Introduction

The members of the AAAAI Program Directors' Core Curriculum Subcommittee hope that you will find the Core Curriculum and Reading list to be a useful aid in selecting educational resources to teach and learn about important concepts in the field of Allergy and Immunology.

How to Use this Document

Immediately following this introductory page and in the "bookmarks" of this document you will find an updated "Program Directors' Core Curriculum Outline". Click on any of the Core Curriculum Topics to view the citation and abstract of the associated reading(s).

Updating the Core Curriculum and Reading List

The members of the Core Curriculum Subcommittee would like to INVITE EVERYONE to help keep the curriculum/reading list as current and useful as possible. The Core Curriculum and Reading List will be posted on the "Blackboard" site at Cincinnati Children's Hospital. This site was designed to allow visitors an opportunity to suggest additional or alternative educational resources to be included into the list. The suggestions will be reviewed by committee members and included in the subsequent iteration of the reading list if deemed appropriate.

In order to access the Blackboard, please obtain a username and password from Katie Muellenbach at the AAAAI (KMuellenbach@aaaai.org), and then go to the website below: http://www.cincinnatichildrens.org/research/cores/informatics/support/software/blackboard/

You can find the Core Curriculum and Reading List as well as a Reading List Suggestion Form by clicking on "My Courses" then "Course Documents".

To suggest an article for the Reading List or to suggest a change to the Core Curriculum, click on "Tools" and then go to "Digital Drop Box" Please attach:

1. **a completed "Reading List Suggestion Form" available in "Course Documents" and**
2. **if possible a file containing the educational resource you would like to submit.**

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Allergy and Immunology Program Directors' Core Curriculum Outline

The Training Program Directors' (TPD) Core Curriculum Outline is updated every three years by the Core Curriculum Subcommittee of the TPD and is consistent with the requirements of the Residency Review Committee for training in allergy and immunology. The TPD Core Curriculum outline serves as a guide for: (1) TPD and trainees in meeting the requirements of the Residency Review Committee, (2) the Reading List Subcommittee, (3) the In-Training Examination Subcommittee. The intent of this outline is to provide 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.

I. Basic Immunology

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.

- A. Overview of the Immune System
  - 1. Organization and Function of the Immune System
    - a. Thymic development and shaping peripheral systemic T-cell immunity
    - b. Cutaneous Immunity
    - c. Intestinal/Mucosal Immunity
    - d. Primary Immune Function of Cellular Elements of the Immune System
      - *i.* T-cells
      - *ii.* B cells
      - iii. Neutrophils
      - iv. Eosinophils
      - v. Mast cells
      - vi. Basophils
      - vii. Antigen presenting cells
      - viii. Natural Killer Cells
      - ix. Platelets

- B. Immune Mechanisms
  - 1. Innate versus adaptive immunity
    - a. complement and the innate immune response
    - b. Pattern Recognition Receptors (MBP, Toll-like Receptors, CD14 etc.)
    - c. Natural Antimicrobial Agents
      - i. Reactive Oxygen Species
      - ii. Releasable granule proteins (defensins, lactoferrin, cathelicidins)
  - 2. The major histocompatibility complex – molecular structure and function
  - 3. Immunogenetics – Gene rearrangements in the generation of immune system diversity
  - 4. Antigen-presenting cells – processing and presentation of conventional and Superantigens

5. Gell and Coombs Classification of Immune Responses
    a. Type I –Immediate Hypersensitivity Response
        i. IgE binding and signal transduction
        ii. preformed and newly synthesized mediator release
        iii. late phase reactions
    b. Type II – Antibody induced reactions Response
    c. Type III – Immune-Complex mediated reactions
    d. Type IV – Cell mediated /Delayed Hypersensitivity Response
6. T cell mediated immunity
    a. T cell activation – T cell receptor structure and function, epitope recognition and accessory molecules in signal transduction
    b. Cytokines and co-stimulatory molecules in T cell activation
    c. T cell mediated immune responses – participating cells. Properties and functions of antigen presenting cells.
    d. T cell subsets
    e Regulatory T cells and memory cells
    f. NK T cells
7. B cell mediated immunity
    a. B cell activation – cytokines and signal transduction
    b. Epitope recognition and immunoglobulin production
    c. Maturation of B lymphocytes
    d. Maturation of the antibody response
    e. Biologic process initiated by antibody: opsonization, complement fixation, antibody dependent cell mediated cytotoxicity
    f. IgE mediated immediate and late phase reactions
    g. Immune complexes – immunologic properties and mechanisms of clearance
8. Other immune and inflammatory mechanisms
    a. Natural killer cells, their CD markers and functions
    b. Lymphokine activated killer cells and their effects
    c. Cutaneous basophil hypersensitivity
    d. Kinin mediated inflammation
    e. Arachidonic Acid Metabolites and Inflammation
    f. Cytokines/Chemokines and their receptors
    g. Growth factors
9. Receptor ligand interactions in immune functioning – Signal transduction resulting from receptor ligand interaction. Genetic polymorphisms producing gain or loss of function.
10. T & B cell Immunologic Memory(Including CD markers of cells involved in immunological memory)

C. Mucosal Immunity
1. Mucosal Barrier Innate defenses
    a. Barrier function and local enzyme systems
    b. Normal Flora
    c. Complement
    d. Defensins
2. Antigen transport

- 3. Adaptive Immunity
  - a. Responses to bacteria viruses and parasites
  - b. Mucosal Immunoglobulins
    - i. Secretory IgA
    - ii Ig Transport
    - iii FcγRII function
    - iv Mucosal associated lymphoid tissue (MALT)
- 4. Passive immunization

D. Transplantation Immunology
- 1. Allograft rejection
- 2. Graft versus host reactions (GVHR)
- 3. Maintenance of tolerance

E. Tumor Immunology
- 1. Tumor specific and tumor associated antigens
- 2. Oncogenes, translocations and tumor suppressor genes

F. Immunoregulatory Mechanisms
- 1. Tolerance
- 2. Idiotypic networks
- 3. Apoptosis
- 4. Anergy

G. Laboratory Measurements
- 1. Principles and methodology of:
  - a. measurements of immunoglobulin levels, immunoglobulin classes and subclasses
  - b. serologic testing
    - i. ELISA, immunoblot
    - ii. autoimmune serology
    - iii. in vitro testing techniques for specific IgE
    - iv. RAST Inhibition techniques
    - v. serologic testing for infectious disease
  - c. flow cytometry -cell surface marker and intracellular techniques
  - d. Cellular functional responses
    - i. Chemotaxis and adhesion
    - ii. mitogen or antigen induced proliferation and activation
    - iii. phagocytosis and intracellular killing
    - iv. cellular cytotoxicity
  - e. measurement of immune complexes, cryoprecipitable proteins, total serum complement activity, complement components and C1 Inhibitor assays.
  - f. histocompatibility typing
  - g. genetic techniques including TRECs, PCR and use of probes.
  - h. hybridoma and monoclonal antibody technology
  - i. cytokine and mediator measurement
- 2. Test-performance characteristics: principles of sensitivity, specificity, predictive value, and ROC analysis

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

II. Anatomy and Physiology

- A. Normal anatomy and physiology
  - 1. Upper airway -nose, sinuses, middle ear
  - 2. Lower Airway
  - 3. Skin
  - 4. Gastrointestinal Tract
  - 5. Lymphoid Tissue

- B. Pathology of primary atopic disorders
  - 1. Asthma (including airway remodeling)
    - a. Children
    - b. Adults
  - 2. Rhinitis and rhinosinusitis
    - a. Allergic
    - b. Infectious
    - c. Nonallergic
    - d. Nasal polyps
  - 3. Atopic Dermatitis
  - 4. Early and late responses to allergen challenge
    - a. nasal
    - b. bronchial challenge
    - c. cutaneous challenge
  - 5. Role of structural cells
    - a. epithelium
    - b. endothelium
    - c. smooth muscle
    - d. fibroblasts
    - e. mucociliary cells

- C. Measurements and interpretation of lower airway function
  - 1. Spirometry: FVC, FEV1, FEV/FVC, FEF 25-75, Flow volume loop, pre-and postbronchodilator values
  - 2. Provocative challenges (exercise, methacholine, allergen, other): indications, performance, and interpretation, predictive value of asthma

III. Pharmacology

- A. Pharmacology and pharmacokinetics of drugs used in allergy/immunology
  - 1. Glucocorticoids
  - 2. Beta-Agonists and Antagonists
  - 3. Mast Cell Active Agents (Cromolyn / Nedocromil)
  - 4. Cyclooxygenase and Leukotriene Pathway Modulators

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

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.

2. Eye Disease

a. Allergic and vernal conjunctivitis, iritis, iridocyclitis

b. Clinical skills: eye examination

3. Dermatologic disease

a. Urticaria, angioedema, dermatographia, atopic dermatitis, contact dermatitis, urticaria pigmentosa, bullous disease, drug rashes, erythema multiforme and toxic epidermal necrolysis, erythema nodosum, and other immunologic skin diseases.

b. Clinical skills: proper cutaneous examination, patch testing, drug skin testing (immediate and delayed type hypersensitivity skin tests), testing for physical urticaria/angioedema, and an understanding of dermatopathology and immunofluorescent tests.

4. Lower respiratory tract disease

a. Asthma and related disorders (exercise-induce, allergic bronchopulmonary aspergillosis, sulfite-related, and intrinsic); 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

b. Specific skills and interpretative strategies to be acquired: chest exam, interpretation of pulmonary function testing, bronchial challenges, sputum and exhaled breath analysis, and gross interpretation of imaging studies.

5. Drug Allergy (See dermatologic disorders and anaphylaxis)

a. Distinction between hypersensitivity and intolerance

b.Cytotoxic, immune complex and delayed hypersensitivity reactions

c. Aspirin and NSAID reactions

d.Reactions to Vaccines

e. Photoallergy, phototoxicity, drug fever, and serum sickness reactions

f. Clinical skills – specific testing and provocative challenges

6. Adverse reactions to ingestants

a. Food sensitivities-IgE mediated, food intolerance, gluten sensitivity

b. Food-additive reactions

c. Eosinophilic esophagitis and gastroenteritis

d. Clinical skills mastered: set up double blind placebo controlled food challenge, interpretation of skin prick and in vitro testing to foods

7. Anaphylaxis and Anaphylactoid Reactions
    a. Causes (ingestants, exercise, allergy immunotherapy, latex, radiocontrast media) case definition and common presentations.
    b. Laboratory evaluation of anaphylactic episode, allergy testing, tryptase
    c. Treatment of Anaphylaxis including Cardiopulmonary Resuscitation
        i. Acute treatment
        ii. Patient education, use of Epi-pen, Epi-pen Jr.
8. Insect Hypersensitivity
    a. Classes of insects associated with hypersensitivity
    b. Skin prick, intradermal and in vitro testing to stinging insects
    c. Predictive value of clinical history and testing for adult and pediatric population
    d. Algorithm for history positive, test negative, stinging insect reactive patient
    e. Venoms, formulation, schedule and duration of immunotherapy.
9. Economic costs of diagnosis and treatment of allergic diseases
10. Psychosocial aspects of allergic disease and chronic illness, failure of adherence to therapy

B. Immunodeficiency Diseases
1. Primary immunodeficiency diseases (including clinical presentation, diagnostic approach, cellular profile, genetic basis, prognostic factors and therapeutic options)
    a. Combined immunodeficiencies syndromes
    b. Predominant antibody deficiencies
    c. Other well defined immunodeficiency syndromes
    d. Complement deficiencies including hereditary acquired C1 inhibitor deficiency
    e. Congenital defects of phagocytic number, function and adhesion
    f. Clinical skills for diagnosis and treatment
2. Acquired immunodeficiency diseases
    a. Due to infection, AIDS and other
    b. Nutrition and metabolic related
    c. Associated with malignancy and infectious processes
    d. Iatrogenic immunodeficiency
    e. Clinical skills for diagnosis and treatment

C. Immunoregulatory Disorders
Interpretation of physical findings, diagnostic tests and management of:
1. The Vasculitides (Small, Medium and Large vessels)
2. Immune rheumatic disorders
3. Immune renal disorders
4. Immune endocrine and reproductive disorders
5. Immune pulmonary disorders
6. Immune gastrointestinal and hepatobiliary disorders
7. Immune neurologic and neuromuscular disorders
8. Immune hematologic disorders
9. Immune ocular disorders
10. Immune skin disorders

D. Transplantation Medicine
- 1. Recognition of alloantigens
- 2. Alloreactive T cell activation
- 3. Allograft rejection
  - a. Hyperacute
  - b. Acute
  - c. Chronic
- 4. Prevention and treatment of allograft rejection
  - a. Immunosupression
  - b. Methods to reduce allograft immunogenicity
  - c. Methods to induce allograft host tolerance
- 5. GVHD: Acute and Chronic
  - a. Prevention
  - b. Treatment

E. Immune System Related Malignancies and Cellular Disorders
- 1. B cell and plasma cell neoplasms
- 2. T cell neoplasms
- 3. Monocyte/macrophage neoplasms
- 4. Mast Cell Dyscrasias
- 5. Eosinophilic Disorders
- 6. Cryopathies & amyloid
- 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.

F. Established and Evolving Immune-based Treatment Modalities
- 1. Glucocorticoids and Immunosuppressants (also see Section III. A.)
- 2. Modified Allergen Immunotherapy
- 3. Cellular immune reconstitution including stem cell and bone marrow transplant
- 4. Immunoglobulin replacement therapy
- 5. Nucleic Acid Based Therapies (DNA vaccines, CpG, gene insertion, antisense nucleotides)
- 6. Cytokine receptors and receptor antagonists (IFN, antiTNF, etc)
- 7. Recombinant molecules and humanized monoclonal antibodies (imatinib, infliximab, omaluzimab, rituximab)
- 8. Plasmapheresis and cytopheresis
- 9. Probiotics
- 10. Unproven and Controversial therapies

Allergy and Immunology Program Directors' Reading List

I. Basic Immunology

A. Overview of the Immune System

1. Organization and Functions of the Immune System

REVIEW:
Delves, PJ and Roitt IM.
The Immune System (Parts 1&2)
N Engl Med 2000:343:37-49 and 108-117.
The immune system is an organization of cells and molecules with specialized roles in defending against infection. There are two fundamentally different types of responses to invading microbes. Innate (natural) responses occur to the same extent however many times the infectious agent is encountered, whereas acquired (adaptive) responses improve on repeated exposure to a given infection. The innate responses use phagocytic cells (neutrophils, monocytes, and macrophages), cells that release inflammatory mediators (basophils, mast cells, and eosinophils), and natural killer cells. The molecular components of innate responses include complement, acute-phase proteins, and cytokines such as the interferons.
OUTLINE…
Three Levels of Defense
Immune Recognition
Innate Immune Responses
Cellular Components of Innate Responses
Soluble Factors in Innate Defense
The Acute Inflammatory Response
Acquired Immune Responses
The Structure of Antigen-Specific Molecules
The B-Cell Receptor and Soluble Antibodies
The T-Cell Receptor
The Diversity of Antigen Receptors
Clonal Selection
Major Populations of B Cells
T Cells and the Thymus
Tolerance Mechanisms

LANDMARK PUBLICATION:

Hogquist KA, Jameson SC, Heath WR et al

T-Cell Receptor Antagonist Peptides Induce Positive Selection.

Cell 1994;76:17-27

We have used organ culture of fetal thymic lobes from T cell receptor transgenic mice to study the role of peptides in positive selection. The TCR used was from a CD8+ T cell specific for ovalbumin 257-264 in the context of K^b. Several peptides with the ability to induce positive selection were identified. These peptide-selected thymocytes have the same phenotype as mature CD8+ T cells and can respond to antigen. Those peptides with the ability to induce positive selection were all variants of the antigenic peptide and were identified as TCR antagonist peptides for this receptor. One peptide tested, E1, induced positive selection on the β2M(-/-) background but negative selection on the β2M(+/-) background. These results show that the process of positive selection is exquisitely peptide specific and sensitive to extremely low ligand density and support the notion that low efficacy ligands mediate positive selection.

RESEARCH FRONTIER:

Matloubian M, Lo CG, Cinamon G, et al

Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. .

Nature 2004;427:355-360.

Adaptive immunity depends on T-cell exit from the thymus and T and B cells traveling between secondary lymphoid organs to survey for antigens. After activation in lymphoid organs, T cells must again return to circulation to reach sites of infection; however, the mechanisms regulating lymphoid organ exit are unknown. An immunosuppressant drug, FTY720, inhibits lymphocyte emigration from lymphoid organs, and phosphorylated FTY720 binds and activates four of the five known sphingosine-1-phosphate (S1P) receptors 1-4. However, the role of S1P receptors in normal immune cell trafficking is unclear. Here we show that in mice whose haematopoietic cells lack a single S1P receptor (S1P1; also known as Edg1) there are no T cells in the periphery because mature T cells are unable to exit the thymus. Although B cells are present in peripheral lymphoid organs, they are severely deficient in blood and lymph. Adoptive cell transfer experiments establish an intrinsic requirement for S1P1 in T and B cells for lymphoid organ egress. Furthermore, S1P1-dependent chemotactic responsiveness is strongly upregulated in T-cell development before exit from the thymus, whereas S1P1 is downregulated during peripheral lymphocyte activation, and this is associated with retention in lymphoid organs. We find that FTY720 treatment downregulates S1P1, creating a temporary pharmacological S1P1-null state in lymphocytes, providing an explanation for the mechanism of FTY720-induced lymphocyte sequestration. These findings establish that S1P1 is essential for lymphocyte recirculation and that it regulates egress from both thymus and peripheral lymphoid organs.

a. Thymic Development and shaping peripheral T-cell repertoire

REVIEW 1 (extensive T-cell):
Sebzda E, Marithasan S, Ohteki T, et al
Selection of the T-cell Repertoire.
Ann Rev Immunol 1999; 17:829-874
Advances in gene technology have allowed the manipulation of molecular interactions that shape the T cell repertoire. Although recognized as fundamental aspects of T lymphocyte development, only recently have the mechanisms governing positive and negative selection been examined at a molecular level. Positive selection refers to the active process of rescuing MHC-restricted thymocytes from programmed cell death. Negative selection refers to the deletion or inactivation of potentially autoreactive thymocytes. This review focuses on interactions during thymocyte maturation that define the T cell repertoire, with an emphasis placed on current literature within this field.

REVIEW 2: (abbreviated B/T cell)
Kamradt T, Mitchison NA.
Tolerance and Autoimmunity.
N Engl J Med 2001;344:655-664.
The immunologic specificity of the antigen receptors of T cells and B cells is the result of randomshuffling of the many genes that form the DNA code for the antigen-binding site of these receptors.[1,2,3] Theoretically, this process could generate 10^9 different T-cell receptors, including some that can bind to auto-antigens (these cells are often called self-reactive T cells). Tolerance is the process that eliminates or neutralizes such auto-reactive cells, and a breakdown in the working of this system can cause autoimmunity Outline…
B-Cell Tolerance
Central T-Cell Tolerance
Peripheral T-Cell Tolerance
Ignorance
Deletion
Regulation
Anergy
Inhibition
Suppression and Deviation
Breakdown of Tolerance
Genetic Susceptibility to Autoimmunity
Therapeutic Implications
Immunomodulation
Purging Autoreactive T Cells from the T-Cell Repertoire
Conclusions

b. Cutaneous Immune System

REVIEW:
Debenedictis C, Joubeh S, Zheng G, et al.

Immune Functions of the Skin.
Clinics in Dermatology 2001;19:573-585.
Introduction: The skin comprises approximately 1.5 to 2 m^2 of the average human's surface and represents the largest organ of the body, providing the principal physical barrier to the environment. In addition, the skin functions as the most peripheral component of the immune system and initiates a primary immune response to foreign antigen. The immune system disseminates throughout all tissues but has evolved to optimize the specialized needs of specific organ systems. During evolution, the skine developed a specific immunologic environment know as the Skin Associated Lymphoid Tissue (SALT). SALT consists mainly of Langerhans cells and dermal antigen presenting cells which circulate between the skin and the lymph nodes, : keratinocytes and endothelial cells, which produce a wide range of immune and growth regulatory cytokines; and lymphocytes, which extravasate from circulation in to the skin. All components work in concert to optimize detection of environmental antigens.

c. Intestinal/Mucosal Immunity

REVIEW:
Spahn TW and Kucharzik
Modulating the intestinal immune system: the role of lymphotoxin and GALT organs.
Gut 2004;53:45-465.
The gut associated immune system fences off potentially harmful intestinal antigens from the systemic circulation and induces systemic tolerance against luminal antigens. Intestinal immune responses against luminal antigens include IgA secretion and induction of regulatory cells. Unlike few other cytokines, lymphotoxin /ß regulates the development of intestinal lymphoid organs. The embryonic development of Peyer's patches, postnatal lamina propria B cell development, and isolated lymphoid follicle development all depend on lymphotoxin ß receptor interactions. Lymphotoxin /ß signalling also contribute to the development of mesenteric lymph nodes. In addition, intestinal inflammation is suppressed by inhibition of lymphotoxin ß signalling, an observation which has initiated clinical studies using this treatment principal. Intestinal follicular lymphoid organs are sites of antigen presentation. Antigen presenting cells tune the delicate balance between intestinal immune tolerance and inflammation. Therefore, gut associated lymphatic organs and factors regulating their development are critical for the prevention of adverse immune reactions.

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

i. T-cells

REVIEW:
VonAndrian UH, Mackay CR.
T cell function and migration.
N Engl J Med 2000;343:1020-1034
Since the pioneering work of Gowans and colleagues in the 1960s,[1,2] much progress has been made in understanding the pivotal role of cell migration in immunity. We now have considerable knowledge of the way in which specialized leukocytes are channeled to distinct target tissues in immune responses and inflammation (Figure 1). This review will concentrate on the migration of T cells, which are at the heart of most adaptive immune responses.

ii. B cells

REVIEW:
McHeyzer-Williams MG
B-cells as effectors.
Curr Opinion Immunol 2003;15:354-361
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 T-cell 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 B-cell fate. These activities culminate in the germinal center reaction, during which somatic hypermutation and antigen-driven selection produce and preserve high-affinity plasma cells with extended longevity and memory B cells as the sensitized precursors for antigen recall.

iii. Neutrophils

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.

iv. Eosinophils

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:

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. T_H2-polarized inflammation elicits a reactive hyperplasia of mast cells at the involved mucosal surfaces in both mice and human subjects. Several recombinant T_H2 cytokines (IL-3, IL-4, IL-5, and IL-9) act synergistically with stem cell factor to facilitate proliferation of non-transformed human mast cells in vitro. IL-4 induces the expression of critical inflammation-associated genes by human mast cells, such as those encoding leukotriene C_4 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 T_H2 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:

Roles of mast cells and basophils in innate and acquired immunity.

Wedemeyer J. Tsai M. Galli SJ.

Current Opinion in Immunology. 12(6):624-31, 2000 Dec

There have been several recent advances in knowledge about mast cells and basophils in immune responses, of which some are particularly important: a role has been found for heparin in the storage of certain proteases and other mediators in mast cell cytoplasmic granules; an important role for mast cells in the development of several chronic aspects of an asthma model in mice has been discovered; and a new approach has been developed, based on the generation of mast cells from embryonic stem cells in vitro, to investigate mast cell function in vitro or in vivo.

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 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.

vii. Antigen presenting cells

REVIEW:

Gatti E. Pierre P.

Understanding the cell biology of antigen presentation: the dendritic cell contribution

Current Opin Cell Biol 2003;15:468-7

The study of the cell biology of antigen processing and presentation has greatly contributed to our understanding of the immune response. The work of many immunologically inclined cell biologists has also permitted us to gain new insights on cellular mechanisms shared by many cell types. Dendritic cells are master regulators of the immune system and consequently have received a lot of attention in recent years. With the aim of controlling antigen processing and presentation, the solutions used by dendritic cells to respond to environmental changes are numerous and surprising. In the presence of pathogens, dendritic cells regulate strongly their endocytic pathway by interfering with uptake, proteolysis, membrane dynamics and transport in and out of the lysosome to become the most potent antigen-presenting cells known.

viii. Natural Killer Cells

REVIEW:

Papamichail M, Perez SA, Gritzapis AD, Baxevanis C.

Natural Killer Lymphocytes:.Biology, development and function.

Cancer Immunol Immunother 2004;53:176-186.

Natural killer (NK) lymphocytes represent the first line of defense against virally infected cells and tumor cells. The role of NK cells in immune responses has been markedly explored, mainly due to the identification of NK cell receptors and their ligands, but also through the analysis of mechanisms underlying the effects of various cytokines on NK cell development and function. A population of lymphocytes that shares function and receptors with NK cells is represented by natural killer T (NKT) cells. NKT lymphocytes are regulators of both innate and adaptive immune responses, but have also been reported to function as effector antitumor cells. The marked progress in our understanding of the biology, development, and function of NK/NKT cells has provided the basis for their potential application in tumor clinical trials.

