-4–positive basophils in AIC-treated patients correlated with lower rhinitis visual-analogue scores (r=0.49, P=0.03). Clinical benefits of AIC were again observed in the subsequent ragweed season, with improvements over placebo in peak-season rhinitis visual-analogue scores (P=0.02) and peak-

season daily nasal symptom diary scores (P=0.02). The seasonal specific IgE antibody response was again suppressed, with no significant change in IgE antibody titer during the ragweed season (P=0.19). CONCLUSIONS: In this pilot study, a 6-week regimen of the AIC vaccine appeared to offer long-term clinical efficacy in the treatment of ragweed allergic rhinitis.

3. Cellular immune reconstruction including stem cell and bone marrow transplant

REVIEW:

TJ Fry and CL Mackall.

"Immune reconstitution following hematopoietic progenitor cell transplantation: challenges for the future,"

Bone Marrow Transplantation 2005; 35, S53–S57.

Successful hematopoietic progenitor cell transplantation requires rapid and complete transfer of the donor hematopoietic and immune systems to the host. Whereas the uncontrolled transfer of a nontolerant donor immune system results in GVHD in many cases, strategies which diminish GVHD also diminish immune reconstitution. Thus, the reliable, rapid and safe transfer of immunity from donor to host remains a major challenge for the field. Advances in the understanding of the biology of immune reconstitution have elucidated that thymic-dependent immune reconstitution can restore global immunity, but is especially vulnerable to toxicities associated with transplant. Alternatively, homeostatic peripheral expansion can be exploited for targeted immunity toward pathogens and tumors, but is difficult to manipulate without exacerbating GVHD risk. New translatable strategies are needed to safely augment one or both of these pathways in the setting of allogeneic hematopoietic progenitor cell transplantation.

RESEARCH FRONTIER:

Ronjon Chakraverty, Guillermo Orti, Michael Roughton, et al.

"Impact of in vivo alemtuzumab dose before reduced intensity conditioning and HLA-identical sibling stem cell transplantation: pharmacokinetics, GVHD, and immune reconstitution,"

Blood 2010;116(16): 3080-3088

In vivo alemtuzumab reduces the risk of graft-versus-host disease (GVHD) and nonrelapse mortality after reduced intensity allogeneic transplantation. However, it also delays immune reconstitution, leading to frequent infections and potential loss of graft-versus-tumor responses. Here, we tested the feasibility of alemtuzumab dose deescalation in the context of fludarabine-melphalan conditioning and human leukocyte antigen (HLA)– identical sibling transplantation. Alemtuzumab was given 1-2 days before graft infusion, and dose reduced from 60 mg to 20 mg in 4 sequential cohorts (total n = 106). Pharmacokinetic studies were fitted to a linear, 2-compartment model in which dose reduction led to incomplete saturation of CD52 binding sites and greater antibody clearance. Increased elimination was particularly evident in the 20-mg group in patients who had CD52-expressing tumors at time of transplantation. The 20-mg dose was also associated with greater risk of severe GVHD (acute grade III-IV or chronic extensive) compared with > 20 mg (hazard ratio, 6.7; 95% CI, 2.5-18.3). In contrast, dose reduction to 30 mg on day 1 was associated with equivalent clinical outcomes to higher doses but better lymphocyte recovery at 12 months. In conclusion, alemtuzumab dose reduction to 30 mg is safe in the context of reduced intensity conditioning and HLA-identical sibling transplantation.

META-ANALYSIS:
Monika Müller, Simon Wandel, Robert Colebunders, et al.
"Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis,"
J Allergy Clin Immunol 2006 Apr;117(4Suppl):S525053
In patients with HIV-1 infection who are starting combination antiretroviral therapy (ART), the incidence of immune reconstitution inflammatory syndrome (IRIS) is not well defined. We did a meta-analysis to establish the incidence and lethality of the syndrome in patients with a range of previously diagnosed opportunistic infections, and examined the relation between occurrence and the degree of immunodeficiency. Systematic review identified 54 cohort studies of 13,103 patients starting ART, of whom 1699 developed IRIS. We calculated pooled cumulative incidences with 95% credibility intervals (CrI) by Bayesian methods and did a random-effects metaregression to analyse the relation between CD4 cell count and incidence of IRIS. In patients with previously diagnosed AIDS-defining illnesses, IRIS developed in 37·7% (95% CrI 26·6–49·4) of those with cytomegalovirus retinitis, 19·5% (6·7–44·8) of those with cryptococcal meningitis, 15·7% (9·7–24·5) of those with tuberculosis, 16·7% (2·3–50·7) of those with progressive multifocal leukoencephalopathy, and 6·4% (1·2–24·7) of those with Kaposi's sarcoma, and 12·2% (6·8–19·6) of those with herpes zoster. 16·1% (11·1–22·9) of unselected patients starting ART developed any type of IRIS. 4·5% (2·1–8·6) of patients with any type of IRIS died, 3·2% (0·7–9·2) of those with tuberculosis-associated IRIS died, and 20·8% (5·0–52·7) of those with cryptococcal meningitis died. Metaregression analyses showed that the risk of IRIS is associated with CD4 cell count at the start of ART, with a high risk in patients with fewer than 50 cells per μL. Occurrence of IRIS might therefore be reduced by initiation of ART before immunodeficiency becomes advanced.

REVIEW:
Hassan HT. El-Sheemy M.
Adult bone-marrow stem cells and their potential in medicine
Journal of the Royal Society of Medicine. 2004;97:465-71

4. Immunoglobulin Replacement Therapy

Orange JS, Hossny EM, Weiler CR et al.
"Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy,Asthma and Immunology,"
J Allergy Clin Immunol 2006 Apr;117(4Suppl):S525-53.

REVIEW:
Darabi K, Abdel-Wahab O, Dzik WH.
Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a REVIEW: of the literature.
Transfusion. 2006;46(5):741-53.
BACKGROUND: Intravenous immune globulin (IVIG) has been approved by the Food and Drug Administration (FDA) for use in 6 conditions: immune thrombocytopenic purpura (ITP), primary immunodeficiency, secondary immunodeficiency, pediatric HIV infection, Kawasaki disease, prevention of graft versus host disease (GVHD) and infection in bone marrow transplant recipients. However, most usage is for off-label indications, and for some of these comprehensive

guidelines have been published. STUDY DESIGN AND METHODS: We retrospectively reviewed all approved IVIG transfusions at Massachusetts General Hospital in 2004 to identify the current usage pattern and completed a literature review. RESULTS: IVIG was most commonly used in the treatment of chronic neuropathy, which included chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy. For such patients, the annual cost of IVIG can exceed 50,000 dollars per patient. Other common indications were the treatment of hypogammaglobulinemia, ITP, renal transplant rejection, myasthenia gravis, Guillain-Barre syndrome, necrotizing fasciitis, autoimmune hemolytic anemia, and Kawasaki disease. IVIG was administered in a variety of other indications each representing <3% of the total treated patients. CONCLUSION: Only a few indications account for most of the usage for IVIG. Reports concerning IVIG continue to grow at a tremendous pace but few high-quality randomized controlled trials have been reported. Randomized trials are especially needed for conditions such as CIDP, which consume large quantities of product.

REVIEW:
Orange JS, Hossny EM, Weiler CR, et al
Use of intravenous immunoglobulin in human disease: a REVIEW: of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology.
J Allergy Clin Immunol. 2006;117:S525-53
Human immunoglobulin prepared for intravenous administration (IGIV) has a number of important uses in the treatment of disease. Some of these are in diseases for which acceptable treatment alternatives do not exist. In this review we have evaluated the evidence underlying a wide variety of IGIV uses and make specific recommendations on the basis of these data. Given the potential risks and inherent scarcity of IGIV, careful consideration of the indications for and administration of IGIV is warranted.

REVIEW:
Toubi E, Etzioni A.
Intravenous immunoglobulin in immunodeficiency states: state of the art.
Clin Rev Allergy Immunol. 2005 Dec;29(3):167-72
Intravenous immunoglobulin (IVIg) has been used successfully for hypogammaglobulinemic states for more than 20 yr. In both primary and secondary situations when hypogammaglobulinemia is of clinical significance, IVIg should be the first line of treatment. In most cases, 400 mg/kg infused every 3 to 4 wk will lead to a trough level higher than 500 mg/dL, which in most cases provides good protection against bacterial infections. Higher doses may be needed in patients with known lung damage. Side effects include headache, nausea, chills, and fever but can be minimized by lowering the infusion speed rate. Rarely, aseptic meningitis may develop but it is always reversible. Although all products have been shown to be beneficial, differences among the various products have still been reported. In this regard, all products should be standardized according to common accepted international parameters. The route of immunoglobulin G replacement (intravenously vs subcutaneously) was reported to be of similar benefit. However, guidelines for usage and choice of route should be established and might be of help.

REVIEW:

Ochs HD, Gupta S, Kiessling P
Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases.
J Clin Immunol. 2006 May;26(3):265-73.
Intravenous immunoglobulin (IVIg) infusions at 3-4 week intervals are currently standard therapy in the United States for patients with primary immune deficiency diseases (PIDD). To evaluate alternative modes of immunoglobulin administration we have designed an open-label study to investigate the efficacy and safety of a subcutaneously administered immunoglobulin preparation (16% IgG) in patients with PIDD. After their final IVIg infusion, 65 patients entered a 3-month, wash-in/wash-out phase, designed to bring patients to steady-state with subcutaneously administered immunoglobulin. This was followed by 12 months of weekly SCIg infusions, at a dose determined in a pharmacokinetic substudy to provide noninferior intravascular exposure. This resulted in a mean weekly dose of 158 mg/kg, calculated to equal 137% of the previous intravenous dose. Two patients (4%) each reported 1 serious bacterial infection (pneumonia), an annual rate of 0.04 per patient-year. There were 4.43 infections of any type per patient-year. Mean trough serum IgG levels increased from 786 to 1040 mg/dl during the study, a mean increase of 39%. The most frequent treatment-related adverse event was infusion-site reaction, reported by 91% of patients; this was predominantly mild or moderate, and the incidence decreased over time. No treatment-related serious adverse events were reported. We conclude that subcutaneous administration of 16% SCIg is a safe and effective alternative to IVIg for replacement therapy of PIDD.

5. Nucleic Acid Based Therapies (DNA vaccines, CpG, gene insertion, antisense nucleotides)

REVIEW:
Li-Chieh Wang, Jyh-Hong Lee, Yao-Hsu Yang, et al.
"New Biological Approaches in Asthma: DNA-Based Therapy,"
Current Medicinal Chemistry, 2007, 14, 1607-1618
Asthma is characterized by airway inflammation, bronchial hyper-responsiveness, and reversible airway obstruction. Medications for asthma include corticosteroids, b2-adrenergic receptor agonists, chromones, methylxanthines, and leukotriene modifiers. Despite these advances in therapy, many symptoms are not well controlled. Since asthma is a chronic airway inflammation with a bias towards a type 2 T helper (Th2) cell response, some new approaches are targeted towards the Th2 inflammation pathway. These include anti-IgE therapy, anti-Th2 cytokine therapy, and therapies aiming at increasing Th1 cytokines. This article will focus on DNA-based therapy, a novel therapeutic strategy for asthma. Immunostimulatory gene therapy using CpG oligodeoxynucleotides with central deoxycytidyl-deoxyguanosine (CpG) dinucleotide, in which the cytosine nucleobase is unmethylated, can stimulate the innate immunity and augment Th1 response. With DNA gene therapy, genes can be introduced to target Th1 cytokines or other mediators in the airway in order to counteract Th2 inflammation in asthma. Also, antisense oligonucleotides can target mRNA species of interest in asthma. Through these therapies, we can expect long-lasting effects, better control of symptoms, and reducing medication in the future.

REVIEW:
Tsalik EL.
DNA-based immunotherapy to treat atopic disease.

Annals of Allergy, Asthama & Immunology: 2005;95:403-10.
OBJECTIVE: To review the current literature regarding DNA-based immunotherapy with respect to signaling mechanisms, cytokine profiles, and the applicability and success of this strategy to treat allergic disease. DATA SOURCES: English-language articles were identified from the PubMed database using both standard and clinical queries. Search terms included CpG, allergy, atopic disease, immunotherapy, DNA vaccination, immunomodulation, and immunostimulatory DNA. Other sources included bibliographies from relevant articles. STUDY SELECTION: Recent studies that provide information about the mechanisms or applications of DNA-based immunotherapy with respect to atopic disease are included in this review. RESULTS: DNA-based immunotherapy composed of unmethylated CpG repeats is capable of inducing a shift in the cytokine profile and immune response that favors the T(H)1 arm. This observation makes DNA-based immunotherapy a promising candidate for the treatment of atopic diseases, which are known to be mediated by T(H)2-based responses. Early animal and human trials of DNA-based immunotherapy have shown the strategy to be both safe and effective. CONCLUSIONS: DNA-based immunotherapy, although still in the early stages of development, has thus far been shown to be both safe and effective for a variety of atopic diseases and offers the potential for significant improvements over current immunotherapy protocols.

LANDMARK ARTICLE:
Tokunaga T, Yamamoto H, Shimada S, et al
Antitumor activity of deoxyribonucleic acid fraction from Mycobacterium bovis BCG. I. Isolation, physicochemical characterization, and antitumor activity.
J Natl Cancer Inst. 1984 Apr;72(4):955-62.
A fraction extracted from Mycobacterium bovis strain BCG, which was composed of 70.0% DNA, 28.0% RNA, 1.3% protein, 0.20% glucose, and 0.1% lipid and of no detectable amounts of cell wall components such as alpha, epsilon-diaminopimelic acid and hexosamine, was found to possess strong antitumor activity. Repeated intralesional injection of this fraction, designated MY-1, without attachment to oil or a single intralesional injection of MY-1 emulsified in mineral oil caused the IMC carcinoma of CDF1 mice and line 10 tumor of strain 2 guinea pigs to regress and/or prevented metastasis very effectively. MY-1 after digestion with RNase, which contained 97.0% single-stranded DNA with a guanine-cytosine content of 69.8%, was more effective than undigested MY-1 against IMC and line 10 tumor, while MY-1 digested with DNase, which contained 97.0% RNA, had reduced activity, suggesting that the DNA from BCG possessed strong antitumor activity under certain conditions. Details of the extraction procedures and physicochemical characterization of MY-1 were also described.

LANDMARK:
Sato Y, Roman M, Tighe H, Lee D,
Immunostimulatory DNA sequences necessary for effective intradermal gene immunization.
Science. 1996 Jul 19;273(5273):352-4.
Vaccination with naked DNA elicits cellular and humoral immune responses that have a T helper cell type 1 bias. However, plasmid vectors expressing large amounts of gene product do not necessarily induce immune responses to the encoded antigens. Instead, the immunogenicity of plasmid DNA (pDNA) requires short immunostimulatory DNA sequences (ISS) that contain a CpG dinucleotide in a particular base context. Human monocytes transfected with pDNA or double-stranded oligonucleotides containing the ISS, but not those transfected with ISS-deficient

pDNA or oligonucleotides, transcribed large amounts of interferon-alpha, interferon-beta, and interleukin-12. Although ISS are necessary for gene vaccination, they down-regulate gene expression and thus may interfere with gene replacement therapy by inducing proinflammatory cytokines.