REVIEW:

Germain RN

An innately interesting decade of research in Immunology

NATURE MED 2004;10:1307-1320

"Nature has provided, in the white corpuscles as you call them-in the phagocytes as we call them-a natural means of devouring and destroying all disease germs. There is at bottom only one genuinely scientific treatment for all diseases, and that is to stimulate the phagocytes." So opined B.B. in G.B. Shaw's The Doctor's Dilemma in a dramatic restatement of a key portion of Ilya Metchnikoff's Nobel Prize address: "Whenever the organism enjoys immunity, the introduction of infectious microbes is followed by the accumulation of mobile cells, of white corpuscles of the blood in particular which absorb the microbes and destroy them. The white corpuscles and the other cells capable of doing this have been designated 'phagocytes,' (i.e., devouring cells) and the whole function that ensures immunity has been given the name of 'phagocytosis'". Based on these insights into the foundation of resistance to infectious disease, Metchnikoff was awarded the 1908 Nobel

Prize in Physiology or Medicine together with Paul Ehrlich (Fig. 1). Although both were cited for discoveries in immunity, the contributions of the two men seem worlds apart. Ehrlich's studies did not deal with generic responses to infection, but rather with the highly specific nature of antibodies and their relationship to the cells producing them: "As the cell receptor is obviously preformed, and the artificially produced antitoxin only the consequence, i.e. secondary, one can hardly fail to assume that the antitoxin is nothing else but discharged components of the cell, namely receptors discharged in excess". But biological systems are just that-systems-and the parts need to work together. And so we arrive, a century later, at an appreciation for just how intimately related these two seemingly disparate aspects of host defense really are.

REVIEW:
Lodoen MB, Lanier LL.
Natural Killer Cells as an initial defense against pathogens
Current Opinion in Immunology 2006, 18:391-398
Natural killer (NK) cells serve as a crucial first line of defense against tumors and a diverse range of pathogens. Recognition of infection by NK cells is accomplished by the activation of receptors on the 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. interleukin 12 and type I interferons), which are products of activated macrophages and dendritic cells. In response to these activating stimuli, NK cells secrete cytokines and chemokines and lyse target cells. 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. Platelets

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.

B. Immune Mechanisms

1. Innate versus adaptive immunity

REVIEW:

Uthaisangsook S, Day NK, Bahna SL, et al.
Innate Immunity and its role against infections
Ann Allergy Asthma and Immunol 2002;88:253-264.

The innate immune system is nonspecific immunity present since birth not requiring repeated exposure to pathogens. It is capable of differentiation between self and nonself. Because of its nonspecificity, it has a broad spectrum of resistance to infection. Further, it is thought to play an important role in the control of adaptive immunity by regulating costimulatory molecules and effector cytokines. Innate immunity includes pattern recognition molecules/receptors, antimicrobial peptides, the complement system, inflammatory mediators, and cytokines produced by immune cells. Pattern recognition molecules/receptors recognize pathogen-associated molecular patterns that are essential for microorganisms' survival and pathogenicity. Although innate immunity has recently gained increasing importance, further studies are necessary for a better understanding of its role.

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:

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:
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 Factor
Factor H Deficiency
C1 Inhibitor Deficiency
Paroxysmal Nocturnal Hemoglobinuria

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.

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 superoxide-generating 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.

2. Major histocompatibility complex – molecular structure and function

REVIEW 1:
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 peptide-presenting ("classical") MHC molecules is given here. No attempt will be made to cover the vast amount of literature in this area.

REVIEW 2:
Benacerraf B. McDevitt HO.
Histocompatibility-linked immune response genes.
Science 1972; 175(19):273-9.

RESEARCH FRONTIER:
Rudolph MG
Specificity of the TCR/pMHC interaction..
Curr Opin Immunol 2002; 14:52-65 (*note: alternatively this may be considered for positioning under TCR basic science)*

Crystal structures of 11 complexes of TCRs with peptide/MHC (pMHC), that represent 6 independent TCRs, constitute the current structural database for deriving general insights into how alphabeta TCRs recognise peptide-bound MHC class I or class II. The TCRs adopt a roughly diagonal orientation on top of the pMHCs, but the identification of a set of conserved interactions that dictate this orientation is not apparent. Furthermore, the specific interaction of each TCR with its cognate pMHC partner is quite variable and also involves bound water molecules at the TCR/pMHC interface. In two of the systems, the structural basis for binding of altered peptide ligands has illustrated that the only significant conformational changes occur in the TCR/pMHC interface, but their small magnitude is inconsistent with the enormous variation in signaling outcomes. The TCRs adjust to different agonist, partial agonist and antagonist peptides by subtle conformational changes in their complementarity-determining regions, as previously observed in induced-fit mechanisms of antibody/antigen recognition. Alloreactivecomplex structures determined or modelled so far indicate increased interactions of the TCR beta-chain with the pMHC compared with their syngeneic counterparts.

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

REVIEW 1:
Vallejo AN, Davila E, Weigand CM and Goronzy JJ.
Biology of T lymphocytes.
Rheum Dis Clin N. America. Feb 2004. 30(1): 135-57
T cells constitute one arm of the adaptive immune system. The accumulating information on various aspects of T-cell biology shows the intricacies in the regulation of immune responses. How we translate the cellular and molecular details of this regulation into innovation and development of therapies for disease management remains a fundamental, but exciting, challenge.

REVIEW 2:
Weinstein E.
B Cell Biology.
Rheum Dis Clin N America. Feb 2004; 30(1):157-74
In recent years, our understanding of B-cell biology and the roles of B cells in normal immune responses and autoimmunity has increased dramatically. We no longer think of B cells simply as antibody factories. It is clear that these diverse and exquisitely regulated cells may contribute in a multitude of ways to immune responses. Animal models, clinical trials of biologic agents, and the ever expanding field of molecular biology have made great contributions to our current knowledge. With this improved understanding, we are afforded the opportunity to consider numerous potential therapeutic targets for treating autoimmune disease. As this growing science evolves, we can expect to see the advent of new therapies and new hope for patients who are afflicted with these disorders.

REVIEW 3:
Cedar H.
Developmental regulation of immune system gene rearrangement. Curr Opin Immunol 1999;11:64-9
Rearrangement of antigen receptors in the immune system is mediated through the action of complex enhancers which function in both a developmentally stage-specific and a celltype-specific manner to demethylate DNA, open chromatin structure and tether the recombination machinery to one preferred allele at each locus.

REVIEW 4:
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.

REVIEW 5:
Livak F and Petrie HT.
Somatic generation of antigen receptor diversity: a reprise.
Trends in Immunol 2001;22:608-12.
Thirty years ago Niels Jerne put forward the hypothesis that the primary antigen (Ag)-receptor repertoire must be restricted towards self-Ags before Ag-mediated selection. The subsequent discovery that Ag receptors are encoded by random rearrangements between discontinuous gene segments was, apparently, at odds with this hypothesis. However, recent findings have begun to reconcile these two concepts. The recombination process is, in fact, relatively precise, exhibiting marked preferences for some gene segments over others, even among members of the same gene family. The result is an intricately patterned primary repertoire that accommodates both sets of predictions, ensuring a balance between the efficiency of selection (requiring limited diversity) and the complexity of the repertoire (requiring maximum diversity).

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

RESEARCH FRONTIER:
Inlay M.
Epigenetic regulation of antigen receptor rearrangement.
Clin Immunol 2003;109:29-36
In the mammalian immune system, V(D)J rearrangement of immunoglobulin (Ig) and T cell receptor (TCR) genes is regulated in a lineage- and stage-specific fashion. Because each of the seven loci capable of rearrangement utilizes the same recombination machinery, it is thought that V(D)J recombination of each antigen receptor locus is regulated through the differential accessibility of each locus to the V(D)J recombination machinery. Accumulating evidence indicates that chromatin remodeling mediated by DNA methylation and demethylation plays important roles in regulating V(D)J recombination and germline transcription through the Ig and TCR loci. DNA demethylation within the antigen receptor loci appears to be regulated by cis-elements also required for coordinated V(D)J recombination and germline transcription. In this paper, the authors critically examine the relationship between demethylation and V(D)J recombination as well as the mechanism to regulate DNA demethylation within the antigen receptor loci.

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

REVIEW 1:
Friedl P and Gunzer M.
Interaction of T cells with APCs: the serial encounter model
Trends in Immunol. 2001;22:187-191
Primary immune responses are initiated by specific physical interaction of antigenspecific T cells and professional antigen-presenting cells (APCs). Productive interactions can be a dynamic process that combines physical T-cell binding to APCs with vigorous crawling across and scanning of the APC surface, resulting in signal induction. After T cell detachment, subsequent migratory contacts to the same or neighboring dendritic cells (DCs) allow the accumulation of sequential signals and interaction time. Here, we develop a serial encounter model of T-cell activation and discuss how the

summation of multiple signals provides an efficient strategy to control an ongoing immune response.

REVIEW 2
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.

REVIEW 3
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 antigenpresenting 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 4
Baker MD
Superantigens: structure-function relationships.
Int J Med Microbiol. 2004; 293:529-37
Superantigens are a class of highly potent immuno-stimulatory molecules produced by Staphylococcus aureus and Streptococcus pyogenes. These toxins possess the unique ability to interact simultaneously with MHC class II molecules and T-cell receptors, forming a trimolecular complex that induces profound T-cell proliferation. The resultant massive cytokine release causes epithelial damage and leads to capillary leak and hypotension. The staphylococcal superantigens are designated staphylococcal enterotoxins A, B, C (and antigenic variants), D, E, and the recently discovered enterotoxins G to Q, and toxic shock syndrome toxin-1. The streptococcal superantigens include the pyrogenic exotoxins A (and antigenic variants), C, G-J, SMEZ, and SSA. Superantigens are implicated in several diseases including toxic shock syndrome, scarlet fever and food poisoning; and their function appears primarily to debilitate the host sufficiently to permit the causation of disease. Structural studies over the last 10 years have provided a great deal of information regarding the complex interactions of these molecules with their receptors. This, combined with the wealth of new information from genomics initiatives, have shown that, despite their common molecular architecture, superantigens are able to crosslink MHC class II molecules and T-cell receptors by a variety of subtly different ways through the use of various structural regions within each toxin.

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 1:
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.

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 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.

6. T cell mediated immunity

REVIEW
Delves PJ, Roitt IM.
The Immune System. Second of Two Parts.
N Engl J Med 2000;343:108-17. (see also 1. Overview of the Immune System)
The complexity of the cellular interactions that occur during acquired immune responses requires specialized microenvironments in which the relevant cells can collaborate efficiently. Because only a few lymphocytes are specific for a given antigen, T cells and B cells need to migrate throughout the body to increase the probability that they will encounter that particular antigen. In their travels, lymphocytes spend only about 30 minutes in the blood during each cycle around the body

LANDMARK PUBLICATION
Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL
Two types of murine helper T cell clone. I. Definition According to Profiles of Lymphokine Activities and Secreted Proteins.
J Immunology 1986;136:2348-57.
A panel of antigen-specific mouse helper T cell clones was characterized according to patterns of lymphokine activity production, and two types of T cell were distinguished. Type 1 T helper cells (TH1) produced IL 2, interferon-gamma, GM-CSF, and IL 3 in response to antigen + presenting cells or to Con A, whereas type 2 helper T cells (TH2) produced IL 3, BSF1, and two other activities unique to the TH2 subset, a mast cell growth factor distinct from IL 3 and a T cell growth factor distinct from IL 2. Clones representing each type of T cell were characterized, and the pattern of lymphokine activities was consistent within each set. The secreted proteins induced by Con A were analyzed by biosynthetic labeling and SDS gel electrophoresis, and significant differences were seen between the two groups of T cell line. Both types of T cell grew in response to alternating cycles of antigen stimulation, followed by growth in IL 2- containing medium. Examples of both types of T cell were also specific for or restricted by the I region of the MHC, and the surface

marker phenotype of the majority of both types was Ly-1+, Lyt-2-, L3T4+, Both types of helper T cell could provide help for B cells, but the nature of the help differed. TH1 cells were found among examples of T cell clones specific for chicken RBC and mouse alloantigens. TH2 cells were found among clones specific for mouse alloantigens, fowl gamma-globulin, and KLH. The relationship between these two types of T cells and previously described subsets of T helper cells is discussed.

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 GM-CSF, 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: .

Ou LS, Goleva E, Hall C, Leung DY

T regulatory cells in atopic dermatitis and subversion of their activity by superantigens.

J Allergy Clin Immunol 2004;113:756-63.

BACKGROUND: Atopic dermatitis (AD) is a chronic inflammatory skin disease involving colonization by superantigen (SAg)-secreting Staphylococcus aureus. CD4+CD25+ T regulatory (Treg) cells are thought to play an important role in controlling inflammatory responses. OBJECTIVE: In this study we examined whether Treg cells might be deficient in patients with AD. METHODS: CD4+CD25+ and CD4+CD25- T cells were isolated from PBMCs by using immunomagnetic beads. Cells were cultured with anti-CD3 or SAg, staphylococcal enterotoxin B (SEB), for 72 hours. Proliferation was measured by means of tritiated thymidine incorporation. CD4, CD8, CD25, and cutaneous lymphocyte-associated antigen expression on PBMCs was assessed by means of flow cytometry. RNA was extracted from isolated subsets of T cells, and the results of real-time PCR for FoxP3 mRNA were determined. RESULTS: Surprisingly, CD4+CD25+ T cells were significantly (P <.01) increased in patients with AD (6.68%+/- 0.99%, n=15) compared with in asthmatic patients (3.42%+/-0.58%, n=12) or nonatopic healthy control subjects (3.34%+/-0.43%, n=14). Patients with AD also had a higher expression of CD25+ in skin-homing, CD4+, cutaneous lymphocyte-associated antigenpositive T cells than asthmatic and nonatopic subjects, with values of 35.95% versus 22.44% versus 23.03%, respectively (P <.006). Only CD4+CD25+ cells expressed FoxP3, whereas CD4+CD25- T cells and CD4- cells did not. Consistent with known properties of Treg cells, CD4+CD25+ cells were anergic to anti-CD3 stimulation. When CD4+CD25+ cells from each study group were mixed with CD4+CD25- cells,

proliferative responses were equally suppressed after anti-CD3 stimulation. In contrast, after SEB stimulation, CD4+CD25+ cells were no longer anergic. Furthermore, when CD4+CD25+ cells were mixed with CD4+CD25- cells and stimulated with SEB, the suppressive function of Treg cells was reversed. CONCLUSION: Patients with AD have significantly increased numbers of peripheral blood Treg cells with normal immunosuppressive activity. However, after SAg stimulation, Treg cells lose their immunosuppressive activity. These data suggest a novel mechanism by which Sags could augment T-cell activation in patients with AD.

RESEARCH FRONTIER:

Stock P, Akbari O, Berry G, et al.

Induction of T helper type 1-like regulatory cells that express Foxp3 and protect against airway hyper-reactivity.

Nat Immunol 2004;5:1149-56.

The range of regulatory T cell (T(R) cell) types that control immune responses is poorly understood. We describe here a population of T(R) cells that developed in vivo from naive CD4(+)CD25(-) T cells during a T helper type 1 (T(H)1)-polarized response, distinct from CD25(+) T(R) cells. These antigen-specific T(R) cells were induced by CD8alpha(+) DCs, produced both interleukin 10 and interferon-gamma, and potently inhibited the development of airway hyper-reactivity. These T(R) cells expressed the transcription factors Foxp3 and T-bet, indicating that these T(R) cells are related to T(H)1 cells. Thus, adaptive T(R) cells are heterogeneous and comprise T(H)1-like T(R) cells as well as previously described T(H)2-like T(R) cells, which express Foxp3 and are induced during the development of respiratory tolerance by CD8alpha(-) DCs.

RESEARCH FRONTIER:

Karagiannidis C, Akdis M, Holopainen P, et al

Glucocorticoids upregulate FOXP3 expression and regulatory T cells in asthma.

J Allergy Clin Immunol 2004;114:1425-33.

BACKGROUND: T regulatory (T reg) cells are characterized by expression of suppressive cytokines and the transcription factor FOXP3. They play a key role in balancing immune responses and maintain peripheral tolerance against antigens and allergens. The loss of peripheral tolerance against allergens causes diseases that can be therapeutically controlled with glucocorticoids. OBJECTIVE: The present study investigates whether glucocorticoids affect the activity of T reg cells on the basis of FOXP3 and cytokine expression. METHODS: CD4 + T cells from healthy donors and glucocorticoid-treated asthmatic patients were isolated, and expression of FOXP3, along with IL-10 and TGF-beta1, was determined. The effect of glucocorticoids on T reg cells was measured in vivo before and after GC treatment and in in vitro cultures. RESULTS: FOXP3 mRNA expression was significantly increased in asthmatic patients receiving inhaled glucocorticoid treatment, systemic glucocorticoid treatment, or both. FOXP3 tightly correlated with IL10 mRNA expression. No correlation of FOXP3 mRNA expression was observed in relation to a (GT)n microsatellite promoter polymorphism on chromosome Xp11.23 or total IgE level. The frequency of CD25 + memory CD4 + T cells and transient FOXP3 mRNA expression by CD4 + T cells significantly increased after systemic glucocorticoid treatment, whereas TGFB1 expression did not change. Furthermore, glucocorticoids induced IL10 and FOXP3 expression in short-term and long-term cultures in vitro. CONCLUSION: These findings demonstrate that glucocorticoid treatment is not only immunosuppressive and anti-inflammatory but also promotes or initiates differentiation toward T R 1 cells by a FOXP3-dependent mechanism. Strategies that convert transient glucocorticoid-induced T reg activity into a stable phenotype might improve allergy and asthma therapy.

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 in vivo, 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.

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

REVIEW :
Nel AE.
T-cell activation through the antigen receptor. Part 1: signaling components, signaling pathways, and signal integration at the T-cell antigen receptor synapse.
J Allergy Clin Immunol 2002;109:758-70.
Part 1 of this review will highlight the basic components and signaling pathways by which the T-cell antigen receptor (TCR) activates mature extrathymic T cells. TCR signaling commences with an early wave of protein tyrosine kinase activation, which is mediated by the Src kinases Lck and Fyn, the 70-kd zeta-associated protein kinase, and members of the Tec kinase family. This early wave of protein tyrosine phosphorylation leads to the activation of downstream signaling pathways, including an increase in intracellular free calcium, protein kinase C, nuclear factor kappaB and Ras-mitogenactivated 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 of macromolecular 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.

REVIEW

Nel AE, Slaughter N

T-cell activation through the antigen receptor. Part 2: role of signaling cascades in T-cell differentiation, anergy, immune senescence, and development of immunotherapy..

J Allergy Clin Immunol 2002;109:901-15.

Part 2 of this review on cellular activation by the T-cell antigen receptor (TCR) will highlight how TCR signaling pathways are adapted to achieve specific biologic outcomes, including different states of T-cell differentiation and the induction of T-cell tolerance. We will also explore how treatment with altered peptide ligands affects TCR signaling to change T-cell differentiation or to induce an anergy state. These changes are accomplished through alteration of protein tyrosine kinase activity, the stoichiometry of phosphorylation of immunoreceptor tyrosine-based activation motifs, intracellular free ionized calcium flux, mitogen-activated protein kinase activity, and transcriptional activation of key cytokine promoters. The CTLA-4 plays an important role in the induction and maintenance of anergy. The second theme will highlight how altered TCR signal transduction, including changes in the compartmentalization of signaling components at the TCR synapse, contributes to decreased T-cell activation during immune senescence. Finally, we will illustrate how the molecular details of TCR activation can be used to modify the function of the immune system. This includes a description of the mechanism of action of altered peptide ligands, CTLA-4Ig, and pharmacologic inhibitors of mitogen-activated protein kinases, nuclear factor kappaB, and protein kinase C cascades.

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

REVIEW:

Tamada K, Chen L.

T lymphocyte costimulatory molecules in host defense and immunologic diseases.

Ann Allergy Asthma and Immunol 2000;85:164-76.

BACKGROUND: Costimulation is an essential component for the optimal induction of T cell-mediated immune responses. Manipulation of the costimulatory pathway with antibodies or genetically-engineered fusion proteins is an important strategy to treat immune-related diseases including allergy, asthma, transplantation and cancer. Recent advances have revealed several new costimulatory molecules, and the functional characteristics of each costimulatory pathway are now becoming clearer. LEARNING OBJECTIVES: In this review, we summarize basic outlines of the costimulatory systems in terms of molecular structure, expression kinetics and immunological function. We further discuss involvement and therapeutic manipulation of costimulation in several clinical diseases. DATA SOURCE: The MEDLINE database was used to review the literature related to costimulation. CONCLUSION: Costimulatory pathways play an essential role in the activation and regulation of T cell immune responses and the induction of T cell tolerance. Therapeutic manipulation of the costimulatory system demonstrates beneficial effects to treat immunological diseases in murine models as well as some clinical situations.

c. Tcell mediated immune responses – participating cells

REVIEW
Lanzavecchia A, Sallusto F
Dynamics of T Lymphocyte Responses: Intermediates, Effectors, and Memory Cells.
Science 2000;290:92-7.
The immune response is initiated in organized lymphoid tissues where antigen-loaded dendritic cells (DCs) encounter antigen-specific T cells. DCs function as packets of information that must be decoded by the T cell before an appropriate immune response can be mounted. We discuss how the dynamics of DC-T cell encounter and the mechanism of T cell differentiation make the decoding of this information stochastic rather than determinate. This results in the generation of both terminally differentiated effector cells and intermediates that play distinctive roles in protection, immunoregulation, and immunological memory.

REVIEW
Bromley SK, Burack WR, Johnson KG, et al.
The Immunological Synapse.
Annu Rev Immunol 2001;19:375-96.
The adaptive immune response is initiated by the interaction of T cell antigen receptors with major histocompatibility complex molecule-peptide complexes in the nanometer scale gap between a T cell and an antigen-presenting cell, referred to as an immunological synapse. In this review we focus on the concept of immunological synapse formation as it relates to membrane structure, T cell polarity, signaling pathways, and the antigen-presenting cell. Membrane domains provide an organizational principle for compartmentalization within the immunological synapse. T cell polarization by chemokines increases T cell sensitivity to antigen. The current model is that signaling and formation of the immunological synapse are tightly interwoven in mature T cells. We also extend this model to natural killer cell activation, where the inhibitory NK synapse provides a striking example in which inhibition of signaling leaves the synapse in its nascent, inverted state. The APC may also play an active role in immunological synapse formation, particularly for activation of naive T cells

REVIEW
Von Andrian UH, Mackay CR
T-cell Function and Migration. Two Sides of the Same Coin.
N Engl J Med 2000;343:1020-34.

d. T cell subsets

SEE RESEARCH FRONTIERS and LANDMARK PUBLICATIONS above.

e. Regulatory T cells and Memory Cells

REVIEW

O'Garra J, Vieira P.

Regulatory T cells and mechanisms of immune system control.

Nat Med 2004;10:801-5.

The immune system evolved to protect the host against the attack of foreign, potentially pathogenic, microorganisms. It does so by recognizing antigens expressed by those microorganisms and mounting an immune response against all cells expressing them, with the ultimate aim of their elimination. Various mechanisms have been reported to control and regulate the immune system to prevent or minimize reactivity to self-antigens or an overexuberant response to a pathogen, both of which can result in damage to the host. Deletion of autoreactive cells during T- and B-cell development allows the immune system to be tolerant of most self-antigens. Peripheral tolerance to self was suggested several years ago to result from the induction of anergy in peripheral self-reactive lymphocytes. More recently, however, it has become clear that avoidance of damage to the host is also achieved by active suppression mediated by regulatory T (T(reg)) cell populations. We discuss here the varied mechanisms used by T(reg) cells to suppress the immune system.

REVIEW

Chatila TA

Role of regulatory T cells in human diseases

J Allergy Clin Immunol 2005;116: 949-959

The discovery of regulatory T lymphocytes (Treg) that are actively involved in maintaining immune tolerance has led to new insights into mechanisms of tolerance breakdown in human diseases, including those resulting from allergic, autoimmune, or infectious causes. Congenital deficiency of $CD4^{+}CD25^{+}$ Treg cells caused by loss-offunction mutations in the gene encoding Foxp3 triggers a syndrome of lymphoproliferation and myeloproliferation, autoimmunity, and allergic dysregulation, whereas deficient allergen-specific Treg cell responses have been associated with a number of allergic and autoimmune disorders. Tolerization to allergens and autoantigens is associated with augmentation of Treg cell numbers and suppressive function, suggesting the manipulation of Treg cell activity as a potential strategy for future therapeutic interventions in allergic and autoimmune diseases.

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 (T_{Reg}) 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 $CD4^{+}CD25^{+}$ T_{Reg} cells and inducible populations of allergen-specific IL-10–secreting T_R1 cells inhibit allergenspecific effector cells in experimental models. Allergen-specific T_{Reg} cell responses contribute to the control of allergic inflammation in several ways. Skewing of allergenspecific effector T cells to a T_{Reg} 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 T_{Reg}

cells can potently suppress IgE production while simultaneously increasing the production of the noninflammatory antibody isotypes IgG4 and IgA, respectively. T_{Reg} 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
Sprent J, Surh CD
T Cell Memory.
Annu Rev Immunol 2002;20:551-79.
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.