RESEARCH FRONTIER:
Scheiblhofer S, Gabler M, Leitner WW
Inhibition of type I allergic responses with nanogram doses of replicon-based DNA vaccines. Allergy 2006: 61: 828–835
Allergic diseases have become a major public health problem in developed countries; yet, no reliable, safe and consistently effective treatment is available. DNA immunization has been shown to prevent and balance established allergic responses, however, the high dose of conventional DNA vaccines necessary for the induction of anti-allergic reactions and their poor immunogenicity in primates require the development of new allergy DNA vaccines. We evaluated protective and therapeutic effects of a Semliki-Forest Virus replicasebased vs a conventional DNA vaccine in BALB/c mice using the model allergen b-galactosidase.

6. Cytokine receptors and receptor antagonists (IFN, antiTNF, etc)

REVIEW:
Scott P. Commins, Larry Borish, and John W. Steinke. "Immunologic messenger molecules: Cytokines, interferons, and chemokines," J Allergy Clin Immunol 2010;125:S53-72.
Cytokines and chemokines are secreted proteins involved in numerous aspects of cell growth, differentiation, and activation. A prominent feature of these molecules is their effect on the immune system with regard to cell trafficking and development of immune tissue and organs. The nature of an immune response determines which cytokines are produced and ultimately whether the response is cytotoxic, humoral, cell mediated, or allergic. For this chapter, cytokines are grouped according to those that are predominantly antigen-presenting cell or T lymphocyte derived; that mediate cytotoxic, humoral, cell mediated, and allergic immunity; or that are immunosuppressive. A discussion of chemokine function and their role in cell trafficking and disease follows.

REVIEW:
Seoung Ju Park and Yong Chul Lee. " Interleukin-17 regulation: an attractive therapeutic approach for asthma," Respiratory Research 2010, 11:78.
Interleukin (IL)-17 is recognized to play a critical role in numerous immune and inflammatory responses by regulating the expression of various inflammatory mediators, which include cytokines, chemokines, and adhesion molecules. There is growing evidence that IL-17 is involved in the pathogenesis of asthma. IL-17 orchestrates the neutrophilic influx into the airways and also enhances T-helper 2 (Th2) cell-mediated eosinophilic airway inflammation in asthma. Recent studies have demonstrated that not only inhibitor of IL-17 per se but also diverse regulators of IL-17 expression reduce antigen-induced airway inflammation, bronchial hyperresponsiveness, and Th2 cytokine levels in animal models of asthma. This review will summarize the role of IL-17 in the context of allergic airway inflammation and discuss the therapeutic potential of various strategies targeting IL-17 for asthma.

REVIEW:
Antonella Viola, and Andrew D. Luster. "Chemokines and Their Receptors: Drug Targets in Immunity and Inflammation," Annu. Rev. Pharmacol. Toxicol. 2008. 48:171–97
The chemokine system coordinates leukocyte migration in immunity and inflammation and is implicated in the pathogenesis of many human diseases. Although several successful strategies have been identified to develop drugs targeting chemokines and their receptors, this has not yet resulted in many new therapeutics. This is likely due to a complexity of the chemokine system, which was not initially appreciated, that is characterized by redundancy, pleiotropy, and differences among species. Nevertheless, our understanding of chemokine biology is continuing to grow and several promising drugs are currently being tested in late-stage clinical trials. In this review, we examine the role of chemokines in health and diseases and discuss strategies to target the chemokine system.

REVIEW:
Charo IF, Ransohoff RM.
The many roles of chemokines and
chemokine receptors in inflammation.
N Engl J Med 2006;354:610-621.
Originally studied because of their role in inflammation, chemokines and their receptors are now known to play a crucial part in directing the movement of mononuclear cells throughout the body, engendering the adaptive immune response and contributing to the pathogenesis of a variety of diseases. Chemokine receptors are some of the most tractable drug targets in the huge battery of molecules that regulate inflammation and immunity. For this reason, clinical trials involving chemokine-receptor antagonists for the treatment of inflammatory conditions have recently begun. In this review, we survey the properties of chemokines and their receptors and highlight the roles of these chemoattractants in selected clinical disorders.

REVIEW:
Nelson RP, Ballow M.
Immunomodulation and immunotherapy: Drugs, cytokines, cytokine receptors and antibodies.
J Allergy Clin Immunol 2003; 111:S720-32.
A number of soluble growth and activation factors are released from various cell populations involved in the immune response. They play vital roles in the initiation, propagation, and regulation of immunologic responses. Pharmacologic immunomodulators include suppressive and stimulatory agents. Immunosuppressive therapies include antimetabolites, cytotoxic drugs, radiation, adrenocortical glucocorticosteroids, immunophilins, and therapeutic antibodies. The field of clinical immunostimulation is emerging as an important therapeutic modality for a number of immunodeficiency diseases, chronic viral infections, and cancer. These compounds will be discussed in terms of general principles, molecular targets, major indications, and adverse effects.

LANDMARK PUBLICATION:
Strander H, Cantell K et al.
Clinical and laboratory investigations on man: systemic administration of potent interferon to man.
J Natl Cancer Inst 1973 Sep; 51(3):733-42.

RESEARCH FRONTIER:
Berry MA et al.
Evidence of a role of Tumor Necrosis Factor Alpha in Refractory Asthma.
N Engl J Med 2006:354:697-708.
As compared with patients with mild-to-moderate asthma and controls, patients with refractory asthma had increased expression of membrane-bound TNF- , TNF- receptor 1, and TNF- – onverting enzyme by peripheral-blood monocytes. In the clinical trial, as compared with placebo, 10 weeks of treatment with etanercept was associated with a significant increase in the concentration of methacholine required to provoke a 20 percent decrease in the forced expiratory volume in one second (FEV1) (mean difference in doubling concentration changes between etanercept and placebo, 3.5; 95 percent confidence interval, 0.07 to 7.0; P=0.05), an improvement in the asthma-related quality-oflife score (by 0.85 point; 95 percent confidence interval, 0.16 to 1.54 on a 7-point scale; P=0.02), and a 0.32-liter increase in post-bronchodilator FEV1 (95 percent confidence interval, 0.08 to 0.55; P=0.01).

7. Recombinant molecules and humanized monoclonal antibodies (imatinib, infliximab, omaluzimab, rituximab)

REVIEW:
Oliver V. Hausmann, Michael Seitz, Peter M. Villiger, Werner J. Pichler.
"The Complex Clinical Picture of Side Effects to Biologicals,"
Med Clin N Am 94 (2010) 791–804.
Adverse drug reactions (ADR) are a common phenomenon. For a long time, most drugs were small chemicals called xenobiotics that occasionally caused side effects. These were explained by the pharmacologic action of the drug (type A) or were related to the susceptibility of the individual to the drug (type B, idiosyncratic drug reactions). Most of the type B reactions were immune mediated. In addition, some investigators extended this classification and used type C for (chemical) reactions related to the chemical structure and its metabolism, for example, paracetamol hepatotoxicity; type D, corresponding to delayed reactions that appear after many years of treatment, for example, bladder carcinoma after treatment with cyclophosphamide; and type E (end of treatment) reactions occurring after drug withdrawal, for example, seizures after stopping phenytoin. This subclassification of side effects is focused on small chemical compounds, but is considered less suitable for proteins used as drugs.1 Biological response modifiers, commonly abbreviated as ''biologicals,'' represent a new category of drugs designed to be as similar to human proteins as possible.1 The nomenclature of biologicals seems to be arbitrary at first glance, but it is strictly regulated.2 Taking infliximab as an example, the first 1 or 2 syllables can be chosen freely; in this case ''inf-.'' The following syllable derives from the target structure or target disease, here ''-li-'' for immune system. The next syllable denotes the species of origin, ''-xi-'' for chimeric murine-human origin. The last syllable stands for the therapeutic principle, in this case ''-mab'' for monoclonal antibody. Alternative final syllables are ''-cept'' for soluble receptors and ''-inib'' for receptor antagonists. Biological response modifiers interact specifically with the immune system (Table 1) and target distinct cell surface structures, for example, cytokine receptors, tumor-specific antigens, or soluble mediators (cytokines, interferons). Biologicals have turned out to be potent and effective therapeutic tools for various inflammatory, autoimmune, and oncologic diseases. Their direct and focused effect renders them superior to classic immunosuppressive or cytotoxic drugs, whose use is often limited by unwanted and frequently

severe generalized side effects. In 2006, the molecular targeted therapies in oncology accounted for 44% of the total sales of the top 20 cancer therapy brands, overtaking the cytotoxic therapies for the first time.3 The side effects seen with classic xenobiotics seem to differ considerably from the ones associated with biologicals concerning their pathogenesis and consequences for future therapy (Table 2). It is beyond the scope of this article to cover the adverse side effects of all biologicals in detail. Instead typical clinical manifestations are presented, and general rules for treating these and guiding later allergological workup as well as a possible classification scheme are proposed.