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.

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.

REVIEW
Miriam Shapiro-Shelef & Kathryn Calame,
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
Lijun Wen, Joni Brill-Dashoff, Susan A. Shinton, Masanao Asano1, Richard R. Hardy and Kyoko Hayakawa
Evidence of Marginal-Zone B Cell- Positive Selection in Spleen
Immunity:Volume 23, Issue 3 , Pages 297-308
Antigen receptor-mediated signaling is critical for the development and survival of B cells. However, it has not been established whether B cell development requires a signal from self-ligand engagement at the immature stage, a process known as "positive selection." Here, using a monoclonal B cell receptor (BCR) mouse line, specific for the self-Thy-1/CD90 glycoprotein, we demonstrate that BCR crosslinking by low-dose selfantigen promotes survival of immature B cells in culture. In spleen, an increase in BCR signaling strength, induced by low-dose self-antigen, directed naive immature B cells to mature, not into the default follicular B cell fate, but instead into the marginal-zone B cell subset. These data indicate that positive selection can occur in developing B cells and that BCR signal strength is a key factor in deciding between two functionally distinct mature B cell compartments in the microenvironment of the spleen.

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.

a. B cell activation – cytokines and signal transduction

REVIEW
Arens R
Signaling through CD70 regulates B cell activation and IgG production.
J Immunol 2004;173: 3901-8
CD70, the cellular ligand of the TNF receptor family member CD27, is expressed transiently on activated T and B cells and constitutively on a subset of B cell chronic lymphocytic leukemia and large B cell lymphomas. The study used B cells constitutively expressing CD70 to examine the functional consequences of signaling through CD70. In vitro, CD70 ligation with anti-CD70 mAbs

strongly supported proliferation and cell cycle entry of B cells submitogenically stimulated with either anti-CD40 mAb, LPS, or IL-4. In this process, the cell surface receptors CD25, CD44, CD69, CD95, and GL7 were upregulated, whereas the expression of CD21, CD62L, surface IgM (sIgM), and sIgD was decreased. Addition of CD70 mAb to low dose LPS-stimulated CD70-positive B cells strongly diminished IgG secretion and enhanced production of IgM. Signaling through CD70 on B cells was dependent on the initiation of both PI3K and MEK pathways. In vivo exposure to either CD70 mAb or the CD70 counterreceptor CD27 down-regulated CD62L and sIgM on CD70-positive B cells. CD70 signaling during T cell-dependent immune responses also decreased IgG-specific Ab titers. Together, the in vitro and in vivo data demonstrate that CD70 has potent reverse signaling properties in B cells, initiating a signaling cascade that regulates expansion and differentiation.

REVIEW
Gauld SB
Src-family kinases in B-cell development and signaling.
Oncogene 2004; 23: 8001-6
The Src-family protein tyrosine kinases (SFKs) are known to play key roles in initiating signal transduction by the B-cell antigen receptor (BCR). In addition, numerous studies have shown that this family of molecules also contributes to signaling by BCR surrogates during B-lymphocyte lineage development and maturation. Paradoxically, ablation of SFKs not only results in obvious defects in B-cell development but also in the onset of autoimmunity. Thus SFKs, most notably Lyn, play both activating and inhibitory roles in B-cell function. Confounding analyses of SFK function in B cells is the varied coexpression of family members that mediate redundant as well as unique functions.This review focuses on the role of Lyn in mediating positive and negative roles in B-cell activation and how these affect immune signaling and disease.

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.

REVIEW
Harnett MM, Katz E, Ford CA.
Differential signaling during B-cell maturation.
Immunol Lett. 2005; Apr 15;98(1):33-44. Epub 2004 Nov 30.
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 B-cell 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

RESEARCH FRONTIER
Janssen E
LAB: a new membrane-associated adaptor molecule in B cell activation.
Nat Immunol 2003;4: 117-23
The adaptor molecule, linker for activation of T cells (LAT), is essential in T cell activation and development; a similar molecule in B cells has not yet been identified. This study is a report of the identification of a new adaptor protein, linker for activation of B cells (LAB). Like LAT, LAB was localized to lipid rafts. Upon activation via the B cell receptor (BCR), LAB was phosphorylated and interacted with the adaptor protein Grb2. Decreased LAB expression led to a reduction in BCR-mediated calcium flux and Erk activation. LAB rescued thymocyte development but not normal T cell activation in LAT(-/-) mice. This study suggests that LAB links BCR engagement to downstream signaling pathways.

b. Epitope recognition and immunoglobulin production

REVIEW
Bishop GA
Antigen-specific B-lymphocyte activation.
Crit Rev Immunol - 2003;23: 149-97
This review highlights recent advances, and summarizes the components of the complex processes involved in B-cell activation

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 antibody response.

A. 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 complementarity-determining 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
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.

d. Maturation of the antibody response

REVIEW
Carsetti R
Peripheral development of B cells in mouse and man. –
Immunol Rev 2004; 197: 179-91
In man and in mouse, B-cell maturation occurs in steps, first in the bone marrow from hematopoietic precursors to immature/transitional B cells, then in the periphery from transitional to fully mature B cells. Each developmental step is tightly controlled by the expression and function of the B-cell receptor (BCR) and by the ability to interact with the microenvironment. Mature B cells collaborate with T cells in the adaptive immune response, leading to the production of high-affinity antibodies. This response is very accurate, but slow. Immediately after pathogen entry, however, antibodies already present in the serum reinforce the innate immune response and contribute to the first-line defense against infection. Low-affinity natural antibodies are produced by B-1a B cells in the mouse and immunoglobulin M (IgM) memory cells in man. These antibodies represent an immediate protection against all microorganisms and the only one against encapsulated bacteria. B-1a and IgM memory B cells may function as a link between the innate and adaptive immune response and thus perform a primordial B-cell function.

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.

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

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.

REVIEW
Colvin RB, Smith RN.
Antibody-mediated organ-allograft rejection.
Nat Rev Immunol. 2005; 5:807--817.
Recent studies show that alloantibodies mediate a substantial proportion of graft-rejection episodes, contributing to both early and late graft loss. Rejection that is caused by antibody is mediated by different mechanisms from rejection that is caused by T cells, thereby requiring other approaches to treatment and prevention. Antibody induces rejection acutely through the fixation of complement, resulting in tissue injury and coagulation. In addition, complement activation recruits macrophages and neutrophils, causing additional endothelial injury. Antibody and complement also induce gene expression by endothelial cells, which is thought to remodel arteries and basement membranes, leading to fixed and irreversible anatomical lesions that permanently compromise graft

REVIEW
Takai T.
Roles of Fc receptors in autoimmunity.
Nat Rev Immunology 2002;2:580--592.
This article provides a current overview of the mechanism of Fc receptor-based immune regulation with a very useful overview of Fc receptors and interaction with Fc regions. Antibody dependent cell mediated cytotoxicity (ADCC) is also discussed.

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
Kawakami T, Galli SJ.
Regulation of mast-cell function and basophil function and survival by IgE.
Nat Rev Immunol. 2002;3:773--786.
This paper describes IgE interaction with basophils and mast cells, with information about signaling through FceR.

REVIEW
Kay AB.
Advances in immunology: allergy and allergic diseases --two parts.
N Engl J Med 2001;344:30-37, N Engl J Med 2001;344:109-113.
The articles by Kay (parts 1 and 2) provide an excellent overview of the basis of atopic allergy, the diseases with which it is associated, and approaches to treatment.

REVIEW
Lukacs NW.
Role of chemokines in the pathogenesis of asthma.
Nat Rev Immunol. 2001;1:108--116.
This paper covers a large group of chemotactic cytokines, also known as chemokines, which are implicated in asthmatic inflammation. These chemokines control and direct the migration and activation of various leukocyte populations. The mechanisms of the early and late phase responses are described.

g. Immune complexes – immunologic properties and mechanisms of clearance

REVIEW
Kosco-Vilbois MH.
Are follicular dendritic cells really good for nothing?
Nat Rev Immunol 2003;3:764-769.
Follicular dendritic cells (FDCs), which reside in the primary B-cell follicles and germinal centres of lymphoid tissues, can sequester antigen in the form of immune complexes and are thought to be pivotal to the germinal-centre reaction and the maintenance of immunological memory. But, many recent studies question the importance of FDCs and their bound immune complexes in B-cell responses. This article asks whether we can truly rule out a requirement for these cells in host defence.

REVIEW
Haberman AM, Shlomchik MJ.
Reassessing the function of immune-complex retention in follicular dendritic cells.
Nat Rev Immunol 2003;3:757-764.
The close association of follicular dendritic cells (FDCs) and germinal-centre B cells has fostered the idea that B-cell recognition of retained antigen that is presented on the surface of FDCs is important for affinity maturation and memory B-cell development. We argue that the retention of immune complexes is not required for germinal-centre development, affinity maturation and memory B-cell maintenance. Instead, it is probable that FDCs support B-cell proliferation and differentiation in a non-specific manner. Other potential roles of immune complexes retained by FDCs are discussed.

REVIEW
Walport MJ.
Advances in Immunology: complement -- Two parts.
N Engl J Med 2001;344:1058-1066, N Engl J Med 2001; 344:1140-1144.
This review(in two parts) is organized around the three main associations between complement and disease: complement deficiency and susceptibility to infection, the consequences of abnormalities in the regulation of the complement system, and the role of complement deficiency in inflammatory diseases.

8. Other immune and inflammatory mechanisms

a. Natural killer cells, their CD markers and functions

REVIEW:
Middleton D. Curran M. Maxwell L.
Natural killer cells and their receptors.
Transplant Immunology 2002;10:147-164.
Natural killer (NK) cells have been known for a long time to be a very important component of the innate immune system. However, it is only during the last 10 years that knowledge of their receptors has emerged. Described in the present review are those receptor families killer inhibitory receptor (KIR) (belonging to the immunoglobulin superfamily), and killer lectin like receptor (KLR) CD94/NKG2, that both use HLA as a ligand and have inhibiting and activating types of receptors, and natural cytotoxic receptors (NCR) which do not associate with HLA. Association of the receptor gives rise to either an inhibiting or activating signal leading to either failure or success in lysing a target cell. The KIR receptors are very polymorphic both in the number of genes expressed in an individual and the alleles present for a gene. They would appear to have had a rapid evolution compared to the CD94/NKG2 receptors. The roles that NK cells and their receptors have with various facets of transplantation, disease, pregnancy and control of virus infection in humans are described.

b. Lymphokine activated killer cells and their effects

REVIEW:
Sinkovics JG. Horvath JC.
Human natural killer cells: a comprehensive review.
International Journal of Oncology 2005;27:5-47.
The senior author of this comprehensive review observed and reported in 1969 that his lymphocytes killed allogeneic tumor cells in vitro. Some of his research associates and technicians and other healthy individuals also yielded such killer lymphocytes. The team considered pre-immunization to cancer occurring in individuals after in-family or professional exposure to patients with cancer (in an era when the concept of viral etiology of cancer was receiving major support); or that lymphocytes can acquire through blastic transformation immune reactivity to allogeneic cells anew in vitro. The phenomenon was eventually referred to as 'lymphocytes practicing Burnet's immunosurveillance.' Project site visitors of the USA NCI first viewed these observations as a matter of 'in vitro artifacts' being in opposition to strong tumor- specific cytotoxicity of tumor-bearing patients' lymphocytes recognized in the vast majority of other assays. After NCI funds were released for intramural studies on the phenomenon of non-specific cytotoxicity by lymphocytes,

recipients (other than the senior author) of these NCI funds later characterized (1973-1975) the 'indiscriminately' cytotoxic lymphocyte populations as those of 'natural killer (NK) cells.' In this article, the original observations made in 1969- 971 are reviewed based on genuine material preserved by the senior author and are explained in view of recent discoveries that were not available at the time of the original observations. NK cells display a fascinating history arising first in urochordates during the cambrian explosion. At that level, NK cells protected their hosts from incompatible cell colony fusions and against intracellular, especially viral, pathogens. Since then, viruses evolved evasive maneuvers to escape NK cell attack on the infected cells. NK cells persisted after the evolution of adaptive immunity in cartilaginous fish fitting seamlessly into the new system. In mammals, NK cells assumed the role of chief arbitrators between the fetal trophoblast and maternal immune reactions to the semiallograft fetus. Tumors induce in NK cells the same (inactivating; mediating Th2-type immunity) reactions the fetal trophoblast engenders in utero, but NK cells may overcome the host's tolerance to its tumor and kill tumor cells, especially when converted into lymphokine-activated killer (LAK) cells by molecular mediators of Th1-type immunity. The authors prepare and utilize LAK cells and IL-2 for adoptive immunotherapy of patients with metastatic melanoma and kidney carcinoma. A patient with malignant ascites due to ovarian carcinoma entered remission on LAK cell therapy. Just as dendritic cells, the major antigen presentors, may undergo malignant transformation, NK cells are also subject to transformation into FasL-producer virulent lymphoma-leukemia cells. The senior author reported in 1970 a patient with 'lymphosarcoma cell leukemia' whose circulating lymphoma cells killed indiscriminately human sarcoma and carcinoma cells. The exemplary case history of another patient with NK cell lymphoma-leukemia treated by the authors is presented.

c. Cutaneous basophil hypersensitivity

REVIEW (Historical Interest) :
Dvorak HF Cutaneous Basophil Hypersenstivity
J Allergy Clin Immunol 1976;58:229-40.
Cutaneous basophil hypersensitivity (CBH) is a distinct form of lymphocyte-mediated hypersensitivity in guinea pigs, separate both from classic delayed hypersensitivity (DH) and from the well-known antibody-mediated reactions. CBH, not DH, is the usual cellular immune response of this species to a wide variety of immunogens (e.g., allografts, certain parasites, and viruses) when these are presented in native form without supplementation with mycobacteria-containing adjuvants, thus attesting to the importance of this response in the guinea pig's overall immune defense mechanism. Basophilcontaining, cell-mediated, delayed-onset reactions occur in other species, including man, as well.

d. Kinin mediated inflammation

REVIEW:

Couture R. Harrisson M. Vianna RM. Cloutier F.

Kinin receptors in pain and inflammation

B. European J Pharmacology 2001;429:161-76

Kinins are among the most potent autacoids involved in inflammatory, vascular and pain processes. These short-lived peptides, including bradykinin, kallidin and T-kinin, are generated during tissue injury and noxious stimulation. However, emerging evidence also suggests that kinins are stored in neuronal elements of the central nervous system (CNS) where they are thought to play a role as neuromediators in various cerebral functions, particularly in the control of nociceptive information. Kinins exert their biological effects through the activation of two transmembrane G-protein-coupled receptors, denoted bradykinin B(1) and B(2). Whereas the B(2) receptor is constitutive and activated by the parent molecules, the B(1) receptor is generally underexpressed in normal tissues and is activated by kinins deprived of the C-terminal Arg (des-Arg(9)-kinins). The induction and increased expression of B(1) receptor occur following tissue injury or after treatment with bacterial endotoxins or cytokines such as interleukin-1 beta and tumor necrosis factor-alpha. This review summarizes the most recent data from various animal models which convey support for a role of B(2) receptors in the acute phase of the inflammatory and pain response, and for a role of B(1) receptors in the chronic phase of the response. The B(1) receptor may exert a strategic role in inflammatory diseases with an immune component (diabetes, asthma, rheumatoid arthritis and multiple sclerosis). New information is provided regarding the role of sensory mechanisms subserving spinal hyperalgesia and intrapleural neutrophil migration that occur upon B(1) receptor activation in streptozotocin-treated rats, a model of insulin-dependent diabetes mellitus in which the B(1) receptor seems to be rapidly overexpressed. Although it is widely accepted that the blockade of kinin receptors with specific antagonists could be of benefit in the treatment of somatic and visceral inflammation and pain, recent molecular and functional evidence suggests that the activation of B(1) receptors with an agonist may afford a novel therapeutic approach in the CNS inflammatory demyelinating disorder encountered in multiple sclerosis by reducing immune cell infiltration (T-lymphocytes) into the brain. Hence, the B(1) receptor may exert either a protective or detrimental effect depending on the inflammatory disease. This dual function of the B(1) receptor deserves to be investigated further.

REVIEW

Cugno M, Nussberger J, Cicardi M, et al

Bradykinin and the pathophysiology of angioedema

Int Immunopharmacol 2003;3 311– 317

Angioedema has different causes and different clinical presentations. Some types of angioedema may be mediated by bradykinin.We measured plasma levels of bradykinin-(1–9)nonapeptide by radioimmunoassay after high-performance liquid chromatography in patients with different types of angioedema during acute attacks and/or in remission, i.e. hereditary C1-inhibitor deficiency, angiotensin converting enzyme (ACE) inhibitor treatment, idiopathic non histaminergic and responders to antihistamines.Eleven patients with the deficiency of C1-inhibitor had very high levels of bradykinin during acute attacks of angioedema (18.0–90.0 pM) (normal range 0.2–7.1 pM). In three patients with history of ACE inhibitor-related angioedema, plasma bradykinin was high during ACE inhibitor treatment (62.0, 8.9 and 27.0 pM) and in a fourth patient was 47.0 pM

during an acute attack and decreased by 93% to 3.2 pM after withdrawal of the ACE inhibitor. The patient with idiopathic angioedema, during an acute attack involving the right arm, had high levels of bradykinin in the venous blood refluent from the angioedematous arm (20.0 pM) while in the contralateral arm bradykinin levels were normal (6.6 pM), similarly to what we previously observed in cases of brachial angioedema due to C1- inhibitor deficiency. The four patients with angioedema responsive to antihistamines had normal levels of bradykinin even during acute attacks (5.7, 3.4, 4.7 and 1.2 pM). In one of these patients who had a brachial angioedema, bradykinin levels were normal in the venous blood refluent from both arms.Bradykinin is involved in hereditary C1-inhibitor deficiency angioedema, in ACE inhibitor-related angioedema, and in idiopathic nonhistaminergic angioedema, while bradykinin is not related to allergen-dependent or idiopathic angioedema that are responsive to antihistamines.

d. Arachidonic Acid Metabolites and Inflammation

REVIEW
Funk, CD
Prostaglandins and Leukotrienes: Advances in Eicosanoid Biology
Science 2001;294:1871-1875
Prostaglandins and leukotrienes are potent eicosanoid lipid mediators derived from phospholipase-released arachidonic acid that are involved in numerous homeostatic biological functions and inflammation. They are generated by cyclooxygenase isozymes and 5-lipoxygenase, respectively, and their biosynthesis and actions are blocked by clinically relevant nonsteroidal anti-inflammatory drugs, the newer generation coxibs (selective inhibitors of cyclooxygenase-2), and leukotriene modifiers. The prime mode of prostaglandin and leukotriene action is through specific G protein-coupled receptors, many of which have been cloned recently, thus enabling specific receptor agonist and antagonist development. Important insights into the mechanisms of inflammatory responses, pain, and fever have been gleaned from our current understanding of eicosanoid biology.

REVIEW
Busse W. Kraft M.
Cysteinyl leukotrienes in allergic inflammation: strategic target for therapy.
Chest 2005;127:1312-26.
Systemically bioavailable leukotriene receptor antagonists (LTRAs) can reduce the essential components of allergic inflammation in allergic rhinitis (AR) and asthma by blocking cysteinyl leukotriene (CysLT) activity, resulting in a wide range of clinical effects. CysLTs, mediators, and modulators in the pathophysiology of asthma and AR are a key target for therapy because they modulate production of hemopoietic progenitor cells, survival and recruitment of eosinophils to inflamed tissue, activity of cytokines and chemokines, quantity of exhaled NO, smooth-muscle contraction, and proliferation of fibroblasts. The mechanism of action of LTRAs leads to their effects on systemic allergic inflammatory processes.

REVIEW
Peters-Golden M Henderson WR.
The role of leukotrienes in allergic rhinitis
Ann Allergy Asthma Immunol. 2005;94:609-18.
Objective: To review the role of cysteinyl leukotrienes (cysLTs) in allergic rhinitis and the scientific rationale for therapy with leukotriene receptor antagonists (LTRAs). Data Sources: Relevant basic science and clinical articles were identified by a search of the PubMed database for articles published from 1984 to 2004 using the following keywords: allergic rhinitis; nose; immune response; allergen challenge; leukotrienes C, D, and E; cysteinyl leukotriene; cysteinyl leukotriene receptor; cytokine; leukocyte; montelukast; zafirlukast; and pranlukast. Study Selection: The authors' expert opinion was used to select studies for inclusion in this review. Results: CysLTs are synthesized via 5-lipoxygenase metabolism of arachidonic acid by mast cells and basophils during the early-phase response to antigen and by eosinophils and macrophages during the late phase. The cysLT levels in nasal secretions are elevated after short-term allergen instillation and in allergy season in patients with allergic rhinitis. These lipid mediators act locally and systemically by interacting with receptors, particularly the cysLT1 receptor, on target cells. Evidence derived from topical application of cysLTs in the nose and from the effects of LTRAs indicates that cysLTs contribute to nasal mucous secretion, congestion, and inflammation. CysLTs promote allergic inflammation by enhancing immune responses and the production, adhesion, migration, and survival of inflammatory cells such as eosinophils. They also increase the generation of an array of other proinflammatory mediators, such as cytokines, which in turn increase the production of and receptors for cysLTs. Clinical trials have demonstrated that LTRAs have significant but modest efficacy as single agents but additive efficacy when used with other classes of agents. Conclusions: CysLTs fulfill the criteria for relevant mediators of allergic rhinitis via their diverse effects on immune, inflammatory, and local structural components of disease. By blocking the cysLT1 receptor responsible for most of these effects, LTRAs represent a useful approach to treatment of this important and prevalent disorder.

f. Cytokines/Chemokines and their receptors

REVIEW
Borish LC. Steinke JW
Cytokines and chemokines
J Allergy Clin Immunol 2003;111:S460-75.
Cytokines and chemokines are redundant secreted proteins with growth, differentiation, and activation functions that regulate and determine the nature of immune responses and control immune cell trafficking and the cellular arrangement of immune organs. Which cytokines are produced in response to an immune insult determines initially whether an immune response develops and subsequently whether that response is cytotoxic, humoral, cell-mediated, or allergic. A cascade of responses can be seen in response to cytokines, and often several cytokines are required to synergize to express optimal function. An additional confounding variable in dissecting cytokine function is that each cytokine may have a completely different function, depending on the cellular source, target, and, most important, specific phase of the immune response during which it is presented. Numerous cytokines have both proinflammatory and anti-inflammatory potential; which activity is observed depends on the immune cells present and their state of responsiveness to the cytokine. For this chapter, cytokines are grouped according to those that are mononuclear phagocytic-derived or T-lymphocytic-derived; that mediate cytotoxic (antiviral and anticancer),

humoral, cell-mediated, or allergic immunity; and that are immunosuppressive. The biology of chemokines are then reviewed, grouped by family.

REVIEW
Hofmann SR. Ettinger R. Zhou Y, et al
Cytokines and their role in lymphoid development, differentiation and homeostasis.
Current Opin Allergy Immunol 2002;2:495-506.
PURPOSE OF REVIEW: The development of lymphoid tissues as well as the ultimate differentiation of naive and memory T cells are dependent on cytokines. In this review, we will focus on recent advances in the understanding of molecular mechanisms that regulate lymphoid development, homeostasis and tolerance. RECENT FINDINGS:
Cytokines play a critical role in the development and differentiation of lymphoid cells. In addition, newer data indicate important roles of interleukin-7 and interleukin-15 in lymphoid homeostasis and memory. Furthermore, a new family of heterodimeric cytokines comprising interleukin-12, interleukin-23 and -27 is important for differentiation of helper T cells and cell-mediated immunity. Finally the importance of tumor necrosis factor superfamily members in the development of lymphoid organs has recently been elucidated and will be discussed in detail. SUMMARY: New cytokines and receptors continue to be identified. The discovery and characterization of cytokines, their receptors and signaling molecules will provide a more complete understanding of normal lymphoid development, differentiation and function. In addition, this knowledge should improve our understanding of the pathogenesis of immunological diseases and hopefully will provide new treatment strategies.