REVIEW:
Aidan A. Long.
"Immunomodulators in the treatment of asthma,"
Allergy Asthma Proc 2009; 30:109 –119.
Asthma represents a syndrome of airway inflammatory diseases with a complex pathology. The immunologic pathogenesis is being increasingly revealed and provides opportunity for targeted biological intervention. This study was designed to describe current experience with immunomodulators as targeted therapy in asthma. A literature review was performed. Targeted therapies have included strategies to activate dendritic cells through the Toll-like receptor (TLR) 9 receptors, to interrupt the action of TH2 cytokines with cytokine blockers and monoclonal antibodies, to promote development of TH1 responses, to interrupt mast cell signaling, to block IgE mediated pathways, and to block TNF-alpha. Omalizumab is the only biological therapy that has an approved indication in asthma at this time. Improved understanding of the heterogeneity of asthma should allow for specific targeting of different disease phenotype-specific therapies including immunomodulators.

REVIEW:
Lawrence B. Schwartz, Javed Sheikh, & Anish Singh.
"Current strategies in the management of hypereosinophilic syndrome, including mepolizumab,"
Current Medical Research & Opinion 2010; Vol. 26, No. 8, 1933–1946.
BACKGROUND: Patients with hypereosinophilic syndrome (HES) vary considerably in their clinical presentation with regard to the severity and pattern of end-organ involvement. Clinical manifestations range from nonspecific symptoms to life-threatening, multisystem damage caused by eosinophil infiltration and local release of proinflammatory mediators and toxic granule products from these invading cells. The primary objective of treatment is to reduce blood and tissue eosinophilia and prevent eosinophil-mediated tissue damage as safely as possible. Systemic corticosteroids, such as prednisone, are first-line therapy for the management of patients with symptomatic HES who lack the Fip1-like 1-platelet-derived growth factor receptor-(FIP1L1-PDGFRA) gene fusion mutation. The tyrosine kinase inhibitor, imatinib, is first-line treatment for FIP1L1-PDGFRA-positive patients. Because of the toxicity and serious side-effects that can occur with oral corticosteroids, alternative therapies may need to be introduced to reduce the cumulative corticosteroid exposure while maintaining disease control. SCOPE: Among corticosteroid-sparing agents are cytotoxic drugs and interferon-α; anti-interleukin-5 (IL-5) monoclonal antibodies are also currently under investigation for the treatment of HES. This manuscript reviews the available treatments for HES and the range of side-effects associated with long-term corticosteroid use, and then focuses on the anti-IL-5 monoclonal antibodies, mepolizumab and reslizumab. Of these, only

mepolizumab has been studied in a randomized, placebo-controlled trial. Literature search methodology utilized www.pubmed.gov and www.clinicaltrials.gov with search terms including hypereosinophilic syndrome and corticosteroid side-effects coupled with search terms including eosinophils, mepolizumab and reslizumab through March 2010. FINDINGS: Three case studies are presented that demonstrate the limitations of corticosteroid therapy in terms of tolerability and quality of life, and the subsequent use of mepolizumab as a corticosteroid-sparing agent in these individuals. CONCLUSION: Targeted eosinophil-directed therapy with an anti-IL-5 neutralizing monoclonal antibody reduced the need for corticosteroids in these three HES patients without disease exacerbations.

REVIEW:
Adcock, I. M., K. F. Chung, et al.
Kinase inhibitors and airway inflammation.
Eur J Pharmacol 2006;533:118-32.
Kinases are believed to play a crucial role in the expression and activation of inflammatory mediators in the airway, in T-cell function and airway remodelling. Important kinases such as Inhibitor of kappaB kinase (IKK)2, mitogen activated protein (MAP) kinases and phsopho-inositol (PI)3 kinase regulate inflammation either through activation of pro-inflammatory transcription factors such as activating protein-1 (AP-1) and nuclear factor kappaB (NF-kappaB), which are activated in airway disease, or through regulation of mRNA half-life. Selective kinase inhibitors have been developed which reduce inflammation and some characteristics of disease in animal models. Targeting specific kinases that are overexpressed or over active in disease should allow for selective treatment of respiratory diseases. Interest in this area has intensified due to the success of the specific Abelson murine leukaemia viral oncogene (Abl) kinase inhibitor imatinib mesylate (Gleevec) in the treatment of chronic myelogenous leukaemia. Encouraging data from animal models and primary cells and early Phase I and II studies in other diseases suggest that inhibitors of p38 MAP kinase and IKK2 may prove to be useful novel therapies in the treatment of severe asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis and other inflammatory airway diseases.

REVIEW:
Mankad V. S. Burks AW
Omalizumab: other indications and unanswered questions.
Clin Rev Allergy Immunol 2005;29:17-30.
Omalizumab, a recombinant humanized monoclonal antibody against immunoglobulin (Ig)E, represents a unique therapeutic approach for the treatment of allergic diseases. This agent acts as a neutralizing antibody by binding IgE at the same site as the high-affinity receptor. Subsequently, IgE is prevented from sensitizing cells bearing high-affinity receptors. Inhibition of the biological effects of IgE targets an early phase of the allergic cascade before the generation of allergic symptoms. Currently, omalizumab has been approved for the treatment of persistent allergic asthma in patients who are poorly controlled with inhaled corticosteroids. However, other allergic disorders may be amenable to treatment with omalizumab because of its ability to inhibit effector functions of IgE. Studies of omalizumab in the treatment of allergic rhinitis comprise the greater part of the literature pertaining to the use of this agent for clinical indications other than asthma. This article summarizes clinical trials of omalizumab in allergic rhinitis and examines the evidence regarding the effects of omalizumab on the pathophysiological mechanisms underlying allergic

rhinitis. Additionally, we consider the role of this novel therapeutic agent in combination with specific allergen immunotherapy and discuss other potential indications for omalizumab in IgE-mediated disorders, including food allergy, latex allergy, atopic dermatitis, and chronic urticaria.

REVIEW:
Rouhani, F. N., C. A. Meitin, et al. (2005).
Effect of tumor necrosis factor antagonism on allergen-mediated asthmatic airway inflammation."
Respir Med 2005; 99: 1175-82.
OBJECTIVE: To assess whether tumor necrosis factor (TNF) antagonism can attenuate eosinophilic airway inflammation in patients with mild-to-moderate allergic asthma. DESIGN: Randomized, double-blind, placebo-controlled trial. SETTING: National Institutes of Health (NIH) Clinical Center. PATIENTS: Twenty-six patients with mild-to-moderate allergic asthma, receiving only inhaled beta-2-agonists, who demonstrated both an early and late phase response to inhalational allergen challenge. INTERVENTION: Injection of a soluble TNF receptor (TNFR:Fc, etanercept, Enbrel) or placebo, 25mg subcutaneously, twice weekly for 2 weeks, followed by a bronchoscopic segmental allergen challenge. MEASUREMENTS: The primary outcome measure was whether TNFR:Fc can access the lung and inhibit TNF bioactivity. Secondary outcome measures included pulmonary eosinophilia, Th2-type cytokines, and airway hyperresponsiveness. RESULTS: Anti-TNF therapy was associated with transient hemiplegia in one patient, which resulted in suspension of the study. Data from the 21 participants who completed the study were analyzed. Following treatment, patients receiving anti-TNF therapy had significantly increased TNFR2 levels in epithelial lining fluid (ELF) ($P<0.001$), consistent with delivery of TNFR:Fc to the lung. TNF antagonism did not attenuate pulmonary eosinophilia and was associated with an increase in ELF IL-4 levels ($P=0.033$) at 24h following segmental allergen challenge. TNF antagonism was not associated with a change in airway hyperresponsiveness to methacholine. CONCLUSIONS: TNF antagonism may not be effective for preventing allergen-mediated eosinophilic airway inflammation in mild-to-moderate asthmatics. Transient hemiplegia, which may mimic an evolving stroke, may be a potential toxicity of anti-TNF therapy.

REVIEW:
Salem Z, Zalloua PA, Chehal A
Effective treatment of hypereosinophilic syndrome with imatinib mesylate
Hematol J. 2003;4:410-2
Imatinib mesylate treatment is highly effective in chronic myeloid leukaemia and recent data have suggested that imatinib mesylate is also effective in the treatment of idiopathic hypereosinophilic syndrome (HES). Six patients with HES were treated daily with 100 mg imatinib mesylate. Five patients had normal karyotype and one showed trisomy 8. RT-PCR was negative for ETV6-PDGFRB and BCR-ABL fusion mRNAs. All patients rapidly achieved complete haematological remission. One patient remained in remission for more than 6 weeks after discontinuing treatment. No significant side effect was noted. Imatinib mesylate should be considered in the first-line therapy of idiopathic HES.

REVIEW:
Shanafelt TD, Madueme HL, Wolf RC, et al

Rituximab for immune cytopenia in adults: idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and Evans syndrome.
Mayo Clin Proc. 2003;78:1340-6
OBJECTIVE: To evaluate the efficacy of rituximab for the treatment of adult patients with immune cytopenia, including idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia, and Evans syndrome. PATIENTS AND METHODS: We retrospectively reviewed the medical charts of all patients treated with rituximab for immune cytopenia at the Mayo Clinic in Rochester, Minn, through January 1, 2003. Fourteen patients (median age at first diagnosis, 51 years; range, 21-79 years) were identified who received 1 or more treatment courses of rituximab for treatment of refractory ITP (12 patients), autoimmune hemolytic anemia (AIHA) (5 patients), or both ITP and AIHA (classified as Evans syndrome) (4 patients). Data regarding age, diagnosis, date of diagnosis, previous treatments, comorbid conditions, blood cell counts before taking rituximab, number of rituximab treatments, and response to treatment were extracted and analyzed. RESULTS: Of 12 patients treated for ITP, 6 were receiving corticosteroid-based treatment either alone or combined with other immunosuppressive therapy at the time they received rituximab. Complete remission occurred in 5 (42%) of 12 patients with ITP and in 2 (40%) of 5 patients with AIHA. Response to rituximab in patients with Evans syndrome was seen in either ITP or AIHA, but not both. Complete response was often durable in ITP. Responses were seen in both splenectomized and nonsplenectomized patients. CONCLUSIONS: Our findings, considered with the results of other studies, suggest that rituximab deserves early consideration as salvage therapy for immune cytopenias that are refractory to both corticosteroid treatment and splenectomy. This series represents the largest series of adult patients with AIHA and Evans syndrome

8. Plasmapheresis and cytophoresis

REVIEW:
M.A. Rockx & W.F. Clark.
"Plasma exchange for treating cryoglobulinemia: A descriptive analysis,"
Transfusion and Apheresis Science 2010; 42, 247–251.
BACKGROUND: Cryoglobulinemia is an immune-complex-mediated systemic vasculitis involving small-to-medium-sized vessels. Plasmapheresis transiently removes the circulating cryoglobulins and has been advocated (in conjunction with immunosuppressive therapy) to be effective in reducing morbidities associated with cryoglobulinemia. The goal of this paper was to review over the past 20 years the medical literature for evidence supporting or refuting the Reported use of plasmapheresis for cryoglobulinemia (January 1988 through June 2008). METHODS: We included all reported literature of the use of plasma exchange for the treatment of cryoglobulinemia that included at least five patients. Electronic searches were performed using MEDLINE (January 1988 through June 2008) and Cochrane Central Register of Controlled Trials (January 1988 through June 2008). RESULTS: Of the 11 articles included in this review, there were a total of 156 patients studied. Two studies used cryofiltration, one compared plasma exchange to double cascade filtration and the other eight dealt with plasma exchange only. Outcome measures were often not clearly defined. CONCLUSIONS: Although plasma exchange is an accepted treatment for cryoglobulinemia, there are no large multicentre randomized controlled trials of plasma exchange versus placebo or versus immunosuppressive therapy. Of the 11 studies from our literature search, none had a clear report of the apheresis procedures and clearly defined quantitative outcomes. The quality and variability of the evidence precludes a meta-analysis or

even a systematic analysis. However, these studies weakly support the use of plasma exchange largely on a mechanistic basis.

REVIEW:
Chang-Qing Xiaa, Kim A. Campbell, & Michael J. Clare-Salzler. "Extracorporeal photopheresis-induced immune tolerance: a focus on modulation of antigen-presenting cells and induction of regulatory T cells by apoptotic cells," Curr Opin Organ Transplant. 2009 August; 14(4): 338–343.
PURPOSE OF REVIEW: This review is intended to introduce recent advances in the research surrounding extracorporeal photopheresis (ECP) with a focus on how apoptotic cells modulate antigen-presenting cells and induce regulatory T cells, given that ECP therapy induces apoptosis of leukocytes collected through leukapheresis. RECENT FINDINGS: It has been suggested that ECP therapy, unlike other immunosuppressive regimens, does not cause global immunosuppression, but induces immune tolerance. Recent clinical and animal studies demonstrate that ECP therapy induces antigen-specific regulatory T cells, including CD4+CD25+FoxP3+ T cells and IL-10-producing Tr1 cells, that may arise secondarily to the induction of tolerogenic antigen-presenting cells (APCs) by infusion of apoptotic cells. It has also been suggested that ECP therapy may induce IL-10-producing regulatory B cells and regulatory CD8+ T cells. Finally, several recent studies, which examined the cellular elements involved in the uptake of apoptotic cells, demonstrated that apoptotic cells modulate APCs through binding to specific receptors, particularly TAM receptors that provide inhibitory signals that block APC activation. SUMMARY: ECP therapy induces immune tolerance through modulation of antigen-presenting cells as well as induction of regulatory T cells. ECP therapy has great potential in the management of allogeneic transplantation and autoimmune diseases.

REVIEW:
Suresh G. Shelat, "Practical Considerations for Planning a Therapeutic Apheresis Procedure," The American Journal of Medicine 2010; 123, 777-784.
The general medicine and critical care services often care for patients that require therapeutic apheresis. Apheresis procedures are performed for various hematologic, neurological, renal, autoimmune, metabolic, and other indications. To facilitate a prompt start to the procedure, the clinical team must coordinate efforts with several services, including those that perform the apheresis procedure, establish venous access, and provide blood or replacement products, in addition to the pharmacy and clinical laboratory. Some of these tasks are performed typically by the clinical teams, while others are performed typically by the apheresis team. Presented and discussed are the indications for therapeutic apheresis, calculations for the ordering of blood products, and several important and practical details to consider, thus preventing delays in starting the apheresis procedure.