REVIEW
Ono SJ, Nakamura T, Miyazaki D. Ohbayashi M, et al.
Chemokines: roles in leukocyte development, trafficking, and effector function.
J AllergyClin Immunology 2003;111:1185-99.
Chemokines, representing a large superfamily of 8- to 15-kd proteins, were originally discovered through their ability to recruit various cell types into sites of inflammation. It is now clear that these molecules play a much wider role in immune homeostasis, playing key roles in driving the maturation, homing, and activation of leukocytes. In this review we analyze the roles chemokines play in the development, recruitment, and activation of leukocytes. Because signaling from the receptors drives these processes, signal transduction from chemokine receptors will also be reviewed. Taken together, we highlight the various points at which chemokines contribute to allergic inflammation and at which their targeting might contribute to new therapies for type I hypersensitivity reactions.

g. Other Growth factors

REVIEW
Holgate ST. Holloway J. Wilson S
Epithelial-mesenchymal communication in the pathogenesis of chronic asthma.
Proc Am Thorac Soc. 2004;1:93-8, 2004
Although Th-2-mediated inflammation is a key therapeutic target in asthma, its relationship to altered structure and functions of the airways is largely unknown. In addition to inflammation, asthma is a disorder involving the airway epithelium that is more vulnerable to environmental injury and responds to this by impaired healing. This establishes a chronic wound scenario that is capable

of sustaining chronic inflammation as well as remodeling. This response occurs as a consequence of activation of the epithelial-mesenchymal unit, involving reciprocal activities of growth factors belonging to the fibroblast growth factor, epidermal growth factor, and transforming growth factorbeta families. The observation that structural changes in the airways in children at or before the onset of asthma occurs irrespective of inflammation might suggest that premodeling is required before Th-2 inflammatory responses can be sustained. Once established, altered function of constitutive airway cells, including fibroblasts, smooth muscle, nerves, and the epithelium, provides an abnormal microenvironment in which to generate a separate set of signals that underpin the acute/subacute inflammation characteristic of asthma exacerbations, triggered by viruses, pollutants, and allergens.

REVIEW 2:
Regulation and role of transforming growth factor-beta in immune tolerance induction and inflammation
Carsten B Schmidt-Weber_ and Kurt Blaser
Current Opinion in Immunology 2004, 16:709–716
Transforming growth factor-beta (TGF-beta) is known to mediate pleiotropic functions both inside and outside the immune system. Recent progress in this field underlines the role of TGF-beta in regulatory T (Treg) cells, where it participates in both suppression and differentiation. In addition, recent information highlights the role of TGF-beta in repair responses that lead to matrix deposition and tissue remodelling. Many chronic inflammatory diseases, such as asthma, profit from the suppression of specific immune responses by TGF-beta; however, TGF-beta-mediated tissue remodelling can be a serious complication in such diseases.

9. Receptor Ligand interactions in immune functioning—signal transduction resulting from receptor ligand interaction. Genetic polymorphisms producing gain or loss of function.

REVIEW
Buckley RH,
Primary immune deficiencies due to defects in lymphocytes.
N Engl J Med, 2000; 343 (18): 1313-24.
Excellent review of genetic defects involved in primary immune deficiencies. Includes description of ligand pair and signaling molecule defects associated with certain primary immune deficiencies.

REVIEW
Clark EA,
How B and T cells talk to each other,
Nature, Feb 1994; 367: 425-8.
Description of ligand pairs involved in the dialogue between T and B cells.

LANDMARK ARTICLE
Noelle RJ,.
A 39-kDa protein on activated helper T cells binds CD40 and transduces the signal for cognate activation of B cells,
Proc. Natal. Acad. Sci. 1992; 89: 6550-54.
Data presented in this article identifies a ligand on T cells (CD40L) which binds to CD40 on B cells and which functions to transducer the signal for Th-dependent B-cell activation.

LANDMARK ARTICLE
Negishi I,
Essential role for ZAP-70 in both positive and negative selection of thymocytes,
Nature 1995; 376: 435-438.
ZAP-70 plays a crucial role in T cell activation and development. Mice lacking ZAP-70 had neither CD4 or CD8 single-positive T cells. The conclusions from the presented data are that ZAP-70 is a central signaling molecule during thymic selection for CD4 and CD8 lineage.

RESEARCH FRONTIER
Allen RC,
CD40 Ligand Gene Defects Responsible for X-Linked Hyper-IgM Syndrome,
Science 1993; 259: 990-93.
Distinct point mutations in CD40L in three of four patients with X-Linked Hyper IgM Syndrome are described.

RESEARCH FRONTIER
Elder ME,
Human Severe Combined Immunodeficiency Due to a Defect in ZAP-70, a T Cell Tyrosine Kinase,
Science, June 1994, 264: 1596-99.
A homozygous mutation in the kinase domain of ZAP-70, a T cell receptor-associated protein tyrosine kinase, produced a distinctive form of human severe combined immunodeficiency. Manifestations of this disorder include profound immunodeficiency, absence of peripheral CD8+ T cells, and abundant peripheral CD4+ T cells that were refractory to T cell receptor-mediated activation. These findings demonstrate that ZAP- 70 is essential for human T cell function and suggest that CD4+ and CD8+ T cells depend on different intracellular signaling pathways to support their development or survival.

10. Immunologic Memory

REVIEW
Manser T,
The roles of antibody variable region hypermutation and selection in the development of the memory B cell compartment,
Immunological Reviews, 1998; 162: 182-96.
Somatic hypermutation and selection of Ig variable region genes are essential for memory B cell development in mammals. This review discusses various contributing factors to the “specificity maturation” of the memory B cell response.

REVIEW:
Champagne P,
Learning to Remember: Generation and Maintenance of T-Cell Memory,
DNA and Cell Biology 2001; 20 (12): 745-60.
This review explores various aspects of the nature, generation, and maintenance of T lymphocyte-mediated immunologic memory, including intracellular and extracellular molecular mechanisms the underlie and modulate T cell memory.

LANDMARK ARTICLE
Jacob J,
Intraclonal generation of antibody mutants in germinal centres,
Nature 1991; 354: 389-92 .
Generation and selection of somatic antibody mutants are key elements of acquired immunity, essential for the affinity maturation of antibody responses dependent on T cells. Somatic mutations arise locally in germinal centers. Mutations are introduced in a step-wise manner at high rate.

RESEARCH FRONTIER
Morel Y,
LIGHT, a new TNF superfamily member, is essential for memory T helper cellmediated activation of dendritic cells,
Eur J Immunol. 2003; 33: 3213-19.
LIGHT is a recently identified member of the TNF superfamily. LIGHT is up-regulated on activated T cells but the up-regulation is delayed on naïve T cells.CD40L and LIGHT are required for optimal secretion of IL-12. LIGHT and CD40L may be involved in the maintenance or reactivation of secondary Th1 response

C. Mucosal Immunity

REVIEW
Tlaskalova-Hogenova H. Tuckova L. Lodinova-Zadnikova R.
Mucosal immunity: its role in defense and allergy
Int Archives Allergy Immunol 2002;128:77-89.
The interface between the organism and the outside world, which is the site of exchange of nutrients, export of products and waste components, must be selectively permeable and at the same time, it must constitute a barrier equipped with local defense mechanisms against environmental threats (e.g. invading pathogens). The boundaries with the environment (mucosal and skin surfaces) are therefore covered with special epithelial layers which support this barrier function. The immune system, associated with mucosal surfaces covering the largest area of the body (200-300 m(2)), evolved mechanisms discriminating between harmless antigens and commensal microorganisms and dangerous pathogens. The innate mucosal immune system, represented by epithelial and other mucosal cells and their products, is able to recognize the conserved pathogenic patterns on microbes by pattern recognition receptors such as Toll-like receptors, CD14 and others. As documented in experimental gnotobiotic models, highly protective colonization of mucosal surfaces by commensals has an important stimulatory effect on postnatal development of immune responses, metabolic processes (e.g. nutrition) and other host activities; these local and systemic immune responses are later replaced by inhibition, i.e. by induction of mucosal (oral) tolerance. Characteristic features of mucosal immunity distinguishing it from systemic immunity are: strongly

developed mechanisms of innate defense, the existence of characteristic populations of unique types of lymphocytes, colonization of the mucosal and exocrine glands by cells originating from the mucosal organized tissues ('common mucosal system') and preferential induction of inhibition of the responses to nondangerous antigens (mucosal tolerance). Many chronic diseases, including allergy, may occur as a result of genetically based or environmentally induced changes in mechanisms regulating mucosal immunity and tolerance; this leads to impaired mucosal barrier function, disturbed exclusion and increased penetration of microbial, food or airborne antigens into the circulation and consequently to exaggerated and generalized immune responses to mucosally occurring antigens, allergens, superantigens and mitogens.

LANDMARK PUBLICATION:

McDermott MR, Bienenstock J

Evidence for a common mucosal immunologic system. I. Migration of B immunoblasts into intestinal, respiratory, and genital tissues

J Immunol. 1979 May;122(5):1892-8

The origins of immunoglobulin-containing cells in intestinal, respiratory, mammary, and genital tissues were studied in CBA/J female mice by using an adoptive lymphocyte transfer method. Within 24 hr after transfer, [3H]thymidine-labeled donor mesenteric lymph node (MLN) cells were observed in recipient gut, cervix and vagina, uterus, mammary glands, and MLN, where approximately 60% contained IgA and 25% IgG. In peripheral lymph nodes (PLN), 44% of the labeled cells after MLN transfer contained IgG, whereas only 8% were of the IgA isotype. The preference of the MLN to populate mucosal sites was clear from the results. Labeled PLN cells were transferred and the majority of these returned to their sites of origin and contained IgG. Of the small number of labeled PLN cells found in mucosal tissues, approximately equal percentages (30%) of IgA- anti IgG-containing cells were seen. Dividing cells prepared from mediastinal (bronchial) lymph nodes (BLN) showed a propensity to localize in the lungs rather than the intestine. However, the predominant immunoglobulin content of these donor cells in gut, lungs, and MLN was IgA. In recipient PLN, most labeled BLN cells contained IgG. These data support the concept of a common mucosal immunologic system.

RESEARCH FRONTIER:

Holmgren J. Czerkinsky C

Mucosal immunity and vaccines.

Nature Med 2005;11:S45-53.

There is currently great interest in developing mucosal vaccines against a variety of microbial pathogens. Mucosally induced tolerance also seems to be a promising form of immunomodulation for treating certain autoimmune diseases and allergies. Here we review the properties of the mucosal immune system and discuss advances in the development of mucosal vaccines for protection against infections and for treatment of various inflammatory disorders.

1 Innate defenses

a. Barrier function and local enzyme systems

REVIEW
Muller CA. Autenrieth IB. Peschel A
Innate defenses of the intestinal epithelial barrier
Cell Mol Life Sci 2005 62:1297-307
The innate immune system plays a crucial role in maintaining the integrity of the intestine and protecting the host against a vast number of potential microbial pathogens from resident and transient gut microflora. Mucosal epithelial cells and Paneth cells produce a variety of antimicrobial peptides (defensins, cathelicidins, crytdinrelated sequence peptides, bactericidal/permeabilityincreasing protein, chemokine CCL20) and bacteriolytic enzymes (lysozyme, group IIA phospholipase A2) that protect mucosal surfaces and crypts containing intestinal stem cells against invading microbes. Many of the intestinal antimicrobial molecules have additional roles of attracting leukocytes, alarming the adaptive immune system or neutralizing proinflammatory bacterial molecules. Dysfunction of components of the innate immune system has recently been implicated in chronic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, illustrating the pivotal role of innate immunity in maintaining the delicate balance between immune tolerance and immune response in the gut.

b. Normal Flora

REVIEW
Kelly D. Conway S. Aminov R.
Commensal gut bacteria: mechanisms of immune modulation.
Trends in Immunology. 2005;26:326-33.
Mucosal immune responses to pathogenic gut bacteria and the mechanisms that govern disease progression and outcome have been researched intensely for decades. More recently, the influence of the resident non-pathogenic or 'commensal' microflora on mucosal immune function and gut health has emerged as an area of scientific and clinical importance. Major differences occur in the mucosal immune response to pathogens and commensals. In part, this functional dichotomy is explained by the presence of virulence factors in pathogenic species, which are generally absent in commensals. Additionally, immunological 'unresponsiveness' towards the resident commensal microflora is thought to permit their successful colonisation and co-existence within the host gut. However, evidence of an active dialogue between members of the commensal microflora and the host mucosal immune system is rapidly unfolding. This crosstalk is likely to affect immunological tolerance and homeostasis within the gut and to explain some of the differential host responses to commensal and pathogenic bacteria.

REVIEW
Cario E.
Bacterial interactions with cells of the intestinal mucosa: Toll-like receptors and NOD2
Gut. 2005;54:1182-93
Toll-like receptors (TLR) and NOD2 are emerging as key mediators of innate host defence in the intestinal mucosa, crucially involved in maintaining mucosal as well as commensal homeostasis. Recent observations suggest new (patho-) physiological mechanisms of how functional versus dysfunctional TLRx/NOD2 pathways may oppose or favour inflammatory bowel disease (IBD). In health, TLRx signalling protects the intestinal epithelial barrier and confers commensal tolerance whereas NOD2 signalling exerts antimicrobial activity and prevents pathogenic invasion. In disease, aberrant TLRx and/or NOD2 signalling may stimulate diverse inflammatory responses leading to acute and chronic intestinal inflammation with many different clinical phenotypes.

c. Complement

REVIEW:
Ogundele M
Role and significance of the complement system in mucosal immunity: particular reference to the human breast milk complement
ImmunolCell Biol. 2001;79:1-10
The complement system plays an important role in a host's defence mechanisms, such as in immune bacteriolysis, neutralization of viruses, immune adherence, immunoconglutination and in enhancement of phagocytosis. The possible role of this important biological system in biological fluids on the mucosal surfaces, including breast milk, has however been largely neglected. Its contribution to the 'common' mucosal immunity is still enigmatic and largely speculative. Assessment of the complement system in human breast milk, which has so far largely been limited to different assays of the individual component proteins, is reviewed. A brief review of the classical and the alternative pathways of complement activation is presented. The potential physiological roles of various complement components and their activation fragments in human milk in particular, and other mucosal surfaces in general, are also presented. It was concluded that the complement system might play a complementary role to other immunological and non-immunological protective mechanisms on the mucosal surfaces.

d. Defensins

REVIEW:
Ganz T
Defensins: Antimicrobial peptides of innate immunity
Nat Rev Immunol 2003;9:710-720
The production of natural antibiotic peptides has emerged as an important mechanism of innate immunity in plants and animals. Defensins are diverse members of a large family of antimicrobial peptides, contributing to the antimicrobial action of granulocytes, mucosal host defence in the small intestine and epithelial host defence in the skin and elsewhere. This review, inspired by a spate of recent studies of defensins in human diseases and animal models, focuses on the biological function of defensins.

2. Antigen transport

REVIEW:
Snoeck V. Goddeeris B. Cox E.
The role of enterocytes in the intestinal barrier function and antigen uptake
Microbes Infect 2005;7:997-1004
The intestinal epithelium is a critical interface between the organism and its environment. The cell polarity and structural properties of the enterocytes, limiting the amount of antigen reaching the epithelial surface, form the basis of the integrity of the epithelium. However, apart from their participation in digestive processes, the enterocytes perform more than just a passive barrier function. The resistance of the tight junctions regulates the paracellular transport of antigens. Furthermore, the enterocytes take up and process antigens, involving two functional pathways. In the major pathway, enzymes in the lysosomes degrade the antigens. In the minor direct transcytotic pathway, the antigens are not degraded and are released into the interstitial space. Moreover, the enterocytes can present processed antigens directly to T cells and are often directly involved in immune processes. In inflammatory conditions, the properties of the epithelial barrier and the outcome of the immune response to luminal antigens can be changed.

3. Adaptive Immunity

a. Responses to bacteria viruses and parasites

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.

REVIEW
Mathias W. Hornef1, Mary Jo Wick2, Mikael Rhen1
Bacterial strategies for overcoming host innate and adaptive immune responses
Nature Immunology 2002;3:1033 - 1040 .
In higher organisms a variety of host defense mechanisms control the resident microflora and, in most cases, effectively prevent invasive microbial disease. However, it appears that microbial organisms have coevolved with their hosts to overcome protective host barriers and, in selected cases, actually take advantage of innate host responses. Many microbial pathogens avoid host recognition or dampen the subsequent immune activation through sophisticated interactions with host responses, but some pathogens benefit from the stimulation of inflammatory reactions. This review will describe the spectrum of strategies used by microbes to avoid or provoke activation of the host's immune response as well as our current understanding of the role this immunomodulatory interference plays during microbial pathogenesis

b. Mucosal Immunoglobulins

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 Fc(alpha)RI, Fc(alpha)/microR, and CD71) and presents examples of the means by which certain pathogens circumvent the protective properties of this important Ig.

i. Secretory IgA

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

REVIEW:
Rojas R. Apodaca G
Immunoglobulin transport across polarized epithelial cells.
Nat Rev Mol Cell Biol. 2002;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 receptormediated transcytosis are providing new insight into the nature and regulation of endocytic pathways

iii Fcγ function

REVIEW:
Yoshida M. Claypool SM. Wagner JS
Human neonatal Fc receptor mediates transport of IgG into luminal secretions for delivery of antigens to mucosal dendritic cells.
Immunity 2004;20:769-83
Mucosal secretions of the human gastrointestinal, respiratory, and genital tracts contain significant quantities of IgG. The mechanism by which IgG reaches luminal secretions and the function of IgG in these locations are unknown. Here, we find that the human neonatal Fc receptor (FcRn) is the vehicle that transports IgG across the intestinal epithelial barrier into the lumen where the IgG can bind cognate antigen. 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. These results explain how IgG is secreted onto mucosal surfaces and scavenges luminal antigens for recognition by the immune system.

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
Kiyono H. Fukuyama S.
NALT- versus Peyer's-patch-mediated mucosal immunity
Nat Rev Immunol 2004;4:699-710
Recent studies indicate that the mechanism of nasopharynx-associated lymphoid tissue (NALT) organogenesis is different from that of other lymphoid tissues. NALT has an important role in the induction of mucosal immune responses, including the generation of T helper 1 and T helper 2 cells, and IgA-committed B cells. Moreover, intranasal immunization can lead to the induction of antigen-specific protective immunity in both the mucosal and systemic immune compartments. Therefore, a greater understanding of the differences between NALT and other organized lymphoid tissues, such as Peyer's patches, should facilitate the development of nasal vaccines.

REVIEW
Smith DW. Nagler-Anderson C
Preventing intolerance: the induction of nonresponsiveness to dietary and microbial antigens in the intestinal mucosa.
J Immunol 2005;174:3851-7.
The gut-associated lymphoid tissue (GALT) is constantly exposed to a variety of Ags and must therefore decipher a large number of distinct signals at all times. Responding correctly to each set of signals is crucial. When the GALT receives signals from the intestinal flora or food Ags, it must induce a state of nonresponsiveness (mucosal tolerance). In contrast, when pathogenic bacteria

invade the intestinal mucosa, it is necessary to elicit strong T and B cell responses. The GALT is therefore in the position of constantly fighting intolerance to food and the commensal flora while effectively battling infectious microbes. Determining precisely which type of response to generate in each case is key to the prevention of immune dysregulation and tissue damage.

4. Passive immunization

REVIEW
Hanson LA. Korotkova M. Lundin S
The transfer of immunity from mother to child.
Ann N Y Acad Sci 2003;987:199-206
The newborn's immune system grows fast from a small size at birth by exposure primarily to the intestinal microflora normally obtained from the mother at and after birth. While building up its immune system, the infant is supported by the transplacental IgG antibodies, which also contain anti-idiotypic antibodies, possibly also actively priming the offspring. The second mode of transfer of immunity occurs via the milk. Numerous major protective components, including secretory IgA (SIgA) antibodies and lactoferrin, are present. The breastfed infant is better protected against numerous common infections than the non-breastfed. Breastfeeding also seems to actively stimulate the infant's immune system by anti-idiotypes, uptake of milk lymphocytes, cytokines, etc. Therefore, the breastfed child continues to be better protected against various infections for some years. Vaccine responses are also often enhanced in breastfed infants. Longlasting protection against certain immunological diseases such as allergies and celiac disease is also noted.

D. Transplantation Immunology

REVIEW:
Buckley RH
Transplantation immunology: organ and bone marrow.
J Allergy Clin Immunol 01-FEB-2003; 111(2 Suppl): S733-44.
The roles of antibodies, antigen-presenting cells, helper and cytotoxic T cells, immune cell surface molecules, and signaling mechanisms and the cytokines they release are reviewed. The development of newer immunosuppressive agents based on the knowledge of immune mechanism and targeting various components of the rejection process is discussed Similarly, the development of effective T-cell depletion techniques for bone marrow transplantation when an HLA-identical sibling is not available is reviewed.

LANDMARK PUBLICATION
Gibson T., Medawar P.B.,
The fate of skin homografts in man
J Anatomy (1943) 77 : 299-310.
WWII treatment of burn victims with repeated skin grafting lead to the observation of accelerated rejection and the concept that skin graft rejection was an immunologic phenomenon. These wartime experiments of necessity in humans were later confirmed in animals by Medawar.(The IRB for PETA would be pleased that human experiments were done before animal experiments)

LANDMARK PUBLICATION
Billingham R.E., Brent L., Medawar P.B.,
"Actively acquired tolerance" of foreign cells
Nature (1953) 172 : 603-606.
This experiment in rodents heralded the dawn of the modern era of tissue and organ transplantation.

LANDMARK PUBLICATION
Bach FH, Amos DB
Hu-1: major histocompatibility locus in man..
Science 1967;156:1506-8.
The discovery of the MHC set the stage for modern day bone marrow and solid organ transplants

RESEARCH FRONTIER
Bradley, Benjamin A..
Prognostic assays for rejection and tolerance in organ transplantation.
Transplant Immunology, Aug 2005;14:193-202
Three processes in organ transplant rejection are described: recognition, rejection and regulation. These processes are altered by powerful immunosuppressive drugs. Many transplant recipients are presensitised to transplantation antigens prior to engraftment. The ultimate goal is to encourage the emergence of a utopian immunological state, wherein patients tolerate organ transplants for life after being weaned from all immunosuppressive drugs. Assays that may be used in the future to reliably monitor this process are still at a very exciting stage of development.

1. Allograft rejection

REVIEW:
Buckley RH -
Review: Transplantation immunology: organ and bone marrow.
J Allergy Clin Immunol - FEB-2003; 111(2 Suppl): S733-44.
Repeat of the REVIEW citation above. Also a good review of the mechanism of graft rejection and one stop shopping as a comprehensive but not cumbersome overview of transplant immunology.

2. Graft versus host reactions (GVHR)

REVIEW:
Higman MA
Chronic graft versus host disease.
Br J Haematol - 01-MAY-2004; 125(4): 435-54.
This review describes the risk factors for developing chronic GvHD, its presentation and the current treatment options for both initial therapy and secondary treatment

3. Maintenance of tolerance

REVIEW:
Chan C
Tolerance mechanisms and recent progress. –
Transplant Proc 01-MAR-2004; 36(2 Suppl): 561S-569S
This article highlights the role of recent discoveries inf central tolerance. The review includes discussions of "ectopic" or "promiscuous" antigens expressed by medullary thymic epithelial cells, the function of the thymus in generating naturally occurring CD4+ CD25+ regulatory T cells, and tolerogenic dendritic cells.

E. Tumor Immunology

REVIEW:
Zhang HG
Aging, immunity, and tumor susceptibility.
Immunol Allergy Clin North Am - 01-FEB-2003; 23(1): 83-102.
This article explores the mechanisms of immune surveillance and the effects of aging on the susceptibility to timors.

RESEARCH FRONTIER:
Reiche EM
Stress, depression, the immune system, and cancer.
Lancet Oncol - 01-OCT-2004; 5(10): 617-25
The links between the psychological and physiological features of cancer risk and progression have been studied through psychoneuroimmunology. This article provides an overview the evidence that various cellular,and molecular immunological factors are compromised in chronic stress and depression and discuss the clinical implications of these factors in the initiation and progression of cancer. The consecutive stages of the multistep immune reactions are either inhibited or enhanced as a result of previous or parallel stress experiences, depending on the type and intensity of the stressor and on the animal species, strain, sex, or age. In general, both stressors and depression are associated with the decreased cytotoxic T-cell and natural-killer-cell activities that affect processes such as immune surveillance of tumours, and with the events that modulate development and ccumulation of somatic mutations and genomic instability.

1.Tumor specific and tumor associated antigens

REVIEW:
Costello RT
Immunobiology of haematological malignant disorders: the basis for novel immunotherapy protocols.
Lancet Oncol - 01-JAN-2004; 5(1): 47-55
This article focuses on the haematological, antigen-specific and HLA-restricted immunity involved in tumor surveillance with respect to tumour antigen presentation and recognition and their possible clinical use.

2.Oncogenes, translocations and tumor suppressor genes

REVIEW:
Vineis P
Individual susceptibility to carcinogens
Oncogene (2004) 23, 6477-6483
The contribution of polymorphisms in carcinogen metabolizing genes to overall cancer rates may vary widely between groups with differing allele frequencies and with varying levels of carcinogenic exposure. Their effects are modified by interactions with each other and with other genes, particularly those involved in DNA repair. Studies on the combined effects of particular polymorphisms on colorectal and other cancers, and also on intermediate markers such as DNA adduct formation, are discussed.

WEBSITE LINK: Tumor suppressor genes
http://web.indstate.edu/thcme/mwking/tumor-suppressors.html.
This link will get you directly to text that summarizes the commonly known oncogene 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 alloantigen independent, 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.

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 anti-erg upregulation and downregulation.

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 amino-terminal 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 celldeath.

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 cells4. 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 receptormediated event that drives Tr1 differentiation and suggest that the complement system has a previously unappreciated role in T-cell-mediated immunity and tolerance.

G. Laboratory Measurements

1. Principles and methodology of:

a. measurements of immunoglobulin levels, immunoglobulin classes and subclasses

REVIEW ARTICLE

Maranon F, Casanovas M, Berrens L

A competitive enzyme immunoassay Subclass for the determination of total IgG-subclass levels in human serum. Comparison with single radial immunodiffusion

J Immunoassay. 1994;15:147-56.

A quantitative immunoassay has been developed for the determination of the total IgG subclass levels in human serum. The method is based on an enzyme immunoassay in which IgG subclass proteins IgGx in an unknown serum sample compete with a known quantity of peroxidase (PO)-labelled IgGx in fluid phase for subclass-specific monoclonal antibodies coated to the solid phase of microtiter wells. Using a series of human blood samples an excellent correlation was observed with the IgG-subclass levels determined by single radial immunodiffusion.

Ataelmannan, M, Levinson SS.

Understanding and identifying monoclonal gammopathies.

Clin Chem. 2000 Aug;46(8 Pt 2):1230-8

Monoclonal gammopathies reflect conditions in which abnormal amounts of immunoglobulins are produced by a clone that developed from a single pro-B germ cell. The condition may reflect a disease process or be benign. The primary purpose of this review is to emphasize routine clinical laboratory techniques that currently are recommended for use in identifying monoclonal gammopathies from serum and urine. Selection of the preferred technique and correct interpretation often is dependent on an understanding of the immunological basis and clinical sequelae associated with these conditions. For this reason, we first briefly discuss the structure, production, and nature

of immunoglobulins, and then describe important features of the associated diseases. Finally, we discuss strengths and weaknesses of the techniques and make reference to current recommendations to facilitate optimal testing. We discuss in detail high-resolution electrophoresis, methods for quantifying immunoglobulins, immunofixation electrophoresis, problems associated with analysis of urine immunoglobulins, and identification of cryoglobulins and immune complexes.

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.

b. serologic testing

i. ELISA, immunoblot

REVIEW ARTICLE
Wheeler, MJ
Immunoassay techniques
Methods Mol Biol 2006;324:1-23
No other development has had such a major impact on the measurement of hormones as immunoassay.Reagents and assay kits can now be bought commercially but not for the more esoteric or new hormones. This chapter explains the basics of the immunoassay reaction and gives simple methods for immunoassays and immunometric assays and for the production of reagents for both antigenic and hapten hormones. Alternative methods are given for the preparation of labeled hormones as well as several possible separation procedures. The methods described here have been previously used in a wide range of assays and have stood the test of time. They will allow the production of usable immunoassays in a relatively short period of time.

ii. autoimmune serology

REVIEW ARTICLE
Tozzoli R, Bizzaro N, Tonutti E,et al
Guidelines for the laboratory use of autoantibody tests in the diagnosis and monitoring of autoimmune rheumatic diseases.
Am J Clin Pathol. 2002 Feb;117:316-24.
The Italian Society of Laboratory Medicine Study Group on the Diagnosis of Autoimmune Diseases has generated a series of guidelines for the laboratory diagnosis and monitoring of systemic

autoimmune rheumatic diseases intended for the use of clinical pathologists and laboratory physicians. These guidelines are based on a systematic review of published works and expert panel discussion and consist of 13 recommendations for antinuclear antibodies, anti-double-stranded native DNA, and antinuclear specific antibodies. To improve analytic performances and help select the most appropriate test for specific autoantibodies, as well as provide education and guidance in the use of these tests, special emphasis is placed on laboratory methods.

iii. in vitro testing techniques for specific IgE

REVIEW ARTICLE

Plebani M ,Bernardi D, Basso D, et al.

Measurement of specific immunoglobulin E: intermethod comparison and standardization

Clinical Chemistry 44: 1974-1979, 1998

Recently introduced "second-generation" techniques for specific IgE measurement have produced some analytical improvement, offering better clinical sensitivity than previous techniques. The aims of our study were to compare the analytical and clinical performances of four second-generation techniques for allergen-specific IgE measurement in serum and to ascertain whether the new system for reporting quantitative results contributes to greater clinical agreement between findings using the techniques considered. Allergen-specific IgE was measured using the CAP® System, CARLA®, ENEA®, and AlaSTAT®, and the findings were compared. A significant disagreement was found between CAP and ENEA for all allergens and between CAP and CARLA for D1 and G5. However, the clinical discrepancies were reduced by selecting method-specific thresholds using ROC analysis. Second-generation techniques enable us to obtain better standardization of results; however, the identification of a specific threshold appears to be a prerequisite for the appropriate clinical interpretation of the test findings

.**REVIEW ARTICLE**

Plebani M

Clinical value and measurement of specific IgE.

Clin Biochem. 2003 Sep;36(6):453-69.

The diagnosis of human allergic diseases involves the combined use of a careful clinical history, physical examination, and in vitro and in vivo assay methods for the detection of IgE antibodies of defined allergen specificities. In vivo (skin testing) and in vitro (measurement of specific IgE in serum) techniques cannot be considered interchangeable, the former reflecting not only the presence of IgE but also mast cell integrity, vascular and neural responsiveness. Both techniques have similarities and differences, advantages and disadvantages. Recently introduced "second generation" immunoassays have continued to improve the analytical sensitivity and reproducibility thanks to automation and improved reagent quality. Quantitative assays may allow the use of specific clinical thresholds able to differentiate symptomatic from asymptomatic patients. False-negative and false-positive results should derive from lability of some major extracts, and from possible cross-reactivities, respectively. Characterization of allergens at a molecular and submolecular level and, where necessary, the use of recombinant allergens can reduce cross-reactions and further improve the quality of immunoassays.The aim of this paper is therefore to review the advantages and limitations of current assays for specific IgE, and the value of its measurement in clinical practice.

REVIEW ARTICLE

Hamilton RG, Adkinson NF Jr

Clinical laboratory assessment of IgE-dependent hypersensitivity

J Allergy Clin Immunol. 2003:S687-701

This chapter reviews clinical and laboratory analyses that aid in the diagnosis and management of human allergic (IgE-dependent) diseases. The diagnostic algorithm for immediate-type hypersensitivity begins with a thorough clinical history and physical examination. Once signs and symptoms compatible with an allergic disorder have been identified, a skin test and/or blood test for allergen-specific IgE antibodies may serve as primary confirmation to strengthen the diagnosis. Puncture and intradermal skin testing provide a biologically relevant immediate-type hypersensitivity response in the skin, with resultant wheal and flare reactions within 15 minutes of allergen application. Bleeding, dermatographism, and antihistamines may confound the quality of the skin test. Allergenspecific IgE antibody may also be detected in the blood using a radioallergosorbent test (RAST). Nonisotopic "second-generation" RAST-type assays have evolved to provide more quantitative, sensitive, precise IgE antibody results. In vivo provocation tests may serve as secondary confirmatory tests when the clinical history is discordant with a primary IgE antibody test result. The multiallergen screen is a qualitative RAST-type assay that detects specific IgE antibody to approximately 15 allergens that evoke a large majority of aeroallergen or food-related allergic disorders. Other useful serological assays performed in the diagnostic allergy laboratory include total serum IgE, Hymenoptera venom-specific IgG antibody, IgG precipitins for organic dusts, mast cell tryptases, and the venom RAST inhibition test. Above all, in vivo or laboratory confirmatory test results that are inconsistent with the clinical history should be repeated as for any laboratory assessment.

iv. RAST Inhibition technique

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 point titrations 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
James. K
Immunoserology of infectious diseases
Clin Microbiol Rev. 1990;3:132-52
The immune response to microorganisms not only participates in the elimination of unwanted organisms from the body, but also assists in diagnosis of infectious diseases. The nonspecific immune response is the first line of defense, assisting the body until the specific immune response can be mobilized to provide protective mechanisms. The specific immune response involves humoral or cellmediated immunity or both, dependent on the nature of the organism and its site of sequestration. A variety of test systems have been developed to identify the causative organisms of infectious diseases. Test systems used in immunoserology have classically included methods of detecting antigen-antibody reactions which range from complement fixation to immunoassay methods. Relevant test systems for detecting antigens and antibodies are described. With numerous test systems available to detect antigens and antibodies, there can be confusion regarding selection of the appropriate system for each application. Methods for detecting antibody to verify immunity differ from immunologic methods to diagnose disease. Techniques to detect soluble antigens present in active infectious states may appear similar to those used to detect antibody, but their differences should be appreciated.

REVIEW
Maddison SE.
Serodiagnosis of parasitic diseases
Clin Microbiol Rev. 1991 Oct;4(4):457-69..
In this review on serodiagnosis of parasitic diseases, antibody detection, antigen detection, use of monoclonal antibodies in parasitic serodiagnosis, molecular biological technology, and skin tests are discussed. The focus at the Centers for Disease Control on developing improved antigens, a truly quantitative FAST-enzyme-linked immunosorbent assay, and the very specific immunoblot assays for antibody detection is highlighted. The last two assays are suitable for field studies. Identification of patient response in terms of immunoglobulin class or immunoglobulin G subclass isotypes or both isdiscussed. Immunoglobulin isotypes may asist in defining the stage of some diseases. In other instances, use of a particular anti-isotype conjugate may increase the specificity of the assay. Monoclonal antibodies have played important roles in antigen purification and identification, in competitive antibody assays with increased sensitivity and specificity, and in assays for antigen detection in serum, body fluids, or excreta. Molecular biological technology has allowed significant advances in the production of defined parasitic serodiagnostic antigens

c. flow cytometry -cell surface marker and intracellular techniques

REVIEW
Pala P, Hussell T, Openshaw PJ
Flow cytometric measurement of intracellular cytokines.
J Immunol Methods. 2000;243:107-24
The identification of distinct T helper lymphocyte subsets (Th1/2) with polarised cytokine production has opened up new fields in immunobiology. Of the several alternative methods of monitoring cytokine production, flow cytometric analysis of intracellular staining has distinct advantages and pitfalls. It allows high throughput of samples and multiparameter characterization of cytokine production on a single cell basis without the need for prolonged in vitro culture and cloning. However, these methods may cause important changes in cell surface phenotype which can make interpretation difficult.

d. Cellular functional responses

i. Chemotaxis and adhesion

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
Bercovici N, Duffour M, Agrawal S, et al
New Methods for Assessing T-Cell Responses.
Clin Diagn Lab Immunol 2000;7 :859-864.
In this review, we describe some of the most widely used techniques for immune monitoring of specific T-cell responses. These various assays can be schematically divided into functional assays, which measure the secretion of a particular cytokine (ELISPOT and intracellular cytokines); assays which assess the specificity of the T cells irrespective of their functionality and which are based on structural features of the TCR (tetramers and immunoscope); and assays aimed at detecting T-cell precursors by amplifying cells that proliferate in response to antigenic stimulation. The sensitivity and immunological relevance of these various methods are discussed. Major findings and future applications in basic and clinical immunology are also presented.

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, 2001, 123.1-123.10.

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.

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

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, 9-14-922.

REVIEW CHAPTER
Yancy KB, Lawley TJ.
Circulating immune complexes and serm sickness.
In Rich RR, Fleisher TA,Shearer WT, Kotzin BL, Schroeder HW (eds). Clinical Immunology: Principles adn Practices. Mosby, New York; 2001, 59:1-59:10.

f. histocompatibility typing

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 adopt molecular 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 lessthan-discriminating 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.

g. 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

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 Q-PCR 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 long-lived 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 T-cell 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.

h. 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

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.

i. 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 RT-PCR 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

REVIEW

Deeks JJ

Systematic reviews of evaluations of diagnostic and screening tests

BMJ. 2001;21;323(7305):157-62.

Summary points

Systematic reviews of studies of diagnostic accuracy differ from other systematic reviews inthe assessment of study quality and the statisticalmethods used to combine results. Important aspects of study quality include the selection of a clinically relevant cohort, the consistent use of a single good referencestandard, and the blinding of results of experimental and reference tests. The choice of statistical method for pooling results depends on the summary statistic and sources of heterogeneity, notably variation indiagnostic thresholds.Sensitivities, specificities, and likelihood ratios may be combined directly if study results are reasonably homogeneous. When a threshold effect exists, study results may be best summarised as a summary receiver operating characteristic curve, which is difficult to interpret and apply to practice.

REVIEW: APPLICATION OF ROC

Verstege A, Mehl A, Rolinck-Werninghaus C, et al.

The predictive value of the skin prick test weal size for the outcome of oral food challenges.

Clin Exp Allergy 2005; 35:1220–1226.

BACKGROUND: The skin prick test (SPT) is regarded as an important diagnostic measure in the diagnostic work-up of food allergy. Objective To evaluate the diagnostic capacity of the SPT in predicting the outcome of oral food challenges, and to determine decision points for the weal size and the skin index (SI) that could render double-blind, placebo-controlled food challenges unnecessary. METHODS: In 385 children (median age 22 months), 735 controlled oral challenges were performed with cow's milk (CM), hen's egg (HE), wheat and soy. Three hundred and thirty-six of 385 (87%) children suffered from atopic dermatitis. SPT was performed in all children. Diagnostic capacity, receiver-operator characteristics (ROC) curves and predictive decision points were calculated for the mean weal size and the calculated SI. RESULTS: Three hundred and twelve of 735 (43%) oral food challenges were assessed to be positive. Calculation of 95% and 99% predicted probabilities using logistic regression revealed predictive decision points of 13.0 and 17.8 mm for HE, and 12.5 and 17.3 mm for CM, respectively. However, using the SI, the corresponding cut-off levels were 2.6 and 3.7, respectively, for HE, and 2.7 and 3.7 for CM. For wheat, 95% and 99% decision points of 2.2 and 3.0 were found in children below 1 year of age. CONCLUSION: Predictive decision points for a positive outcome of food challenges can be calculated for HE and CM using weal size and SI. They may help to avoid oral food challenges.

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

REVIEW
Wuthrich B
Unproven techniques in allergy diagnosis.
J Investig Allergol Clinic Immunol 2005;15:86-90
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 CHAPTER
Abba I. Terr,
Unconventional Theories and Unproved Methods in Allergy
in Middleton's Allergy: Principles and Practice, 6th ed., Copyright © 2003 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 to the offending agent, a delay in onset of symptoms after exposure, and lack 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

NOTE:
Current Standard Anatomy/Physiology or Otolaryngology, Pulmonary Medicine, Dermatology, Gastroenterology are recommended for overview-level information on anatomy and physiology of the upper and lower airway, skin, and gastrointestinal tract.

1. Upper airway -nose, sinuses, middle ear

REVIEW:
Current Diagnosis & Treatment in Otolaryngology-Head & Neck Surgery.
Edited by Anil Lalwani, MD. McGraw-Hill Professional, 2004.
This text is the premier resource for the detailed anatomy of the head and neck.
Used as a reference in the training of otolaryngologists and maxillofacialsurgeons.

WEB REVIEW
Chang EW
eMedicine - Nose Anatomy :
www.emedicine.com/ent/topic6.htm
This electronic web based review is a comprehensive up to date review that includes helpful links to graphics, additional resources and references.

2. Lower Airway

REVIEW TEXT
Corren J, Togias A, Bousquet J.
In: Upper and Lower Respiratory Disease. Marcel Dekker, 2003
The pathophysiology, epidemiology, diagnosis and treatment of allergic airway dysfunction affecting the entire respiratory tract is presented in an easy to use format.

REVIEW TEXT
West JB
Pulmonary Physiology and Pathophysiology, An Integrated, Case-Based Approach
Lippincott, Williams and Wilkins, 2001, 162 pp

3. Skin

REVIEW
Kanitakis J.
Anatomy, histology and immunohistochemistry of normal human skin.
Eur J Derm 2002;12:390-9 (quiz 400-401)
The skin is the largest organ of the body, accounting for about 15% of the total body weight in adult humans. It exerts multiple vital protective functions against environmental aggressions, rendered possible thanks to an elaborate structure, associating various tissues of ectodermal and mesodermal origin, arranged in three layers, including (from top to bottom) the epidermis (and its appendages), the dermis and the hypodermis. This article reviews the main data concerning the anatomy, histology and immunohistochemistry of normal human skin.

4. Gastrointestinal Tract

REVIEW
Grant JP.
Anatomy and physiology of the luminal gut: enteral access implications.
J Parenter Enteral Nutr. 2006; 30:S41-6.
Successful long-term enteral nutrition requires enteral access that is comfortable and easy to maintain. However, to be successful, the enteral access must also satisfy conditions of gut anatomy and physiology.

5. Lymphoid Tissue

REVIEW
Azzali G.
Structure, lymphatic vascularization and lymphocyte migration in mucosa-associated lymphoid tissue.
Immunol Rev 2003;195:178-89
In this review, we consider the morphological aspects and topographical arrangement of gut-associated lymphoid tissue (GALT) (solitary and aggregate lymph nodules or Peyer's patches) and of vermiform appendix in the human child and in some mammals. The spatial arrangement of the vessels belonging to apparatus lymphaticus peripheric us absorbens (ALPA) and of blood vessels within each lymphoid follicle as well as the ultrastructural characteristics of the lymphatic endothelium with high absorption capacity are considered. Particular attention is also paid to the morphological and biomolecular mechanisms inducing lymphocyte transendothelial migration to the bloodstream by means of lymphatic vessels as well as their passage from blood into lymphoid tissue through the high endothelial venules (HEVs). The preferential transendothelial passage of lymphocytes and polymorphonuclear neutrophils within ALPA vessels of the interfollicular area does not occur following the opening of intercellular contacts, but rather it occurs by means of 'intraendothelial channels'. In HEVs, on the contrary, the hypothesis is plausible that lymphocyte transendothelial migration into lymphoid tissue occurs through a channel-shaped endothelial invagination entirely independent of interendothelial contacts. The lymph of ALPA vessels of the single Peyer's patch is conveyed into precollector lymphatic vessels and into prelymph nodal collectors, totally independent of the ALPA vessels of the gut segments devoid of lymphoid tissue. The quantitative distribution of T lymphocytes in the lymph of mucosal ALPA vessels suggests a prevalent function of fluid uptake, whereas a reservoir and supply function is implicated for the vessels of interfollicular area. The precollector lymphatic vessels and prelymph nodal collectors are considered to be vessels with low absorption capacity, whose main function is lymph conduction and flow.

REVIEW
Vinuesa CG. Cook MC.
The molecular basis of lymphoid architecture and B cell responses: implications for immunodeficiency and immunopathology.
Curr Mol Med 2001;1:689-725.
Immune responses usually take place in secondary lymphoid organs such as spleen and lymph nodes. Most lymphocytes within these organs are in transit, yet lymphoid organ structure is highly organized; T and B cells segregate into separate regions. B cell compartments include naive cells within follicles, marginal zones and B-1 cells. Interactions between TNF family molecules on

hematopoietic cells and their receptors on mesenchymal cells guide the initial phase of lymphoid organogenesis, and regulate chemokine secretion that mediates subsequent T-B cell segregation. Recruitment of B cells into different compartments depends on both the milieu established during organogenesis, and the threshold for B cell receptor signaling, which is modulated by numerous coreceptors. Novel intrafollicular (germinal center) and extrafollicular (plasma cell) compartments are established when B cells respond to antigen. These divergent B cell responses are mediated by different patterns of gene expression, and influenced again by BCR signaling threshold and cellular interactions that depend on normal lymphoid architecture. Aberrant B cell responses are reviewed in the light of these principles taking into account the molecular and architectural aspects of immunopathology. Histological features of immunodeficiency reflect defects of B cell recruitment or differentiation. B cell hyper-reactivity may arise from altered BCR signaling thresholds (autoimmunity), defects in stimuli that guide differentiation in response to antigen (follicular hyperplasia vs plasmacytosis), or defective B cell gene expression. Interestingly, in diseases such as rheumatoid arthritis, Sjogren's syndrome and Hashimoto's thyroiditis lymphoid organogenesis may be recapitulated in non-lymphoid parenchyma, under the influence of molecular interactions similar to those that operate during embryogenesis.

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.

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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
Boguniewicz M, Schmid-Grendelmeier P, Leung DYM
Atopic dermatitis
J Allergy Clinical Immunol 2006;118:40-43.
Article Outline
What should the approach be to the patient with AD and recurrent skin infections?
What is the role of fungi, such as Malassezia species, in AD?
What role do antihistamines play in the management of AD?
How do you make sense of multiple positive skin test responses or ImmunoCAP assay results to food allergens in patients with AD?
When would you choose a topical calcineurin inhibitor rather than a topical steroid, and do topical calcineurin inhibitors cause cancer?
What about the patient with very recalcitrant disease?
Is there a role for specific immunotherapy or omalizumab in AD?
Final question: Water avoidance or frequent bathing?
References

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:

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 hasdiscussed 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 methodscan be recommended to be used and their respective value is depending on the specific scientificpurposes.

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.

b. Bronchial Challenge:

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, et al.

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

KEY INVESTIGATION
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;86:44-50
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:

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 SO_2 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:

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:

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 thatreversible 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:

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:

KEY INVESTIGATION:

O'Riordan TG, Zwang J, Smaldone GC
Mucociliary clearance in adult asthma.
Am. J. Respir. Cell Mol. Biol. 1999;21: 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. Seventeenasthmatic 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 percentageretention 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 groupwas 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

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

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 -GROWTH

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.

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.

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.

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.

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.

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.

7. Antihistamines

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 H_1-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 H_1-histamine and H_2-histamine receptors were cloned and characterized in the early 1990s, as were the human H_3-histamine and H_4-histamine receptors several years ago. H_1-antihistamines, historically known as histamine H_1-receptor blockers or antagonists, are specific for the H_1-receptor. In addition, some H_1-antihistamines inhibit transmission through the muscarinic, - adrenergic, and serotonin receptors and through ion channels. The H_1-antihistamines have recently been reclassified as inverse agonists, rather than as H_1-receptor antagonists, which is consonant with an increased understanding of their molecular pharmacologic features. More than 40 H_1-antihistamines are available worldwide — indeed, these agents are among the most widely used of all medications. The H_1-antihistamines astemizole and terfenadine, which are associated with cardiac toxic effects, are no longer approved for use. New H_1-antihistamines have been developed and introduced. Both health care professionals and consumers generally assume that all approved H_1-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 H_1-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 the ophthalmologist.

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 harmacokinetics, 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

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.

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.

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.

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.

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.

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.

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; randomized 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 diseases

a. Rhinitis, sinusitis, nasal polyposis, otitis and laryngeal disorders.

- Rhinitis

REVIEW
Nelson H.
Advances in upper airway diseases and allergen immunotherapy,
J Allergy Clin Immunol; 2004;113, 635-42,
Evidence for one airway continues to accumulate. Nasal allergen challenges increase lower airway inflammation, and nasal corticosteroid treatment reduces lower airway inflammation. Allergic respiratory inflammation might even spread systemically to involve nonrespiratory organs. Eosinophilic enteritis and eosinophilic esophagitis are reported during pollen seasons in patients with seasonal allergic rhinitis. Chronic hypertrophic sinusitis (CHS) is found in the majority of patients with asthma. Like asthma, the histology of CHS is characterized by epithelial damage, basement membrane thickening, and eosinophilic inflammation. The damaged epithelium might explain the acute bacterial exacerbations seen in patients with CHS. Studies have extended evidence of the safety and efficacy of the second- and third-generation antihistamines to younger children and to patients with perennial rhinitis but continue to show improvement of symptom scores over that seen with placebo of less than 20%. Studies on antihistamine use in the first trimester in nearly 500 women (65% taking loratadine) revealed no increase in the complications of pregnancy or congenital anomalies. Positive skin prick test responses to birch in asymptomatic young adults predicted later development of clinical allergic rhinitis. A dose response was demonstrated for immunotherapy with cat dander extract. The best results were in subjects receiving a dose containing 15 microg of the major cat allergen Fel d 1 (equivalent to approximately 2500 bioequivalent allergen units). Both topical intranasal immunotherapy and high-dose sublingual immunotherapy have been repeatedly proved to be safe and effective in double-blind, placebo-controlled studies. CD4+CD25+ regulatory T cells secreting IL-10, TGF-beta, or both appear important in normal individuals and in patients treated with allergen immunotherapy in maintaining or restoring normal T(H)1/T(H)2 balance and overall suppression of both phenotypes.