REVIEW:
Stephen M. Ansell, Robert A. Kyle, & Craig B. Reeder. "Diagnosis and Management of Waldenström Macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines," Mayo Clin Proc 2010;85(9):824-833.
Waldenström macroglobulinemia is a B-cell malignancy with lymphoplasmacytic infiltration in the bone marrow or lymphatic tissue and a monoclonal immunoglobulin M protein (IgM) in the serum. It is incurable with current therapy, and the decision to treat patients as well as the choice

of treatment can be complex. Using a risk-adapted approach, we provide recommendations on timing and choice of therapy. Patients with smoldering or asymptomatic Waldenström macroglobulinemia and preserved hematologic function should be observed without therapy. Symptomatic patients with modest hematologic compromise, IgM-related neuropathy that requires therapy, or hemolytic anemia unresponsive to corticosteroids should receive standard doses of rituximab alone without maintenance therapy. Patients who have severe constitutional symptoms, profound hematologic compromise, symptomatic bulky disease, or hyperviscosity should be treated with the DRC (dexamethasone, rituximab, cyclophosphamide) regimen. Any patient with symptoms of hyperviscosity should first be treated with plasmapheresis. For patients who experience relapse after a response to initial therapy of more than 2 years' duration, the original therapy should be repeated. For patients who had an inadequate response to initial therapy or a response of less than 2 years' duration, an alternative agent or combination should be used. Autologous stem cell transplant should be considered in all eligible patients with relapsed disease.

Grattan, C. E., D. M. Francis, et al.
Plasmapheresis for severe, unremitting, chronic urticaria.
Lancet 1992;339: 1078-80.
Histamine-releasing autoantibodies have been identified in chronic idiopathic urticaria. 8 patients with severe disease and histamine-releasing activity in their sera underwent plasmapheresis. Symptoms were abolished for 2 months in 1 patient and for 3 weeks in another, 2 showed almost complete resolution of symptoms, 2 had temporary relief, and the other 2 showed little change. Further investigation in 4 of the patients showed significantly reduced skin-test responses to fresh post-exchange autologous sera after plasmapheresis compared with stored pre-exchange sera, but the response to intradermal histamine remained unchanged. Blood cellular histamine increased as in-vitro serum histaminereleasing activity fell after plasmapheresis. These results favour a pathogenetic role for histamine-releasing autoantibodies in patients with chronic urticaria.

9. Probiotics

REVIEW:
A.R. Lomax & P.C. Calder. "Probiotics, Immune Function, Infection and Inflammation: A Review of the Evidence from Studies Conducted in Humans," Current Pharmaceutical Design 2009, 15, 1428-1518.
A number of studies have been performed examining the influence of various probiotic organisms, either alone or in combination, on immune parameters, infectious outcomes, and inflammatory conditions in humans. Some components of the immune response, including phagocytosis, natural killer cell activity and mucosal immunoglobulin A production (especially in children), can be improved by some probiotic bacteria. Other components, including lymphocyte proliferation, the production of cytokines and of antibodies other than immunoglobulin A appear less sensitive to probiotics. Probiotics, including lactobacilli and bifidobacteria, administered to children can reduce incidence and duration of diarrhoea, but the precise effects depend upon the nature of the condition. Probiotic supplementation can reduce the risk of travellers' diarrhoea in adults, but does not affect duration. The effect of probiotics on other infectious outcomes is less clear. Probiotics may benefit children and adults with irritable bowel syndrome and adults with ulcerative colitis; studies in Crohn's Disease are less clear. Probiotics have little effect in rheumatoid arthritis. Probiotic supplementation, especially with lactobacilli and bifidobacteria, can reduce risk and severity of allergic disease, particular atopic dermatitis; early supplementation appears to be

effective. Overall, the picture that emerges from studies of probiotics on immune, infectious and inflammatory outcomes in humans is mixed and there appear to be large species and strain differences in effects seen. Other reasons for differences in effects seen will include dose of probiotic organism used, duration of supplementation, characteristics of the subjects studied, sample size, and technical differences in how the measurements were made.

REVIEW:
Anil Minocha.
"Probiotics for Preventive Health,"
Nutrition in Clinical Practice 2009; 24 227-241.
Gut flora and probiotics have potential to affect health and disease far beyond the gut. There is increasing evidence that Probiotics have beneficial effects in preventing a wide range of conditions and improving health. Randomized, double-blind studies have provided evidence of the effectiveness of Probiotics for preventing various diarrheal illnesses as well as allergic disorders. Evidence for their efficacy for use in the prevention and treatment of bacterial vaginosis and urinary tract infections is also mounting. In addition, probiotics may be useful for preventing respiratory infections, dental caries, necrotizing enterocolitis, and certain aspects of inflammatory bowel disease. Data also suggest that probiotics may promote good health in day care and work settings, and may enhance growth in healthy as well as ill and malnourished children. Results from meta-analyses and systematic reviews that combine results of studies from different types of probiotics to examine the effects in any disease state should be interpreted with caution. Specific strains are effective in specific disease states. No 2 probiotics are exactly alike; we should not expect reproducible results from studies that employ different species or strains, variable formulations, and diverse dosing schedules. (Nutr Clin Pract. 2009;24:227-241)

LANDMARK ARTICLE:
Majmaa H and Isolauri E.
Probiotics: A Novel Approach in the Management of Food Allergy.
J Allergy Clin Immunol. 1997 Feb; 99(2): 179-85.
BACKGROUND: The gastrointestinal microflora is an important constituent of the gut mucosal defense barrier. We have previously shown that a human intestinal floral strain, Lactobacillus GG (ATCC 53103), promotes local antigen-specific immune responses (particularly in the IgA class), prevents permeability defects, and confers controlled antigen absorption. OBJECTIVE: The aim of this study was to evaluate the clinical and immunologic effects of cow's milk elimination without (n = 14) and with (n = 13) the addition of Lactobacillus GG (5 x 10(8) colony-forming units/gm formula) in an extensively hydrolyzed whey formula in infants with atopic eczema and cow's milk allergy. The second part of the study involved 10 breast-fed infants who had atopic eczema and cow's milk allergy. In this group Lactobacillus GG was given to nursing mothers. METHODS: The severity of atopic eczema was assessed by clinical scoring. The concentrations of fecal alpha 1- antitrypsin, tumor necrosis factor-alpha, and eosinophil cationic protein were determined as markers of intestinal inflammation before and after dietary intervention. RESULTS: The clinical score of atopic dermatitis improved significantly during the 1-month study period in infants treated with the extensively hydrolyzed whey formula fortified with Lactobacillus GG. The concentration of alpha 1-antitrypsin decreased significantly in this group (p = 0.03) but not in the group receiving the whey formula without Lactobacillus GG (p = 0.68). In parallel, the median (lower quartile to upper quartile) concentration of fecal tumor

necrosis factor-alpha decreased significantly in this group, from 709 pg/gm (91 to 1131 pg/gm) to 34 pg/gm (19 to 103 pg/gm) (p = 0.003), but not in those receiving the extensively hydrolyzed whey formula only (p = 0.38). The concentration of fecal eosinophil cationic protein remained unaltered during therapy. CONCLUSION: These results suggest that probiotic bacteria may promote endogenous barrier mechanisms in patients with atopic dermatitis and food allergy, and by alleviating intestinal inflammation, may act as a useful tool in the treatment of food allergy.