REVIEW
Reed, Lee and McCrory,
The economic burden of allergic rhinitis: a critical evaluation of the literature,
Pharmacoeconomics; 2004;22, 345-61,
Although a large number of economic analyses of allergic rhinitis have been published, there are relatively few empirically based studies, particularly outside the US. The majority of these analyses can be classified as burden-of-illness studies. Most estimates of the annual cost of allergic rhinitis range from dollars US 2-5 billion (2003 values). The wide range of estimates can be attributed to differences in identifying patients with allergic rhinitis, differences in cost assignment, limitations associated with available data and difficulties in assigning indirect costs (associated with reduced productivity) of allergic rhinitis. Approximately one-third of burden-of-illness studies include direct and indirect costs of allergic rhinitis, about one-third focus on direct costs only, and the remaining one-third focus exclusively on indirect costs due to reduced productivity. Indirect costs attributable

to allergic rhinitis were higher in studies only estimating indirect costs (dollars US 5.5-9.7 billion) than in those estimating both direct and indirect costs (dollars US 1.7-4.3 billion). Although there are many economic evaluations of allergic rhinitis treatments in the published medical literature, very few represent formal cost-effectiveness evaluations that compare the incremental costs and benefits of alternative treatment strategies. Those that are incremental cost-effectiveness analyses have several limitations, including small samples, short study periods and the lack of a standardized measure of effectiveness. To date, the medical literature is lacking a comprehensive economic evaluation of general treatment strategies for allergic rhinitis. In undertaking such an analysis, serious consideration must be given to the study population of interest, the choice of appropriate comparators, the perspective from which the analysis is conducted, the target audience, the changing healthcare marketplace and the selection of a measure of effectiveness that incorporates both positive and negative aspects of treatments for allergic rhinitis. Future work would benefit from the development of a consensus on a summary measure of effectiveness that could be used in cost-effectiveness analyses of therapies for allergic rhinitis as well as additional empirical work to measure the association between severity of disease and its impact on worker productivity.

REVIEW

Reissman, Price and Leibman,

Cost efficiency of intranasal corticosteroid prescribing patterns in the management of allergic rhinitis,

J Manag Care Pharm; 2004;10, S9-13,

BACKGROUND: Effective treatment of seasonal or perennial allergic rhinitis often requires use of topical intranasal corticosteroids (INSs). Despite differences in recommended starting dosages, the 4 leading INSs by market share are packaged in bottles containing 120 metered-dose sprays. OBJECTIVE: To determine the relative prescribed dosages of the leading INSs and compare economic differences resulting from these prescribing behaviors. METHODS: The IMS National Disease and Therapeutic Index (NDTI) was used to identify prescribing habits for the 4 leading INSs: fluticasone propionate nasal spray (FPNS), mometasone furoate aqueous nasal spray (MFNS), triamcinolone acetonide aqueous nasal spray (TANS), and budesonide aqueous nasal spray (BANS). The NDTI uses a national, randomly drawn, 2-stage stratified clustersampling methodology. Physicians are sampled during the first stage, with 2 workdays per month subsampled from each physician in the second stage. Each physician reports on all patient contacts during the 2 consecutive days, offering a continuing compilation of statistical information about patterns and treatment of disease encountered by office-based physicians. In a given month, the NDTI reports on 1180 unique physicians. RESULTS: From January 1, 2002, to December 31, 2002, 58% of prescriptions for FPNS were for 4 sprays daily with 37% for 2 sprays daily, MFNS: 44% for 4 sprays and 52% for 2, TANS: 65% for 4 sprays and 31% for 2, and BANS: 29% for 4 sprays and 68% for 2. These equated to mean prescribed daily dosages of 3.47 sprays per day for FPNS, 3.33 for MFNS, 3.50 for TANS, and 2.73 for BANS. Because each INS is packaged in a bottle with 120 metered-dose sprays, the differences in dosage offer varying days of supply per unit filled. BANS offered the most days of treatment (44 days), followed by MFNS (38 days) and FPNS and TANS (means of 35 and 34 days, respectively) per single prescription filled. Cost per day of treatment was calculated by multiplying the prescribed dosage with the average wholesale price of the products. BANS had the lowest cost per day of treatment at US dollars 1.54, with each other INS costing at least an additional US dollars 0.26 daily (MFNS US dollars 1.80; FPNS US dollars 1.88; TANS US dollars 1.97). CONCLUSION: Based on physician prescribing patterns of INSs from the NDTI database, BANS offers more days of treatment at a lower cost per day than other leading INSs.

FRONTIER ARTICLE:

Bousquet, Jacot, Vignola, Bachert and Van Cauwenberge,
Allergic rhinitis: a disease remodeling the upper airways?,
J Allergy Clin Immunol; 2004;113, 43-9,

The nasal and bronchial mucosa present similarities and differences. Remodeling is defined as "model again or differently, reconstruct" and is present in the airways of most if not all asthmatic patients. Even though inflammation is similar in allergic rhinitis and asthma, the pathologic extent of nasal remodeling in patients with rhinitis seems to be far less extensive than that in the bronchi of asthmatic patients. Epithelial damage is only minimal, and the reticular basement membrane does not appear to be largely pseudothickened. Moreover, the demonstration of fibrogenic growth factors in the nasal mucosa of patients with allergic rhinitis is lacking because of the paucity of studies. The reasons why remodeling appears to be less extensive in the nasal mucosa than in the bronchial mucosa are still unclear, but 2 hypotheses can be put forward. On one hand, the cytokine production of smooth muscle cells might partly explain differences in remodeling of the 2 sites of the airways. On the other hand, the genes of the embryologic differentiation might persist in the nose and bronchi or might be re-expressed in asthma and rhinitis. Because the nose is of ectodermal origin and the bronchi of endodermal origin, these genes might also govern remodeling patterns. More studies are urgently required to better characterize nasal remodeling in patients with rhinitis. A better understanding of nasal and bronchial remodeling might help to identify new pathways and new therapeutic strategies to reduce long-term remodeling in asthma.

PRACTIICE PARAMETER / GUIDELINE:

Joint Task Force on Practice Parameters
Allergen immunotherapy: a practice parameter.
Ann Allergy Asthma Immunol; 2003;90, 1-40,

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.

PRACTICE PARAMETER:

Joint Task Force on Practice Parameters
Diagnosis and Management of Rhinitis. .
Ann Allergy Asthma Immunol 1998;81:478-515

-Sinusitis

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
Therapy
- Symptomatic Therapy
- Uncomplicated Sinusitis
- Complicated or Severe Sinusitis
- Patients with Allergic Rhinitis

Areas of Uncertainty
Guidelines
Conclusions and Recommendations

LANDMARK ARTICLE:

Wald, Milmoe, Bowen, Ledesma-Medina, Salamon and Bluestone,
Acute maxillary sinusitis in children,
N Engl J Med; 1981;304, 749-54,

We sought to correlate the clinical, radiographic, and bacteriologic findings in maxillary sinusitis in 30 children who had both upper-respiratory-tract symptoms and abnormal maxillary radiographs. Cough, nasal discharge, and fetid breath were the most common signs, but fever was present inconsistently. Facial pain or swelling and headache were prominent symptoms in older children. Bacterial colony counts of greater than or equal to 10(4) colony-forming units per milliliter were found in 34 of 47 sinus aspirates obtained from 23 children. The most common species recovered were Streptococcus pneumoniae, Haemophilus influenzae, and Branhamella catarrhalis. No anaerobic bacteria were isolated. Viruses were isolated from only two sinus aspirates. There was a poor correlation between the predominant species of bacteria recovered from either the nasopharyngeal or throat culture and the bacteria isolated from the sinus aspirate. This study demonstrates that children with both upper-respiratory-tract symptoms and abnormal sinus radiographs are likely to harbor bacteria in their sinuses, suggesting that such children have bacterial sinusitis.

PRACTICE PARAMETER / 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 use by pharmaceutical companies in drug promotion.

-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

-Otitis

REVIEW / GUIDELINE:
Rosenfeld, Culpepper, Doyle, Grundfast et al,
Clinical practice guideline: Otitis media with effusion,
Otolaryngol Head Neck Surg; 2004;130, S95-118,
The clinical practice guideline on otitis media with effusion (OME) provides evidencebased recommendations on diagnosing and managing OME in children. This is an update of the 1994 clinical practice guideline "Otitis Media With Effusion in Young Children," which was developed by the Agency for Healthcare Policy and Research (now the Agency for Healthcare Research and Quality). In contrast to the earlier guideline, which was limited to children aged 1 to 3 years with no craniofacial or neurologic abnormalities or sensory deficits, the updated guideline applies to children aged 2 months through 12 years with or without developmental disabilities or underlying conditions that predispose to OME and its sequelae (truncated)

-Laryngeal disorders

REVIEW
Tutuian and Castell,
Diagnosis of laryngopharyngeal reflux,
Curr Opin Otolaryngol Head Neck Surg; 2004;12, 174-9,
PURPOSE OF REVIEW: Laryngopharyngeal reflux is of great interest to otolaryngologists, speech and language therapists, and gastroenterologists. This is a brief review of recent publications in the diagnosis of laryngopharyngeal reflux. RECENT FINDINGS: Otolaryngologic signs and symptoms can be found in 4 to 10% of patients with gastroesophageal reflux and those presenting for ear, nose, and throat evaluations. Laryngeal signs are not pathognomonic for laryngopharyngeal reflux because many of these signs can be found in healthy volunteers. A combination of signs and symptoms should be sought before suspecting this diagnosis. Most investigators consider pH monitoring the best currently available instrument to diagnose gastroesophageal reflux, even though it is not considered to be 100% sensitive and specific. Studies in normal volunteers indicate that a minimal number of reflux episodes reach the hypopharynx. The correlation between laryngeal signs and symptoms and pH-documented reflux is

less than perfect, whereas the combination of pH testing and signs and symptoms is better in detecting patients with a favorable response to acid-suppressing therapy. Using an empiric trial of high-dose proton pump inhibitors over a prolonged period of time to diagnose laryngopharyngeal reflux is supported mainly by uncontrolled studies. To date, double-blind, placebo-controlled studies suggest that empiric trials of proton pump inhibitors may not have high accuracy for the diagnosis of laryngopharyngeal reflux. SUMMARY: Multidisciplinary trials are needed to establish the optimal combination of sign and symptom scores, reflux monitoring results, and empiric treatment trials for the most accurate diagnosis of laryngopharyngeal reflux.

REVIEW
Soli CG, Smally AJ.
Vocal cord dysfunction: an uncommon cause of stridor
J Emerg Med. 2005 28:31-3
We present a case of vocal cord dysfunction syndrome (VCDS) presenting as acute angioedema of the upper airway. The presentation of this syndrome and its differentiation from other upper airway conditions that require far different and more urgent treatment is discussed.

b.Clinical skills needed for diagnosis of upper airway diseases

- Skin testing

REVIEW -
American Academy of Allergy, Asthma and Immunology
The use of standardized allergen extracts.
J Allergy Clin Immunol;1997;99, 583-6

REVIEW
Fullerton, Fischer, Lahti, Wilhelm, Takiwaki and Serup,
Guidelines for measurement of skin colour and erythema.: A report from the Standardization Group of the European Society of Contact Dermatitis,
Contact Dermatitis; 1996;35, 1-10,
This report reviews individual-related variables (age, sex, race, anatomical site, skin surface properties), intra- and interindividual variation (temporal, physical and mental activity, orthostatic effect, menstrual cycle/menopause), environment-related variables (light conditions, temperature) and various instrument-related variables that influence skin colour. CIE colorimetry (Minolta Chroma Meter) and spectrophotometric measurement (Derma Spectrometer) are considered. The guidelines give recommendations for measuring conditions and procedures.

POSITION PAPER:
The European Academy of Allergology and Clinical Immunology,
Allergen standardization and skin tests.
Allergy; 1993;48, 48-82,

PRACTICE PARAMETER:
Board of Directors. American Academy of Allergy and Immunology
Allergen skin testing.
J Allergy Clin Immunol; 1993;92, 636-7,

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 reference extract using parallel line bio-assay. The practical performance, limitations, and advantages of skin prick test are discussed.

REVIEW / PRACTICE GUIDELINE – Allergy Immunotherapy
Li JT, Lockey RF, Bernstein IL, et al.
Allergen immunotherapy: a practice parameter (Includes recommendations for skin testing)
Ann Allergy Asthma Immunol 2003;90:S1-40
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.

- Cytology of nasal secretions

REVIEW:
Watelet, Gevaert, Holtappels, Van Cauwenberge and Bachert,
Collection of nasal secretions for immunological analysis,
Eur Arch Otorhinolaryngol; 2004;261, 242-6,
The biochemical analysis of nasal secretions has become essential in the study of nasal or sinus diseases and the monitoring of medical and surgical treatment. The nasal fluid greatly reflects the inflammatory activity within the nasal mucosa. This paper discusses techniques for nasal fluid collection described before and proposes a new approach for the collection and calculation of nasal secretions based on sinus packs. The method is non-invasive, well standardized and reproducible and therefore may serve as a valid tool for future investigations.

- Nasal challenges:

REVIEW
Dunagan and Georgitis,
Intranasal disease and provocation,
Clin Allergy Immunol; 2000;15:151-73,

REVIEW: -
Litvyakova LI. Baraniuk JN
Nasal provocation testing: a review
Ann Allergy Asthma Immunol. 2001;86:355-64
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.

- Rhinoscopy:

REVIEW:
Benninger M
Nasal endoscopy: its role in office diagnosis,
Am J Rhinol; 1997;11, 177-80,
To clarify the role of nasal endoscopy in the diagnosis and treatment planning for patients with nasal or sinus complaints, 100 consecutive new patients were evaluated. Patients were excluded if their only complaint was obstruction and they had a septal deviation as the only clinical finding. Each patient underwent a thorough history and head and neck examination, including anterior rhinoscopy before and after decongestion, and the diagnosis and treatment plans were documented. Each then underwent nasal endoscopy, and the diagnosis and treatments were compared. The most common diagnoses after anterior rhinoscopy were allergic rhinitis (21), nonallergic rhinitis (12), chronic sinusitis with polyps (19) or without polyps (9), and nonsinus pain (13). Nasal endoscopy played a role in 11% of patients, although in no case did endoscopy change the diagnosis or treatment plan. Endoscopy allowed visualization past an enlarged turbinate or septal deviation in six patients, confirmed a suspected diagnosis in three by visualization of the middle meatus, and detected the site of a large choanal polyp in one. In one case, endoscopy identified a paradoxical turbinate on the side opposite the symptoms and radiological findings. Routine nasal endoscopy need not be part of the evaluation of all patients with nasal sinus disorders but is particularly valuable in confirming diagnoses, particularly in patients where anterior rhinoscopy is limited by anatomic obstruction.

REVIEW
Druce and Ledford,
Fiberoptic rhinoscopy,
Clin Allergy Immunol; 2000;15, 233-45,

- Nasal and ear exam

REVIEW:

Schumacher MJ

Nasal congestion and airway obstruction: the validity of available objective and subjective measures.

Current Allergy & Asthma Reports. 2002;2:245-51.

Rhinomanometry and acoustic rhinometry provide the best methods for objective assessment of nasal obstruction. Advanced equipment for these methods is now available, and most devices are reliable provided that care is taken to calibrate the device properly and, for rhinomanometers, the user is completely familiar with the mathematical algorithm for resistance used by the accompanying software. Suggestions for improvement in standardization of rhinomanometry are given. Rhinomanometry and rhinometry are both capable of objectively measuring nasal obstruction, but they are complementary methods that assess different nasal attributes, the former being a test of nasal function, and the latter a representation of nasal geometry. Objective methods are strongly recommended for use in the evaluation of pharmacologic agents that are expected to improve nasal airflow. When further studies needed to validate their use for long-term comparisons are done, these methods should find an increasing place in clinical practice.

- Upper airway imaging

REVIEW -

Anzai, Weymuller, Yueh, Maronian and Jarvik,

The impact of sinus computed tomography on treatment decisions for chronic sinusitis,

Arch Otolaryngol Head Neck Surg; 2004;130, 423-8,

OBJECTIVES: To determine the impact of sinus computed tomography (CT) on treatment decisions by otolaryngologists and to explore the factors leading to choice of surgical treatment for patients suspected of having chronic sinusitis. DESIGN: Prospective cohort study. SETTING: A tertiary academic medical center. PATIENTS: Questionnaires were administered to 3 otolaryngologists in a tertiary academic institution regarding diagnosis and treatment decisions in 27 patients suspected of having chronic sinusitis, before and after they reviewed sinus CT scans. MAIN OUTCOME MEASURES: The dichotomous decisions regarding surgical or nonsurgical treatment and the agreement of treatment decisions among surgeons were evaluated. The factors strongly influencing surgeons' treatment decisions regarding patients selected for surgery were also determined. RESULTS: The dichotomous treatment decisions were changed in one third of patients (9 of 27) after the sinus CT scans were reviewed. The agreement of treatment decisions among the 3 surgeons was markedly improved after they reviewed sinus CT scans. The factors favorably influencing surgical treatment were obstruction of the ostiomeatal complex on CT and concordance of CT abnormality with a patient's symptoms. Lund-Mackay stage, symptoms, and corticosteroid or antibiotic use were not significant predictors. CONCLUSIONS: Despite the common belief that treatment decisions for chronic sinusitis should be solely based on clinical grounds, with sinus CT providing only anatomic detail before surgery, our study indicates that the decision to perform surgery was altered by CT in a substantial portion of the patients. In our preliminary study, CT increased the tendency to elect surgical treatment by all 3 surgeons.

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 base rate prevalence of CRS in the population being evaluated.

- Environmental assessment and control

REVIEW-

Custovic and Simpson,

Environmental allergen exposure, sensitisation and asthma: from whole populations to individuals at risk,

Thorax; 2004;59, 825-7,

Sensitisation to inhalant allergens remains a major risk factor for asthma, but the size of the effect is hotly debated. Several cross sectional studies have suggested a simple doseresponse relationship between dust mite allergen exposure and specific sensitisation, both within communities and between communities exposed to differing levels of mite allergens. The threshold concentration of 2 µg Group 1 mite allergen per gram of dust for developing mite sensitisation in children at high risk has been suggested, but a much higher cut off level of 80 µg/g appeared significant in low risk children. For other allergens the relationship between exposure and sensitisation is less well defined. Several studies in the US inner city areas reported that children are more likely to become sensitised to cockroach with increasing cockroach allergen exposure,[9] and that high exposure to mouse allergen appears to be associated with an increased prevalence of sensitisation to mouse. Some studies in older children and adults reported a close relationship between specific allergen sensitisation and current domestic exposure for mite and cockroach, but not cat allergen. This, together with studies reporting a protective effect of high cat allergen exposure on sensitisation raises the question of whether the dose-response relationship between exposure and sensitisation may be different for different allergens. However, there are remarkably few published data on the longitudinal relationship between allergen exposure and the development of specific sensitisation.

REVIEW / Guideline
Asher, Baena-Cagnani, Boner, Vichyanond et al.
World Allergy Organization guidelines for prevention of allergy and allergic asthma
Int Arch Allergy Immunol; 2004;135, 83-92,

RESEARCH FRONTIER:
Morgan WJ, Crain EF, Gruchalla RS et al.
Results of a home-based environmental intervention among urban children with asthma.
N Engl J Med 2004;351:1068-1080.
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 dustmite 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.

2. Eye Diseases

REVIEW
Stahl JL and Barney NP
Ocular allergic disease. NP.
Current Opinion in Allergy and Clinical Immunology 2004;4:455-459.
PURPOSE OF REVIEW: This review will focus on recent advances in our understanding of the pathogenesis of allergic eye diseases. Common findings in acute allergic conjunctivitis (seasonal and perennial) and chronic allergic conjunctivitis (vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis) include evidence of mast cell activation and eosinophil attraction and activation. Cytokine levels found in tears, conjunctival impression cytology and biopsy specimens, and serum have been evaluated as markers of disease, and as targets of therapeutic intervention. RECENT FINDINGS: Human conjunctival epithelial cells respond to tumor necrosis factor alpha, interleukin-1 beta, and interferon-gamma individually and in combination. Intracellular adhesion molecule-1 expression is upregulated by interleukin-1 beta and tumor necrosis factor alpha. Conjunctival epithelial cells release interleukin-8 in response to

interleukin-1 beta and tumor necrosis factor alpha but not interferongamma. Supernatants from activated mast cells cause increased adhesion of eosinophils to conjunctival epithelium. Tear levels of tumor necrosis factor alpha were elevated in vernal keratoconjunctivitis patients compared with normal controls. T cell lines from chronic allergic eye disease patients showed inconsistent production of cytokines in atopic and vernal keratoconjunctivitis and low levels in giant papillary conjunctivitis. Vernal keratoconjunctivitis patients have differing levels of eosinophil cationic protein in their serum if they were serum specific immunoglobulin E positive compared to serum specific immunoglobulin E negative patients. SUMMARY: Recent findings continue to expand our basic knowledge of mechanisms and differences between seasonal and perennial allergic conjunctivitis and atopic and vernal keratoconjunctivitis. Understanding the complex interactions and cross talk between cells, cytokines and other mediators is relevant for new therapeutic approaches directed at specific disease entities.

FRONTIER DEVELOPMENTS:
Chambless SL and Trocme S.
Current Developments in ocular allergy.
Current Opinion in Allergy and Clinical Immunology 2004;4:431-434.
PURPOSE OF REVIEW: The goal of this article is to evaluate developments in the knowledge of inflammatory mechanisms and treatments of ocular allergy. RECENT FINDINGS: Research developments in ocular allergy summarized in this article include the following findings: (1) ocular epithelial cells play a role in inflammation; (2) respiratory syncytial virus is a pathogen in allergic conjunctivitis; (3) transglutaminase inhibitors reverse allergic related inflammation; (4) eosinophils and neutrophils both play a role in ocular allergy; (5) eotaxin-1 and eotaxin-2 play a role in eosinophilic recruitment; and (6) loteprednol etabonate, desonide phosphate, and cyclosporine have been shown to be effective and safe in the treatment of ocular allergy. SUMMARY: This article summarizes the research conducted for each of the above recent findings and outlines their clinical applications.

a. Allergic and vernal conjunctivitis, iritis, iridocyclitis

REVIEW
Bielory L
Allergic and immunologic disorders of the eye. Part I: Immunology of the eye. .
J Allergy Clin Immunol 2000;106:805-816.
Immuno-ophthalmology evolved during the 20th century as a subspecialty linking ophthalmologists and immunologists. This emerging subspecialty has focused on the use of immunology to better understand and treat ocular disorders. To help the allergist/clinical immunologist better appreciate the growing field of immunoophthalmology, this 2-part review series (Part II: Ocular Allergy will appear in the December issue of the Journal) will provide an overview of the impact that immunology has had on our understanding and treatment of allergic and immunologic eye diseases. The current review will focus on mechanisms by which mast cells, T cells, eosinophils, cytokines, and other inflammatory constituents contribute to the unique features of eye disease and their link to allergic responses that occur in other organs of the body.

REVIEW
Bielory L.
Allergic and immunologic disorders of the eye. Part II: Ocular allergy.
J Allergy Clin Immunol 2000;106:1019-1032.
Allergy affects more than 15% of the world population, and some studies have shown that up 30% of the US population has some form of allergy. Most of these patients have various target organs for their allergies, and most have ocular involvement. The ocular component may be the most prominent and sometimes disabling feature of their allergy. Some are affected for only a few weeks to months, whereas others have symptoms that last throughout the year. The seasonal forms may present to clinical allergists, whereas the more chronic forms may present to ophthalmologists. Thus, in the second of this 2- part review series (Part I: Ocular Immunology appeared in the November issue of the Journal), an overview is provided of the spectrum of ocular allergy that ranges from acute seasonal allergic conjunctivitis to chronic variants of atopic keratoconjunctivitis. With a better understanding of the immunologic mechanisms, we now can develop better treatment approaches and design further research in intervention of allergic eye diseases.

b. Clinical Skills and Eye Examination

REVIEW:
Leibowitz HM.
The red eye.
N Engl J of Med 2000; 343:345-51.

REVIEW:
Cook EB.
Tear cytokines in acute and chronic ocular allergic inflammation.
Current Opinion in Allergy and Clinical Immunology 2004;4:441-445.
PURPOSE OF REVIEW: Elevated levels of inflammatory cytokines have been reported in tears from ocular allergic disease states. The purpose of this review is to assimilate recent research contrasting tear cytokine concentrations in non-allergic subjects versus subjects with acute (seasonal allergic conjunctivitis) and chronic (giant papillary conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis) ocular allergic inflammation to discover whether the cytokine profiles could provide useful insight into disease mechanisms and therapeutic targets. RECENT FINDINGS: Recent studies have revealed distinct differences in the cytokine/chemokine concentrations in tears between the various manifestations of ocular allergy. The acute (seasonal allergic conjunctivitis) and iatrogenic (giant papillary conjunctivitis) forms of ocular allergic inflammation are characterized by an overall lack of significant cytokine changes in tears compared with chronic disease (vernal keratoconjunctivitis, atopic keratoconjunctivitis). Chronic ocular allergic inflammation produces increased concentrations of T helper 1 and 2, and proinflammatory cytokines as well as chemokines. However, vernal and atopic keratoconjunctivitis portray distinct differences in the patterns of tear cytokines/chemokines expressed. SUMMARY: The plethora of increased cytokines and chemokines in vernal and atopic keratoconjunctivitis compared with non-allergic, seasonal allergic conjunctivitis and giant papillary conjunctivitis provides a new perspective into the complex inflammatory processes occurring on the ocular surface in chronic disease. The ability to measure multiple cytokines in tears, combined with knowledge obtained from in-vitro analysis of the individual and combined effects of these cytokines on various conjunctival cells (i.e. mast cells, epithelial cells, fibroblasts) has facilitated further understanding of specific

processes contributing to maintenance of inflammation and progression of vision-threatening disease and paved the way toward new therapeutic targets.

3. Dermatologic Diseases

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.

FRONTIER DEVELOPMENTS:
Leung DY and Boguniewicz M
Advances in allergic skin diseases.
J Allergy Clin Immunol 2003;111:S805-12.
During the past year there have been significant advances in our understanding of the mechanisms underlying allergic skin diseases. This article reviews some of these advances in atopic dermatitis and urticaria. The introduction of a new class of topical anti-inflammatory medications, topical calcineurin inhibitors, has significantly increased our treatment options and led to a rethinking of potential management approaches in atopic dermatitis.

FRONTIER DEVELOPMENTS:
Novak N, Bieber T, Leung DY
Immune mechanisms leading to atopic dermatitis.
J Allergy Clin Immunol 2003;112:S128-39.
The incidence of atopic dermatitis is increasing, and this poses a major burden on health care costs. A precise understanding of the genetic and immunologic mechanisms is crucial for development of effective treatment strategies for atopic dermatitis. Various studies indicate that it has a multifactorial cause, with activation of complex immunologic and inflammatory pathways. The current review will examine recent advances that have been made in our understanding of the genetic and pathophysiologic prerequisites that form the basis of this common recalcitrant skin disorder.

a. Urticaria, angioedema, dermatographia, atopic dermatitis, contact dermatitis, urticaria pigmentosa, bullous disease, drug rash, erythema multiforme and toxic epidermal necrolysis, erythema nodosum, and other immunologic skin 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.

ALTERNATE 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.

REVIEW

Spergel JM and Paller AS
Atopic dermatitis and the atopic march.
J Allergy Clin Immunol 2003;112:S118-27.

Atopic dermatitis (AD), one of the most common skin disorders seen in infants and children, usually has its onset during the first 6 months of life. The prevalence of AD is similar in the United States, Europe, and Japan and is increasing, similar to that of other atopic disorders, particularly asthma. AD has been classified into 3 sequential phases: infantile, childhood, and adult, each with characteristic physical findings. AD has a tremendously negative effect on the quality of life of patients as well as family, most commonly disturbing sleep. The condition also creates a great financial burden for both the family and society. The cutaneous manifestations of atopy often represent the beginning of the atopic march. On the basis of several longitudinal studies, approximately half of AD patients will develop asthma, particularly with severe AD, and two thirds will develop allergic rhinitis. Epicutaneous sensitization has been thought to be responsible, with

subsequent migration of sensitized T cells into the nose and airways, causing upper and lower airway disease. Animal models and human observation concur with this theory. Preliminary prevention studies with oral antihistamines provide evidence that early intervention might slow the atopic march.

REVIEW
Boguniewicz M, Eichenfield LF, Hultsch T
Current management of atopic dermatitis and interruption of the atopic march. . J Allergy Clin Immunol 2003;112:S140-50
Treatment of atopic dermatitis requires a comprehensive approach that includes evaluation of potential triggers and education of the patient and family regarding proper avoidance measures. Hydration of the skin and maintenance of an intact skin barrier remain integral to proper management. Although topical corticosteroids have been a mainstay of anti-inflammatory therapy, the newer topical calcineurin inhibitors offer advantages for treatment of this chronic, relapsing disease. Studies aimed at defining optimal combination therapy and early intervention might change the treatment paradigm for atopic dermatitis.

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.

b. Clinical skills: proper skin examination, patch testing, drug skin testing (immediate and delayed) testing for physical urticaria and an understanding of dermatopathology and immunofluorescent tests.

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.

REVIEW / PRACTICE 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.

REVIEW / PRACTICE GUIDELINE – Drug Hypersensitivity
Joint Task Force on Practice Parameters
Disease Management of Drug Hypersensitivity: A Practice Parameter
Ann Allergy Asthma Immunol 1999;83:S665-700
This document includes recommendations and an algorithm for evaluation of drug hypersensitivity reactions.

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.

4. Lower respiratory tract disease

a. Asthma and related disorders (exercise-induce, allergic bronchopulmonary aspergillosis, sulfiterelated, and intrinsic); 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

REVIEW ASTHMA (PEDIATRIC):
CHIPPS, BRADLEY E. MD; MURPHY, KEVIN R. MD
Assessment and Treatment of Acute Asthma in Children
J Pediatrics 2005;147:288–294
Over the last decade, significant advances in asthma therapy have been made. Yet asthma remains the leading cause of emergency care in children, and hospitalization rates continue to increase. The direct costs of asthma are estimated to exceed 6 billion dollars per annum in the United States alone; 35% to 50% of this expense occurs in the emergency department (ED) and hospital. In 2002, asthma affected approximately 6.1 million children younger than 18 years of age, with an inner-city prevalence of 8.6%. Thus, asthma is a disease that pediatricians can expect to encounter. The ability to effectively treat asthma is therefore essential. This article will discuss the assessment of acute pediatric asthma and we will review recent studies pertaining to its treatment.

REVIEW ASTHMA (MILD):
Bisgaard H. Szefler SJ.
Understanding mild persistent asthma in children: the next frontier.
J Allergy Clin Immunol 2005:115:708-13.
Limitations in asthma prevalence studies and difficulties in diagnosing pediatric asthma lead to uncertainty over the full extent of mild persistent asthma in children and adolescents. Although recent surveys have reported that the majority of pediatric patients with asthma in the United States and Europe have symptoms consistent with mild disease, these surveys have limitations in design. Thus, the true prevalence of mild asthma remains unknown. It is unclear whether children with mild persistent asthma progress to more severe asthma, but the risk of severe asthma exacerbations seems

to be unrelated to the symptom severity. Clinical studies restricted to pediatric patients with mild asthma are limited, but available data do suggest substantial morbidity of mild persistent asthma in this population and support inhaled corticosteroid intervention. There is a need for further investigation into the true prevalence of mild persistent asthma in children and adolescents, and optimal treatment.

REVIEW ASTHMA (SEVERE):
Sally Wenzel
Severe Asthma in Adults
Am J Respir Crit Care Med. 2005;172:149-60
Severe asthma remains poorly understood and frustrating to care for, partly because it is a heterogeneous disease. Patients with severe asthma disproportionately consume health care resources related to asthma. Severe asthma may develop over time, or shortly after onset of the disease. The genetic and environmental elements that may be most important in the development of severe disease are poorly understood, but likely include both allergic and nonallergic elements. Physiologically, these patients often have air trapping, airway collapsibility, and a high degree of methacholine hyperresponsiveness. Specific phenotypes of severe asthma are only beginning to be defined. However, describing severe asthma by age at onset (early- vs. late-onset) appears to describe two phenotypes that differ at immunologic, physiologic, epidemiologic, and pathologic levels. In particular, early-onset severe asthma is a more allergic-associated disease than late-onset severe asthma. In addition, patients with severe asthma can be defined on the basis of presence and type of inflammation. Severe asthma with persistent eosinophilia (of either early or late onset) is more symptomatic and has more near-fatal events. However, at least 50% of patients with severe asthma have very little identifiable inflammation. Thus, "steroid resistance" may occur at numerous levels, not all of which are caused by a lack of effect of steroids on inflammation. Treatment remains problematic, with corticosteroids remaining the most effective therapy. However, 5-lipoxygenase inhibitors, anti-IgE, and immunomodulatory drugs are also likely to have a place in treatment. Improving therapy in this disease will require a better understanding of the phenotypes involved.

REVIEW NOCTURNAL ASTHMA:
E. Rand Sutherland
Nocturnal Asthma
J Allergy Clin Immunol 2005;116:1179-1186
Nocturnal symptoms and overnight decrements in lung function are a common part of the asthma clinical syndrome. As many as 75% of asthmatic subjects are awakened by asthma symptoms at least once per week, with approximately 40% experiencing nocturnal symptoms on a nightly basis. An extensive body of research has demonstrated that nocturnal symptoms of cough and dyspnea are accompanied by circadian variations in airway inflammation and physiologic variables, including airflow limitation and airways hyperresponsiveness. Alterations in β_2-adrenergic and glucocorticoid receptors and hypothalamic-pituitary-adrenal axis function might play a role in modulating the nocturnal asthma phenotype, and recent studies have suggested that melatonin, a neurohormonal controller of circadian rhythms, might be important as well. Treatment strategies in nocturnal asthma are similar to those used in persistent asthma, although dosing of medications to target optimum effect during periods of nocturnal worsening is beneficial.

PRACTICE PARAMETER / GUIDELINE (ASTHMA):
NAEPP expert panel report 2
Guidelines for the Diagnosis and Management of Asthma
NIH Publication 97-4051, July 1997
www.nhlbi.nih.gov/guidelines/asthma/index.htm

PRACTICE PARAMETER / GUIDELINE (ASTHMA UPDATE):
NAEPP expert panel report
Guidelines for the Diagnosis and Management of Asthma-Update on Selected Topics- 2002
NIH Publication 02-5075, June 2002
www.nhlbi.nih.gov/guidelines/asthma/index.htm

PRACTICE PARAMETER / GUIDELINE (PEDIATRIC ASTHMA):
AAAAI / NAEPP Inititative
Pediatric Asthma: Promoting Best Practices
Web Publication at
www.aaaai.org/members/resources/initiatives/pediatricasthma.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/index.htm

REVIEW EXERCISE INDUCED ASTHMA:
Storms WW.
Asthma associated with exercise.
Immunol Allergy Clin North Am. 2005;25:31-43.
Exercise is a potent stimulus to asthma. The diagnosis is not always straightforward, and health care providers should have a high index of suspicion. Treatment usually controls exercise-induced asthma but usually requires therapy tailored for each individual patient.

REVIEW VIRAL INDUCED ASTHMA:
Gern JE. Rosenthal LA. Sorkness RL. Lemanske RF Jr.
Effects of viral respiratory infections on lung development and childhood asthma.
J Alergy Clinical Immunol 2005;115-668-674.
Viral infections are closely linked to wheezing in infancy, and those children with recurrent virus-induced wheezing episodes are at great risk for chronic childhood asthma. Infancy is a time of increased susceptibility to viral infections, and this stage is also characterized by pulmonary alveolar multiplication and extensive remodeling of the airways to accommodate growth. This coincidence, together with the observation that children with asthma can have structural lung changes and functional deficits at an early age, suggests that viral infections could adversely affect lung development. Inflammatory mediators induced by viral infection are known to have effects on the remodeling process, suggesting a plausible mechanism to support this theory. Furthermore, animal models of viral infection during lung growth and development suggest that developmental factors are important in determining the consequences of infection on long-term lung function.

Greater understanding of the effects of viral infections on lung development and growth in early childhood might lead to the discovery of additional strategies for the prevention of recurrent wheezing and chronic asthma.

REVIEW OCCUPATIONAL ASTHMA:
Mapp CE, Boschetto P, Maestrelli P, Fabbri LM.
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.

REVIEW ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS:
Greenberger PA.
Allergic bronchopulmonary aspergillosis
J Allergy Clin Immunol 2002;110:685-92
Allergic bronchopulmonary aspergillosis (ABPA) complicates asthma and cystic fibrosis. The survival factors in Aspergillus fumigatus that support saprophytic growth in bronchial mucus are not understood. Prednisone remains the most definitive treatment but need not be administered indefinitely. MHC II -restricted CD4(+) T(H)2 clones have been derived from patients with ABPA. The total serum IgE concentration is elevated sharply but is "nonspecific. " IgE serum isotypic antibodies to A fumigatus are useful in diagnosis; this is in contrast to the situation for patients with asthma without ABPA. High-resolution computed tomography of the chest demonstrates multiple areas of bronchiectasis in most patients with ABPA and is a useful radiologic tool. Some asthma control patients might have a few bronchiectatic airways, but not to the extent seen in or of the same character as those in ABPA. This review discusses clinical, radiologic, investigational, pathogenetic, and treatment issues of ABPA.

ABPA TREATMENT TRIAL:
Stevens D. A., Schwartz H. J., Lee J. Y.,et al
A Randomized Trial of Itraconazole in Allergic Bronchopulmonary Aspergillosis
N Engl J Med 2000; 342:756-762
Background Allergic bronchopulmonary aspergillosis is a hypersensitivity disorder that can progress from an acute phase to chronic disease. The main treatment is systemic corticosteroids, but data from uncontrolled studies suggest that itraconazole, an orally administered antifungal agent, may be an effective adjunctive therapy. Methods We conducted a randomized, double-blind trial of treatment with either 200 mg of itraconazole twice daily or placebo for 16 weeks in patients who met immunologic and pulmonary-function criteria for corticosteroid-dependent allergic

bronchopulmonary aspergillosis. A response was defined as a reduction of at least 50 percent in the corticosteroid dose, a decrease of at least 25 percent in the serum IgE concentration, and one of the following: an improvement of at least 25 percent in exercise tolerance or pulmonary-function tests or resolution or absence of pulmonary infiltrates. In a second, open-label part of the trial, all the patients received 200 mg of itraconazole per day for 16 weeks.
Results There were responses in 13 of 28 patients in the itraconazole group (46 percent), as compared with 5 of 27 patients in the placebo group (19 percent, P=0.04). The rate of adverse events was similar in the two groups. In the subsequent open-label phase, 12 of the 33 patients who had not had a response during the double-blind phase (36 percent) had responses, and none of the patients who had a response in the double-blind phase of the trial had a relapse.
Conclusions For patients with corticosteroid-dependent allergic bronchopulmonary aspergillosis, the addition of itraconazole can lead to improvement in the condition without added toxicity.

REVIEW HYPERSENSITIVITY PNEUMONITIS
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.

REVIEW HYPERSENSITIVITY PNEUMONITIS:
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.

REVIEW COPD DIAGNOSIS:

Pauwels RA. Rabe KF.

Burden and clinical features of chronic obstructive pulmonary disease

Lancet 2004;364:613-20

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality and represents a substantial economic and social burden throughout the world. It is the fifth leading cause of death worldwide and further increases in its prevalence and mortality are expected in the coming decades. The substantial morbidity associated with COPD is often underestimated by health-care providers and patients; likewise, COPD is frequently underdiagnosed and undertreated. COPD develops earlier in life than is usually believed. Tobacco smoking is by far the major risk for COPD and the prevalence of the disease in different countries is related to rates of smoking and time of introduction of cigarette smoking. Contribution of occupational risk factors is quite small, but may vary depending on a country's level of economic development. Severe deficiency for alpha-1-antitrypsin is rare and the impact of other genetic factors on the prevalence of COPD has not been established. COPD should be considered in any patient presenting with cough, sputum production, or dyspnoea, especially if an exposure to risk factors for the disease has been present. Clinical diagnosis needs to be confirmed by standardised spirometric tests in the presence of not-fully-reversible airflow limitation. COPD is generally a progressive disease. Continued exposure to noxious agents promotes a more rapid decline in lung function and increases the risk for repeated exacerbations. Smoking cessation is the only intervention shown to slow the decline. If exposure is stopped, the disease may still progress due to the decline in lung function that normally occurs with aging, and some persistence of the inflammatory response.

REVIEW COPD TREATMENT:

Sutherland ER.

Outpatient treatment of chronic obstructive pulmonary disease: comparisons with asthma.

J Allergy Clin Immunol 2004;114:715-24.

Chronic obstructive pulmonary disease (COPD) is a progressive syndrome of expiratory airflow limitation caused by chronic inflammation of the airways and lung parenchyma. The airway inflammatory response in COPD is initiated by smoking in the overwhelming majority of cases, and chronic exposure to cigarette smoke initiates a series of events that cause damage to central airways, peripheral airways, and terminal airspaces, leading to physiologic and clinical abnormalities. The contrasting inflammatory phenotypes of asthma and COPD have important implications for clinical and physiologic manifestations of disease, as well as for therapy. The outpatient treatment of COPD

differs from the approach used in asthma and can be divided into 3 subgroups: health care maintenance, drug therapy, and nondrug therapy. Smoking cessation, regular spirometry, and immunization are important components of health care maintenance. Drug therapy consists of optimal bronchodilator therapy supplemented, when necessary, with either inhaled corticosteroids or theophylline. Nondrug therapies include pulmonary rehabilitation, supplemental oxygen, and surgery.

PRACTICE PARAMETER / GUIDELINE (COPD)
Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. 2005 Update
available at www.goldcopd.com

REVIEW:IMMOTILE CILIA
Cowan MJ. Gladwin MT. Shelhamer JH
Disorders of ciliary motility
Am J Medical Sci 2001;321:3-10.
Clearance of mucus and other debris from the airways is achieved by 3 main mechanisms: mucociliary activity, coughing, and alveolar clearance. Disorders of ciliary structure or function results in impaired clearance, and result in chronic sinopulmonary disease manifested as chronic sinusitis, otitis media, nasal polyposis, and ultimately bronchiectasis. In addition, situs inversus, dextrocardia, and infertility can be associated with dysfunctional ciliary activity. The term primary ciliary dyskinesia has been proposed for the spectrum of these diseases. The term Kartagener syndrome applies to this syndrome when accompanied by infertility and dextrocardia or situs inversus. The more common types of ciliary dysmotility syndromes are characterized by missing dynein arms, central microtubule pairs, inner sheath, radial spokes, or nexin links. In addition to structural defects within the cilia, disordered ciliary beating and disordered ciliary arrays on epithelial cell surfaces have been described in this syndrome. Treatment includes rigorous lung physiotherapy, prophylactic and organism-specific antibiotics, and immunization against common pulmonary pathogens. Late stages of the disease may require surgical intervention for ronchiectasis or lung transplant for end-stage lung disease.

REVIEW:SARCOIDOSIS
Cox CE. Davis-Allen A. Judson MA
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.

REVIEW:CYSTIC FIBROSIS

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.

REVIEW:CYSTIC FIBROSIS

Berger M

Inflammatory mediators in cystic fibrosis lung disease

Allergy Asthma Proc. 2002;23:19-25

Cystic fibrosis (CF) is a complex multisystem disorder caused by mutations in a membrane glycoprotein called the CF transmembrane regulator (CFTR), which has as its major function serving as a Cl- channel. The relationship between defects in CFTR and development of lung disease remains incompletely understood. Chronic lung disease, characterized by persistent infection with a peculiar type of Pseudomonas aeruginosa, bronchiectasis, and airway obstruction is the major cause of morbidity and mortality in CF patients. The inflammatory response to the chronic infection resembles that induced by lipopolysaccharide (LPS) and is mediated primarily by cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, and IL-8, whose synthesis is activated by the transcription factor nuclear factor kappa B (NF-kappa B). Large numbers of neutrophils dominate the inflammatory response and excessive concentrations of their products create a vicious cycle that becomes injurious rather than protective and eventually claims the life of the patient.

REVIEW: CHRONIC COUGH

Irwin RS. Madison JM.

The persistently troublesome cough

Am J Respir Crit Care Med 2002 16511:1469-74.

The focus of this commentary is on the management of the adult immunocompetent patient who has a persistently troublesome cough for a duration of at least 2 months. Because, by definition, the so-called postinfectious cough resolves spontaneously within 2 months, that diagnosis is not considered herein. However, when a respiratory infection precedes the development of chronic cough, it is presumed that the infection led to or exacerbated other conditions commonly causing chronic cough, such as postnasal drip syndrome, symptomatic asthma, and GERD.

b. Specific skills and interpretative strategies to be acquired: chest exam, interpretation of pulmonary function testing, bronchial challenges, sputum and exhaled breath analysis, and gross interpretation of imaging studies.

REVIEW PFT INTERPRETATION:

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-based 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.

REVIEW BRONCHIAL CHALLENGE:

Tan RA. Spector SL.
Provocation studies in the diagnosis of occupational asthma.
Immunol Allergy Clin of North Am. 2003;23:251-67.

Specific and nonspecific provocation studies, although not always essential for diagnosing OA, help confirm the diagnosis and identify the offending agent. Nonspecific bronchial challenge testing is used to detect airway hyperresponsiveness and to clarify the nature of the patient's symptoms. Pharmacologic bronchoconstrictor agents (eg, methacholine, histamine) most commonly are used for the challenge, but nonisotonic aerosols, exercise and hyperventilation also can show airway hyperresponsiveness. Nonspecific challenges usually are done in the laboratory, but can be done at the workplace if emergency equipment is available. A comparison of results obtained at and away from the workplace (at least 1 week apart) may be helpful in diagnosing OA. Specific bronchial challenge testing is considered the gold standard for OA diagnosis. It can be crucial in helping physicians, employers, and employees make decisions about continued employment, compensation, career changes, and treatment. Testing can pinpoint new industrial agents that cause OA, enabling dissemination of information on its hazards to the public and within the industry. The nature of the agent determines the type of protocol that is used for testing. Agents can be in the form of dusts, powders, aerosols, vapors gases, and animal dander. Exposure can be as simple as having patients simulate their work activities, or as complicated as using special challenge chambers with controlled environments and precise delivery of agents. Performing control challenges with a component that is separate from the test agent is essential to avoid false-positive results. The timing, duration, and dosing of exposure depend on the type of reaction that has been experienced previously, the nature of the agent, and the patient's baseline airway hyperresponsiveness. Serial spirometry and observation often are done for up to 8 hours to monitor early and late reactions. SBC testing should be performed in the proper medical setting in which emergency equipment available and should be administered only by healthcare personnel who are trained and experienced in the procedures. Safety of the patient is the primary consideration.

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: SPUTUM ANALYSIS IN ASTHMA

Kim CK. Hagan JB
Sputum tests in the diagnosis and monitoring of asthma.
Ann Allergy Asthma Immunol 2004; 93:112-22.

OBJECTIVE: To review the techniques of sputum analysis with relevance to the diagnosis and monitoring of asthma. DATA SOURCES: MEDLINE databases were searched to identify all publications involving sputum studies related to the diagnosis and treatment of asthma from 1990 to October 2003. We also used internal reference files related to sputum and searched bibliographies of relevant articles. The review was limited to human data in English-language publications. STUDY SELECTION: Studies were selected by the expert opinions of the authors for quality and relevance to the evaluation of asthmatic inflammation by induced sputum. RESULTS: During the past 10 years, there have been an increasing number of publications concerning the diagnosis and treatment of asthma using sputum analysis. Analysis of induced sputum provides similar data to secretions obtained through bronchial wash, bronchoalveolar lavage, and, to some extent, bronchial biopsy. The techniques of cellular counting and immunochemical analysis are described along with potential problems and pitfalls of these methods. Clinical application of sputum analysis is discussed as it pertains to the diagnosis and monitoring of asthma and asthma-related conditions. CONCLUSIONS: Analysis of induced sputum is increasingly being considered as a noninvasive means of evaluating airway inflammation and may provide useful information with regard to the diagnosis and monitoring of asthma in select individuals.

REVIEW 1:EXHALED BREATH CONDENSATE

Hunt J.
Exhaled breath condensate: an evolving tool for noninvasive evaluation of lung disease.
J Allergy Clin Immunol 2002;110:28-34.

Exhaled breath condensate (EBC) contains aerosolized airway lining fluid and volatile compounds that provide noninvasive indications of ongoing biochemical and inflammatory activities in the lung. Rapid increase in interest in EBC has resulted from the recognition that in lung disease this easily sampled fluid has measurable characteristics that differ prominently from health. These assays have provided evidence of airway and lung redox deviation, acid-base status, and degree and type of inflammation in acute and chronic asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, occupational diseases, and cystic fibrosis. Characterized by uncertain and variable degrees of dilution, EBC does not provide precise assessment of individual solute concentrations within native airway lining fluid. However, it can provide useful information when concentrations differ substantially between health and disease or are based on ratios of solutes found in the sample. Because they can be used to measure the targets of modern therapy, EBC assays are likely to become integral components of future clinical studies, and after further technical work is accomplished, they might be used to diagnose and monitor therapy in individual patients.

REVIEW :EXHALED BREATH CONDENSATE

Liu J. Thomas PS.

Exhaled breath condensate as a method of sampling airway nitric oxide and other markers of inflammation.

Med Sci Monit. 2005;11:MT53-62.