REVIEW:
Ogden NS and Bielort L.
Probiotics: A Complementary Approach in the Treatment and Prevention of Pediatric Atopic Disease.
Curr Opin Allergy Clin Immunol. 2005 Apr; 5(2):179-84.
PURPOSE OF REVIEW: The goal of this article is to review recent primary research and developments in the area of probiotics and pediatric atopic disease. RECENT FINDINGS: Research developments in probiotics summarized in this article include the following: (1) the role of probiotics in primary prevention of atopic disease, (2) the effect of probiotics on cytokines involved in the allergic immune response, (3) the long-term effects of peri-natal probiotic use and (4) the relationship between the gut microflora and atopic dermatitis. SUMMARY: Probiotics continue to be an area of active investigation as our understanding evolves of the gut microbiota's role in the altered immune response of atopic patients. Physicians should be aware of these developments as probiotics may be an important complementary approach in the treatment and the natural and long-term course of various pediatric diseases. This article summarizes the research conducted over the past 10 years with a primary focus on the literature published since January 2003.

RESEARCH FRONTIER:
Prescott SL, Dunstan JA, Hale J, Breckler L, Lehmann H, Weston S, Richmond P.
Clinical Effects of Probiotics are Associated with Increased Interferon-gamma Responses in Very Young Children with Atopic Dermatitis.
Clin Exp Allergy. 2005 Dec; 35(12):1557-64.
BACKGROUND: We recently demonstrated that administration of probiotics resulted in significant clinical improvement in very young children with moderate-to-severe atopic dermatitis (AD). The purpose of this study was to determine the underlying immunological effects that are associated with these apparent clinical benefits. METHODS: Peripheral blood mononuclear cells (PBMC) were isolated from children (n = 53) at baseline and at the end of an 8-week supplementation period during which they received a probiotic (Lactobacillus fermentum PCCtrade mark) (n = 26) or a placebo (n = 27). A further sample was collected at 16 weeks (8 weeks after ceasing the supplement). Cytokine (IL-5, IL-6, IL-10, IL-13, IFN-gamma and TNFalpha) responses to allergens (egg ovalbumin (OVA), beta lactoglobulin (BLG), house dust mite (HDM)), vaccines (tetanus toxoid (TT)), diphtheria toxoid (DT)), intestinal flora (heat-killed Lactobacillus (HKLB)), heat-killed Staphylococcus aureus (HKSA), Staphylococcus aureus enterotoxin B (SEB) and mitogen (phytohaemaglutinin (PHA)) were compared. RESULTS: The administration of probiotics was associated with a significant increase in T-helper type 1(Th1-type) cytokine IFN-gamma responses to PHA and SEB at the end of the supplementation period (week 8: P = 0.004 and 0.046) as well as 8 weeks after ceasing supplementation (week 16: P = 0.005 and 0.021) relative to baseline levels of response. No significant changes were seen in the

placebo group. The increase in IFN-gamma responses to SEB was directly proportional to the decrease in the severity of AD (r = -0.445, P = 0.026) over the intervention period. At the end of the supplementation period (week 8) children receiving probiotics showed significantly higher TNF-alpha responses to HKLB (P = 0.018) and HKSA (P = 0.011) but this was no longer evident when supplementation ceased (week 16). Although IL-13 responses to OVA were significantly reduced in children receiving probiotics after 8 weeks (P = 0.008), there were no other effects on allergen-specific responses, and this effect was not sustained after ceasing supplementation (week 16). There were no effects on vaccine-specific responses, or on responses to any of the stimuli assessed. CONCLUSION: The improvement in AD severity with probiotic treatment was associated with significant increases in the capacity for Th1 IFN-gamma responses and altered responses to skin and enteric flora. This effect was still evident 2 months after the supplementation was ceased. The lack of consistent effects on allergen-specific responses suggests that the effects of probiotics may be mediated through other independent pathways, which need to be explored further.

10. Unproven and Controversial therapies

REVIEW:

B. Wüthrich. "Unproven techniques in allergy diagnosis," J Invest Allergol Clin Immunol 2005; Vol. 15(2): 86-90.

Summary: Mainstream allergy diagnosis and treatment is based on classical allergy testing which involves well validated diagnostic methods and proven methods of treatment. By contrast, a number of unproven tests have been proposed for evaluating allergic patients including cytotoxic food testing, ALCAT test, bioresonance, electrodermal testing (electroacupuncture), reflexology, applied kinesiology a.o. There is little or no scientific rationale for these methods. Results are not reproducible when subject to rigorous testing and do not correlate with clinical evidence of allergy. Although some papers suggest a possible pathogenetic role of IgG, IgG4 antibody, no correlation was found between the outcome of DBPCFC and the levels of either food-specific IgG or IgG4, nor was any difference seen between patients and controls. The levels of these and other food-specific immunoglobulins of non-IgE isotype reflect the intake of food in the individual and may thus be a normal and harmless finding. The so-called "Food Allergy Profile" with simultaneous IgE and IgG determination against more than 100 foodstuffs is neither economical nor useful for diagnosis. DBPCFC must be the reference standard for food hypersensitivity and any new test must be validated by it. As a result, all these unproven techniques may lead to misleading advice or treatments, and their use is not advised.

REVIEW:

Kirsten Beyer & Suzanne S. Teuber. "Food allergy diagnostics: scientific and unproven procedures," Current Opinion in Allergy and Clinical Immunology 2005, 5:261–266.

PURPOSE OF THE REVIEW: The accurate diagnosis of food allergy is crucial not only for the right treatment but also for the avoidance of unnecessary diets. The diagnostic work-up of suspected food allergy includes the measurement of food-specific IgE antibodies using serologic assays, the skin prick test, elimination diets and oral provocation tests. In addition, some approaches are either under further rigorous investigation (the atopy patch test) or are already in widespread use, particularly by practitioners of alternative or complementary medicine, but are considered unproven. These diagnostic methods include specific IgG to foods, provocation/neutralization testing, kinesiology, cytotoxic tests and electrodermal testing. This

review covers some of the most common scientifically validated and unproven approaches used in the diagnosis of food allergy. RECENT FINDINGS: For specific serum IgE and the SPT, decision points have been established for some foods, allowing prediction of clinical relevance. The APT may be helpful, especially when considered in combination with defined levels of specific IgE. In regard to other approaches, most scientific studies do refute the usefulness of these approaches. SUMMARY: In most patients, controlled oral food challenges remain the gold standard in the diagnostic work-up of suspected food allergy. The skin prick test and measurement of specific IgE antibodies to food extracts, individual allergens or allergenic peptides are helpful in the diagnostic approach. Foodspecific IgG continues to be an unproven or experimental test. The other alternative and complementary techniques have no proven benefit and may endanger patients via misdiagnosis.

REVIEW:
Terr AI
Unproven and controversial forms of immunotherapy
Clin Allergy Immunol. 2004;18:703-10.

REVIEW:
Graham DM, Blaiss MS
Complementary/Alternative Methods in the treatment of asthma
Ann Allergy Asthma Immunol. 2000;85:438-47

OBJECTIVE: This review will familiarize clinical allergists/immunologists with the common forms of complementary/alternative medicine (CAM) that are being used frequently by their patients. It reviews reasons that patients seek alternative health care therapies and the most common illnesses that are treated with this form of medicine. Cultural differences in CAM are also reviewed. The article focuses on specific therapies used to treat asthma and reviews the efficacy of these therapies based on the available scientific literature. The reader will also learn about views of other physicians on CAM and how this topic is being addressed in US medical schools. DATA SOURCES: Computer-assisted MEDLINE searches for articles on "complementary/alternative medicine" or "herbal therapy" and "asthma" or "atopy." STUDY SELECTION: Pertinent abstracts and articles in the above areas were selected. Articles selected for detailed review included review articles of the subjects along with randomized, double-blind placebo-controlled studies in animals and humans. RESULTS: Complementary/alternative medicine is commonly used by patients with chronic conditions including asthma. One-third of the US population has tried CAM. The literature supporting the efficacy of these therapies is lacking. Some reports elucidate the mechanism of action of certain herbal therapies that could possibly be helpful in the treatment of allergic diseases. There are, however, few well-controlled studies that support the efficacy of CAM in the treatment and clinical improvement of human subjects with asthma or atopic disorders. CONCLUSION: Available scientific evidence does not support a role for CAM in the treatment of asthma. The studies in the literature often have significant design flaws that weaken the conclusions such as insufficient numbers of patients, lack of proper controls, and inadequate blinding. Further studies are needed to prove or disprove the efficacy of CAM. Physicians often find CAM intimidating because they are unaware of the clinical evidence and feel uncomfortable advising their patients on its efficacy. There is definitely a need for more education among physicians in this area. It is also important that physicians inquire and discuss the use of CAM with their patients since the majority of patients are using some form of CAM.

REVIEW:
Ziment I, Tashkin DP.
Alternative Medicine for allergy and asthma
J Allergy Clin Immunol. 2000 Oct;106(4):603-14
Orthodox medical approaches to asthma and allergic respiratory diseases are provided in guidelines developed by professional societies and national or state organizations that represent organized medicine. Alternative therapies may include such orthodox medical therapies as obsolescent formerly used agents, unusual but accepted agents, and agents that are in favor for orthodox therapy in other countries. However, the current growth of complementary and alternative medicine is based on the use of nonorthodox remedies that are becoming increasingly popular with patients and that should be familiar to physicians. Asthma and allergies are frequently treated with such remedies by patients, either as part of self-therapy or on the advice of a complementary and alternative medicine practitioner. The most popular alternative medical treatments are herbs (Western and Asiatic), acupuncture, various types of body manipulation, psychologic therapies, homeopathy, and unusual allergy therapies. There is little evidence in favor of most of these unorthodox treatments, although they are very often reported on favorably by patients. The published evidence that might support some alternative medical practices is reviewed so as to help physicians select alternatives that could appropriately be integrated into orthodox practice.

VI. Basics of ACGME Core Competencies

NOTE:
"Educating Physicians for the 21st Century," is a planned series of five PowerPoint presentations with a Facilitator's Manual addressing the ACGME Core Competencies. 3 of these modules are currently available:

- Module 1 – Introduction to Competency-Based Resident Education
- Module 2 – Practical Implementation of the Competencies
- Module 3 – Developing an Assessment System and two additional modules are to be released in the near future...
- Module 4 - Curriculum Planning
- Module 5 - Educational Quality Improvement

www.acgme.org/outcome/ and clicking on the "FACULTY DEVELOPMENT" and "FACULTY DEVELOPMENT TOOLS" tabs.

NOTE:
The Graduate Medical Education Community is still in the developmental stage of creating valid educational and assessment activities for the ACGME Core Competencies. The submission of well developed, A&I specific, educational activities directed toward the individual competencies are encouraged by the Core Curriculum and Education Committee. Listed below are some published examples of activities developed to address the Core Competencies. In addition, an array of example activities may be found in the "members only" area of the AAAAI Website www.aaaai.org - under the PD Core ACGME-Required Competencies Web Site section.

A. Professionalism

COMPETENCY DEVELOPMENT EXAMPLE:
Klein EJ, Jackson JC. Kratz L, et al
Teaching professionalism to residents
Acad Med. 2003;78:26-34.

The need to teach professionalism during residency has been affirmed by the Accreditation Council for Graduate Medical Education, which will require documentation of education and evaluation of professionalism by 2007. Recently the American Academy of Pediatrics has proposed the following components of professionalism be taught and measured: honesty/integrity, reliability/responsibility, respect for others, compassion/empathy, selfimprovement, self-awareness/knowledge of limits, communication/collaboration, and altruism/advocacy. The authors describe a curriculum for introducing the above principles of professionalism into a pediatrics residency that could serve as a model for other programs. The curriculum is taught at an annual five-day retreat for interns, with 11 mandatory sessions devoted to addressing key professionalism issues. The authors also explain how the retreat is evaluated and how the retreat's topics are revisited during the residency, and discuss general issues of teaching and evaluating professionalism.

B. Communication Skills

COMPETENCY DEVELOPMENT EXAMPLE:
Egnew TR, Mauksch LB, Greer T, et al.
Integrating communication training into a required family medicine clerkship.
Acad Med 2004;79:737-43.

Persistent evidence suggests that the communication skills of practicing physicians do not achieve desired goals of enhancing patient satisfaction, strengthening health outcomes and decreasing malpractice litigation. Stronger communication skills training during the clinical years of medical education might make use of an underutilized window of opportunity-students' clinical years-to instill basic and important skills. The authors describe the implementation of a novel curriculum to teach patient-centered communication skills during a required third-year, six-week family medicine clerkship. Curriculum development and implementation across 24 training sites in a five-state region are detailed. A faculty development effort and strategies for embedding the curriculum within a diverse collection of training sites are presented. Student and preceptor feedback are summarized and the lessons learned from the curriculum development and implementation process are discussed.

C. Practice Based Learning

COMPETENCY DEVELOPMENT EXAMPLE:
Ogrinc G, Headrick LA, Mutha S, et al.
A framework for teaching medical students and residents about practice-based learning and improvement, synthesized from a literature review.
Acad Med 2005;78:748-56.

PURPOSE: To create a framework for teaching the knowledge and skills of practice-based learning and improvement to medical students and residents based on proven, effective strategies. METHOD: The authors conducted a Medline search of English-language articles published between 1996 and May 2001, using the term "quality improvement" (QI), and crossmatched it with "medical education" and "health professions education." A thematic-synthesis method of review

was used to compile the information from the articles. Based on the literature review, an expert panel recommended educational objectives for practice-based learning and improvement. RESULTS: Twenty-seven articles met the inclusion criteria. The majority of studies were conducted in academic medical centers and medical schools and 40% addressed experiential learning of QI. More than 75% were qualitative case reports capturing educational outcomes, and 7% included an experimental study design. The expert panel integrated data from the literature review with the Dreyfus model of professional skill acquisition, the Institute for Healthcare Improvement's (IHI) knowledge domains for improving health care, and the ACGME competencies and generated a framework of core educational objectives about teaching practicebased learning and improvement to medical students and residents. CONCLUSION: Teaching the knowledge and skills of practice-based learning and improvement to medical students and residents is a necessary and important foundation for improving patient care. The authors present a framework of learning objectives-informed by the literature and synthesized by the expert panel-to assist educational leaders when integrating these objectives into a curriculum. This framework serves as a blueprint to bridge the gap between current knowledge and future practice needs.

D. Systems-Based Practice

COMPETENCY DEVELOPMENT EXAMPLE:

Tomolo A. Caron A, Perz ML.

The outcomes card. Development of a systems-based practice educational tool

J Gen Intern Med 2005;20:769-71

INTRODUCTION: The Accreditation Council for Graduate Medical Education requires competence in systems-based practice (SBP) demonstrating understanding of complex interactions between systems of care and its impact upon care delivery. Patient safety is a useful vehicle to facilitate learning about these interactions. AIM: Develop an educational tool, Outcomes Card (OC), to reinforce core concepts of SBP. SETTING: Urgent Care Center at Louis Stokes Cleveland Department of Veterans Affairs Medical Center. PROGRAM DESCRIPTION: Pilot study of an educational intervention for residents that included patient safety didactic sessions and analysis of 2 self-identified clinical cases using the OC. Residents entered the following information on the OC: case description, type of event (error, near miss, and/or adverse event), error type(s), systems, and system failures. PROGRAM EVALUATION: Two reviewers independently analyzed 98 cards completed during 60 two-week trainee rotations (81.7% return rate). Interrater reliability for error types between residents and physician supervisor and between reviewers was excellent (kappa=0.88 and 0.95, respectively), and for system identification was good (kappa=0.66 and 0.68, respectively). The self-assessment survey (56.6% return rate) suggests that residents improved their knowledge of patient safety and had positive attitudes about the curriculum. DISCUSSION: This pilot study suggests that OCs are feasible and reliable educational tools for enhancing competence in SBP.