Most of the methods of investigating lung diseases have been invasive until the discovery that exhaled nitric oxide can be used as a surrogate marker of airway inflammation, particularly in asthma. Exhaled nitric oxide (NO) is now established as a marker of airway inflammation. It has been shown to correlate well with eosinophilic asthmatic airway inflammation, and to be able to predict decline in asthma control and airway function. Altered levels of NO are also associated with other inflammatory lung diseases. In addition, polymorphisms of the genes encoding the three nitric oxide synthases are associated with phenotypic differences associated with lung diseases. Exhaled NO is, however, non-specific. It is therefore of importance that collecting exhaled breath condensate (EBC) has emerged as a potential tool in the study of pulmonary diseases. The exhaled breath is collected in a cooling system which allows water vapour to condense. The EBC contains a number of mediators relating to the NO pathway, including nitrite as a metabolite of nitric oxide, nitrotyrosine, nitrosothiols plus small molecular mediators associated with oxidative stress, including hydrogen ions, and hydrogen peroxide. In addition, reports are emerging of the detection of larger molecules which not only include leukotrienes, prostaglandins, albumin and other proteins, such as cytokines, but also macromolecules, for example, DNA. EBC is becoming a technique which will allow repeated non-invasive sampling from the respiratory tract thus assisting pulmonary research and possibly the monitoring of lung diseases.

REVIEW : EXHALED NITRIC OXIDE

Bates CA. Silkoff PE.

Exhaled nitric oxide in asthma: from bench to bedside.

J Allergy Clin Immunol 2003;111(2):256-62.

With more than 600 publications, exhaled nitric oxide (NO) has been extensively investigated as a noninvasive marker of airway inflammation in a research setting. This clinical rostrum presents a synopsis of the latest research about this novel marker in asthma and suggests how it might move from bench to bedside. Specifically, we review the evidence citing the applicability of exhaled NO in diagnosing asthma, monitoring the response to therapy, evaluating current symptom control, and predicting exacerbations of asthma. These studies support a role for exhaled NO in the evaluation and treatment of asthma in the clinical arena.

REVIEW : EXHALED NITRIC OXIDE

Smith AD. Taylor DR

Is exhaled nitric oxide measurement a useful clinical test in asthma?

Curr Opin Allergy Clin Immunol.2005:5:49-56

PURPOSE OF REVIEW: Exhaled nitric oxide measurements (FENO) are easy to perform and are repeatable. Given the strong correlations between FENO and bronchial biopsy and induced sputum eosinophilia, as well as airway hyper-responsiveness, FENO may now be advocated as a surrogate for these tests in certain circumstances. They provide the opportunity to assess pathological rather than physiological changes in asthma. This review highlights recent advances in applying this technology to the diagnosis and ongoing assessment of asthma in the clinical and epidemiological settings. RECENT FINDINGS: Epidemiological data confirm that whereas FENO measurements reflect the presence and severity of airway inflammation, levels do not correlate strongly with symptoms or lung function abnormalities. Although reference values and thresholds for an

abnormal test still need to be agreed internationally, there are now sufficient data for clinicians to use the test meaningfully in clinical practice. Studies confirm the relatively high diagnostic accuracy of FENO measurements compared with conventional tests to distinguish asthma from nonasthma. Further, dose-response relationships for changes in FENO with inhaled steroids have been confirmed, and provide the basis for using FENO to assess asthma control and, potentially, to determine anti-inflammatory treatment requirements. SUMMARY: The measurement of FENO is evolving to provide a complementary role alongside existing pulmonary function tests. Further work is required to establish reference values and possibly prediction equations in relation to age and height. Its role in determining optimum steroid requirements in chronic asthma and to identify steroid responsiveness in chronic obstructive pulmonary disease are two important areas for future research.

5. Drug Allergy (also see dermatologic disorders and anaphylaxis)

REVIEW / PRACTICE GUIDELINE – Drug Hypersensitivity
Joint Task Force on Practice Parameters
Disease Management of Drug Hypersensitivity: A Practice Parameter
Ann Allergy Asthma Immunol 1999;83:S665-700
This document includes recommendations and an algorithm for evaluation of drug hypersensitivity reactions.

REVIEW:
Gruchalla RS
Clinical assessment of drug-induced disease. Lancet 2000;356:1505-11
Physicians are often confronted with patients who state that they are “allergic” to a drug or drugs. Knowing which medications can be prescribed safely is therefore difficult, and care of such patients frustrating. The goal of this review is to help physicians develop management plans for patients who present with drug-induced diseases. It provides information that allows physicians to differentiate between reactions that are truly allergic in nature and those that are not immunologically mediated. Relevant information on medical history, physical findings, and laboratory tests that may be helpful in the assessment are discussed, and guidance is provided on when and if a drug may be safely readministered. Unfortunately, however, until we are able to better understand the mechanisms responsible for drug-induced reactions, our management tools will remain limited.

LANDMARK PUBLICATION:
Brown BC, Price EV, Moore MD
Penicilloyl-polylysine as an intradermal test of penicillin sensitivity. JAMA 1964;189:599-604.

RESEARCH FRONTIER:

Merk HF

Diagnosis of drug hypersensitivity: lymphocyte transformation test and cytokines.
Toxicology 2005;209:217-220.

For all types of allergic reactions including immediate type of reactions, types II and III reactions as well as delayed-type reactions the recognition of the antigen by specifically sensitized T-lymphocytes is a prerequisite. Evidences for the key role of T-lymphocytes in the pathophysiology of allergic drug reactions are positive patch test reactions and the LTT. The proliferative response that can be measured by means of the incorporation of 3H-thymidine during DNA synthesis can be expressed as stimulation index (SI) which is the relation between the cell proliferation with antigen compared without antigen. In addition drug-specific activation of PBMC consistently resulted in IL-5 expression and secretion. The sensitivity of the LTT for the detection of drug sensitization could be improved up to 92% by the measurement of released interleukin-5. The expression and secretion of other cytokines such as IFN-gamma and IL-10 was less consistently and had a diagnostic sensitivity of 36 and 50%, respectively. Microarrays are a promising new technical platform to look for better markers which can be used as a read out in the LTT and other similar assays and to study pharmacological interactions between drugs including cytokines such as interferons and the immune system.

REVIEW :

Pichler WJ, Tilch J

The lymphocyte transformation test in the diagnosis of drug hypersensitivity.
Allergy 2004;59:809-820

Diagnosis of drug hypersensitivity is difficult, as an enormous amount of different drugs can elicit various immune-mediated diseases with distinct pathomechanism. The lymphocyte transformation test (LTT) measures the proliferation of T cells to a drug in vitro--from which one concludes to a previous in vivo reaction due to a sensitization. This concept of the LTT has been confirmed by the generation of drug-specific T-cell clones and the finding that drugs can directly interact with the T-cell receptor, without previous metabolism or need to bind to proteins. In this review, technical aspects and usefulness of this test for the diagnosis of drug hypersensitivity are discussed. The main advantage of this test is its applicability with many different drugs in different immune reactions, as drug-specific T cell are almost always involved in drug hypersensitivity reactions. Its main disadvantages are that an in vitro proliferation of T cells to a drug is difficult to transfer to the clinical situation and that the test per se is rather cumbersome and technically demanding. In addition, its sensitivity is limited (for beta-lactam allergy it is in the range of 60-70%), - although at least in our hands - it is higher than of other tests for drug hypersensitivity diagnosis. Consequently, drug hypersensitivity diagnosis needs to rely on a combination of history and different tests, as none of the single tests available has per se a sufficiently good sensitivity. Within this setting, the LTT has proven to be a useful test for the diagnosis of drug hypersensitivity reactions and helped to better understand these reactions. Further work on the simplification of this test and systematic evaluation of its sensitivity and specificity in some main groups of drugs are necessary to make this test more widely available.

a. Distinction between hypersensitivity and intolerance

REVIEW:
Park BK, Naisbitt DJ, Gordon SF, Kitteringham, NR, Pirmohamed
Metabolic activation in drug allergies.
Toxicology 2001;158:11-23.
Drug allergies are a major problem in the clinic and during drug development. At the present time, it is not possible to predict the potential of a new chemical entity to produce an allergic reaction (hypersensitivity) in patients in preclinical development. Such adverse reactions, because of their idiosyncratic nature, only become apparent once the drug has been licensed. Our present chemical understanding of drug hypersensitivity is based on the hapten hypothesis, in which covalent binding of the drug (metabolite) plays a central role in drug immunogenicity and antigenicity. If this theory is correct, then it should be possible to develop in vitro systems to assess the potential of drugs to bind to critical proteins, either directly or indirectly after metabolic activation to protein-reactive metabolites (bioactivation) and initiate hypersensitivity. The purpose of this review is to assess critically the evidence to support the hapten mechanism, and also to consider alternative mechanisms by which drugs cause idiosyncratic toxicity.

b. Cytotoxic, immune complex and delayed hypersensitivity reactions

REVIEW:
Pichler WJ
Immune mechanism of drug hypersensitivity.
Immunol Allergy Clin N Am 2004;24:373-397.
Drug hypersensitivity reactions can lead to a great variety of different diseases. The main cause is a specific interaction of antibodies or T cells with a drug. In addition to the hapten concept, some drugs can bind directly to T-cell receptors and stimulate them. Based on recent investigation on different exanthemas, an extended classification of the Gell and Coombs type IV reaction is proposed.

c. Aspirin and NSAID reactions

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.

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:

Gollapudi RR, Teirstein PS, Stevenson DD, et al.

Aspirin Sensitivity: Implications for Patients with Coronary Artery Disease

JAMA 2004;292:3017-3023

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.

d. 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.

e. 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 :
Johnson DH, Cunha BA
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.

f. Clinical skills – specific testing and provocative challenges

REVIEW:
Aberer W, Bircher A, Romano A, Bianca M, Campi P et al.
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 :
Demoly P.
Anaphylactic reactions—value of skin and provocation tests.
Toxicology 2005;209:221-3.
Drug hypersensitivity reactions are a daily worry for the clinicians, in particular anaphylactic reactions. The tools allowing a definite diagnosis are few and poorly validated. They include a thorough clinical history, standardized skin tests, reliable biological tests, and sometimes drug provocation tests. These tools are currently being evaluated by the European Network of Drug Allergy, under the aegis of the EAACI drug hypersensitivity group of interest.

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.

6. Adverse reactions to ingestants

REVIEW:
Sampson HA
Update on food allergy
J Allergy Clin Immunol 2004;113:805-19.
Tremendous progress has been made in our understanding of food-based allergic disorders over the past 5 years. Recent epidemiologic studies suggest that nearly 4% of Americans are afflicted with food allergies, a prevalence much higher than appreciated in the past. In addition, the prevalence of peanut allergy was found to have doubled in American children less than 5 years of age in the past 5 years. Many food allergens have been characterized at the molecular level, which has contributed to our increased understanding of the immunopathogenesis of many allergic disorders and might soon lead to novel diagnostic and immunotherapeutic approaches. The management of food allergies continues to consist of educating patients on how to avoid relevant allergens, to recognize early symptoms of an allergic reaction in case of an accidental ingestion, and to initiate the appropriate emergency therapy. However, the recent successful clinical trial of anti-IgE therapy in patients with peanut allergy and the number of immunomodulatory therapies in the pipeline provide real hope that we will soon be able to treat patients with food allergy

LANDMARK PUBLICATION:
Sampson H. A., Jolie P. L.
Increased plasma histamine concentrations after food challenges in children with atopic dermatitis
N Engl J Med 1984;311:372-376.
Thirty-three patients with atopic dermatitis underwent double-blind placebo-controlled food challenges for evaluation of the role of histamine in hypersensitivity to food. After suspect foods were eliminated for 10 days, oral challenges were performed with up to 8 g of dehydrated food. A total of 35 positive challenges elicited symptoms that were cutaneous (31), gastrointestinal (17), nasal (8), and respiratory (6) within 10 to 90 minutes. Forty-one food challenges were negative, and all 60 placebo challenges were negative. Only the group of patients with positive food challenges had a significant mean (+/- S.E.M.) rise in the plasma histamine concentration, from 296 +/- 80 pg per milliliter before challenge to 1055 +/- 356 after challenge (P less than 0.001). Rises in plasma histamine that were seen after these positive oral food challenges implicate mast-cell or basophil mediators in the pathogenesis of food allergy, including cutaneous changes in patients with atopic dermatitis.

RESEARCH FRONTIER

Smith DW. Nagler-Anderson C

Preventing intolerance: the induction of nonresponsiveness to dietary and microbial antigens in the intestinal mucosa.

J Immunol 2005;174:3851-7.

The gut-associated lymphoid tissue (GALT) is constantly exposed to a variety of Ags and must therefore decipher a large number of distinct signals at all times. Responding correctly to each set of signals is crucial. When the GALT receives signals from the intestinal flora or food Ags, it must induce a state of nonresponsiveness (mucosal tolerance). In contrast, when pathogenic bacteria invade the intestinal mucosa, it is necessary to elicit strong T and B cell responses. The GALT is therefore in the position of constantly fighting intolerance to food and the commensal flora while effectively battling infectious microbes. Determining precisely which type of response to generate in each case is key to the prevention of immune dysregulation and tissue damage.

RESEARCH FRONTIER

Leung DY, Sampson HA, Yunginger JW et al.

Effect of anti-IgE therapy in patients with peanut allergy

N Engl J Med. 2003;348:986-93

BACKGROUND: Peanut-induced anaphylaxis is an IgE-mediated condition that is estimated to affect 1.5 million people and cause 50 to 100 deaths per year in the United States. TNX-901 is a humanized IgG1 monoclonal antibody against IgE that recognizes and masks an epitope in the CH3 region of IgE responsible for binding to the highaffinity Fc(epsilon) receptor on mast cells and basophils. METHODS: We conducted a double-blind, randomized, dose-ranging trial in 84 patients with a history of immediate hypersensitivity to peanut. Hypersensitivity was confirmed and the threshold dose of encapsulated peanut flour established by a double-blind, placebo-controlled oral food challenge at screening. Patients were randomly assigned in a 3:1 ratio to receive either TNX-901 (150, 300, or 450 mg) or placebo subcutaneously every four weeks for four doses. The patients underwent a final oral food challenge within two to four weeks after the fourth dose. RESULTS: From a mean base-line threshold of sensitivity of 178 to 436 mg of peanut flour in the various groups, the mean increases in the oral-food-challenge threshold were 710 mg in the placebo group, 913 mg in the group given 150 mg of TNX- 901, 1650 mg in the group given 300 mg of TNX-901, and 2627 mg in the group given 450 mg of TNX-901 ($P<0.001$ for the comparison of the 450-mg dose with placebo, and P for trend with increasing dose <0.001). TNX-901 was well tolerated. CONCLUSIONS: A 450-mg dose of TNX-901 significantly and substantially increased the threshold of sensitivity to peanut on oral food challenge from a level equal to approximately half a peanut (178 mg) to one equal to almost nine peanuts (2805 mg), an effect that should translate into protection against most unintended ingestions of peanuts.

RESEARCH FRONTIER

Nordlee JA, Taylor SL, Townsend JA

Identification of a Brazil-nut allergen in transgenic soybeans

N Engl J Med. 1996;14;334:688-92

BACKGROUND. The nutritional quality of soybeans (Glycine max) is compromised by a relative deficiency of methionine in the protein fraction of the seeds. To improve the nutritional quality, methionine-rich 2S albumin from the Brazil nut (Betholletia excelsa) has been introduced into transgenic soybeans. Since the Brazil nut is a known allergenic food, we assessed the allergenicity of the 2S albumin. METHODS. The ability of proteins in transgenic and non-transgenic soybeans,

Brazil nuts, and purified 2S albumin to bind to IgE in serum from subjects allergic to Brazil nuts was determined by radioallergosorbent tests (4 subjects) and sodium dodecyl sulfate-polyacrylamide-gel electrophoresis (9 subjects) with immunoblotting and autoradiography. Three subjects also underwent skin-prick testing with extracts of soybean, transgenic soybean, and Brazil nut. RESULTS. On radioallergosorbent testing of pooled serum from four subjects allergic to Brazil nuts, protein extracts of transgenic soybean inhibited binding of IgE to Brazil-nut proteins. On immunoblotting, serum IgE from eight of nine subjects bound to purified 2S albumin from the Brazil nut and the transgenic soybean. On skin-prick testing, three subjects had positive reactions to extracts of Brazil nut and transgenic soybean and negative reactions to soybean extract. CONCLUSIONS. The 2S albumin is probably a major Brazil-nut allergen, and the transgenic soybeans analyzed in this study contain this protein. Our study show that an allergen from a food known to be allergenic can be transferred into another food by genetic engineering.

a. Food sensitivities-IgE mediated, food intolerance, gluten sensitivity

REVIEW / PRACTICE GUIDELINE – Food Allergy
Chapman JA, Bernstein IL, Lee RE, et al
Food allergy: a practice parameter
Ann Allergy Asthma Immunol 2006;96:S1-68
Food allergy, as defined for the purposes of this document, is a condition caused by an IgE-mediated reaction to a food substance. Adverse reactions to foods may also occur due to non–IgE-mediated immunologic and nonimmunologic mechanisms. Representing an important subset of all adverse food reactions, food allergy is often misunderstood. However, because of important new scientific information, its evaluation and management have changed substantially in recent years. The prevalence of potentially life-threatening food allergy to peanuts and tree nuts is increasing. This has resulted in anincreased awareness among the general public, leading to policy changes in schools, eating establishments, and the airline industry. At the same time, diagnostic evaluation in more sophisticated and more challenging. The objective of Food Allergy: A Practice Parameter is to improve the care of patients by providing the practicing physician with an evidence- based approach to the diagnosis and management of IgE-mediated (allergic) food reactions. The Task Force recognizes the importance of non–IgE-mediated immunologic and nonimmunologic food reactions and the role of the allergist-immunologist in their identification and management.

REVIEW
Scurlock AM. Lee LA. Burks AW
Food allergy in children
Immunol Allergy Clin N Amer 2005;25:369-88
Food allergic reactions have generated increasing concern in the United States, with approximately one fourth of American households altering their dietary habits because a member of the family is perceived to suffer from food allergies. IgE-mediated (type I) hypersensitivity accounts for most well-characterized food allergic reactions, although non-IgE-mediated immune mechanisms are believed to be responsible for a variety of hypersensitivity disorders. This article examines adverse food reactions that are IgEmediated, non-IgE-mediated, and those entities that have characteristics of both.

REVIEW
Dewar DH. Ciclitira PJ.
Clinical features and diagnosis of celiac disease
Gastroenterology 2005;128:S19-24.
Celiac disease is a chronic enteropathy caused by intolerance to gluten. The true prevalence of this condition is much greater than previously recognized, with increasing numbers of silent cases being diagnosed. Population-based studies, using serologic screening, have indicated that the prevalence of celiac disease in Caucasian populations is .5%-1%. The pattern of incidence is changing, with a greater proportion of cases diagnosed later in adulthood. The pathologic lesion is characterized by a flattened small intestinal mucosa with a lymphocytic infiltrate, crypt hyperplasia, and villous atrophy. Absorptive function may be impaired and patients can experience gastrointestinal symptoms and malabsorption leading to development of anemia, osteoporosis, or other complications. Untreated celiac disease is associated with significant morbidity and increased mortality, largely owing to the development of enteropathy-associated intestinal lymphoma. The pathologic changes and symptoms resolve when gluten is excluded from the diet for a sustained period.

b. Food-additive reactions

REVIEW:
Simon RA
Adverse reactions to food additives
Curr Aller Asthma Reports 2003:62-6
There are thousands of additives used by the food industry for a variety of purposes in the foods we eat. However, only a small number have been implicated in causing adverse reactions in humans. Although there are reported cases of individuals who have reactions to single additives, most of the medical literature involves patients with asthma or chronic idiopathic urticaria/angioedema whose conditions are exacerbated after ingestion of food additives. Many of these reports are characterized by poorly controlled challenge procedures. Recent studies performed under properly controlled conditions imply that sensitivity to food additives in patients with chronic urticaria/angioedema is very uncommon.

REVIEW
Spergel JM. Fiedler J.
Food allergy and additives: triggers in asthma
Immunol Allergy Clin N Am 2005;25149-67
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:

Rothenberg M

Eosinophilic gastrointestinal disorders

J Allergy Clin Immunol 2004;113:11-28

Primary eosinophilic gastrointestinal disorders are defined as disorders that selectively affect the gastrointestinal tract with eosinophil-rich inflammation in the absence of known causes for eosinophilia (eg, drug reactions, parasitic infections, and malignancy). These disorders include eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis and are occurring with increasing frequency. Significant progress has been made in elucidating that eosinophils are integral members of the gastrointestinal mucosal immune system and that eosinophilic gastrointestinal disorders are primarily polygenic allergic disorders that involve mechanisms that fall between pure IgE-mediated and delayed TH2-type responses. Preclinical studies have identified a contributory role for the cytokine IL-5 and the eotaxin chemokines, providing a rationale for specific disease therapy. An essential question is to determine the cellular and molecular basis for each of these clinical problems and the best treatment regimen, which is the main subject of this review.

REVIEW:

Liacouras CA. Ruchelli E

Eosinophilic esophagitis

Curr Opin Ped. 2004;16:560-6.

Eosinophilic esophagitis (EE) is an isolated, eosinophilic inflammation of the esophagus. In the past, the symptoms of EE were often confused for gastroesophageal reflux (GER). Thus, many physicians unsuccessfully treated patients with EE with medications used for GER. Because the incidence of EE is rising and EE is easily diagnosed by endoscopy with biopsy, it is important for physicians to not only accurately identify patients with EE but also understand the treatment options available. RECENT FINDINGS: While patients with acid reflux may have a few eosinophils, patients with EE have high levels of eosinophils in their esophagus as part of an allergic response to food antigens. The inflammation may cause abdominal pain, nausea, or vomiting. If EE persists for years, it may cause a narrowing of the esophagus that leads to dysphagia. In young children, many of the symptoms of EE mimic those of gastroesophageal reflux. Medications used to treat reflux are not effective against EE. Over the past few years, many new reports and retrospective studies have been written on the subject of EE. The focus of these papers concentrated on the etiology and treatment of EE. SUMMARY: The diagnosis of EE requires a biopsy of the esophagus. Typical allergy tests are not effective for diagnosis of EE because the allergic reaction involved in EE is non-IgE mediated. The most commonly involved foods include milk, eggs, nuts, beef, wheat, fish, shellfish, corn, and soy; however, almost all foods have been implicated. Because allergy tests are often unable to determine the causative foods, complete elimination of all foods is often required. In these cases, patients must be placed on a strict elemental formula for 1 to 3 months to heal the esophagus. Repeat endoscopy with biopsy is often necessary. Several medications have been used including corticosteroids, cromolyn sodium, and leukotriene inhibitors. This review discusses the past year's literature, concentrating on the etiology, diagnosis, and treatment of EE in both children and adults.

d. Clinical skills mastered: set up double blind placebo controlled food challenge, interpretation of skin prick and in vitro testing to foods

REVIEW / PRACTICE GUIDELINE – Food Allergy
Chapman JA, Bernstein IL, Lee RE, et al
Food allergy: a practice parameter
Ann Allergy Asthma Immunol 2006;96:S1-68
Food allergy, as defined for the purposes of this document, is a condition caused by an IgE-mediated reaction to a food substance. Adverse reactions to foods may also occur due to non–IgE-mediated immunologic and nonimmunologic mechanisms. Representing an important subset of all adverse food reactions, food allergy is often misunderstood. However, because of important new scientific information, its evaluation and management have changed substantially in recent years. The prevalence of potentially life-threatening food allergy to peanuts and tree nuts is increasing. This has resulted in an increased awareness among the general public, leading to policy changes in schools, eating establishments, and the airline industry. At the same time, diagnostic evaluation in more sophisticated and more challenging. The objective of Food Allergy: A Practice Parameter is to improve the care of patients by providing the practicing physician with an evidence- based approach to the diagnosis and management of IgE-mediated (allergic) food reactions. The Task Force recognizes the importance of non–IgE-mediated immunologic and nonimmunologic food reactions and the role of the allergist-immunologist in their identification and management.

REVIEW:
Niggemann B, Rolinck-Werninghaus C, Mehl A.
Controlled oral food challenges in children--when indicated, when superfluous?
Allergy. 2005;60:865-70.
The diagnostic work-up of suspected food allergy includes the skin prick test (SPT), the measurement of food specific immunoglobulin E (IgE) antibodies using serologic assays, and more recently the atopy patch test (APT). For specific serum IgE and the SPT, decision points have been established for some foods allowing prediction of clinical relevance in selected cases. The APT may be helpful, especially when considered in combination with defined levels of specific IgE. Controlled oral food challenges still remain the gold standard in the diagnostic work-up of children with suspected food allergy. Most food allergic children will lose their allergy over time. As there is no laboratory parameter, which can accurately predict when clinical tolerance has been developed, controlled oral food challenges are the measure of choice. In this article, the current knowledge of predictors for the outcome of oral food challenges is reviewed and proposals for the daily practical work-up in the case of suspected food related clinical symptoms are presented.

REVIEW:
Sicherer SH.
Food allergy: when and how to perform oral food challenges
Pediatr Allergy Immunol. 1999 Nov;10(4):226-34.
In many situations, the diagnosis of food allergy rests simply upon a history of an acute onset of typical symptoms, such as hives and wheezing, following the isolated ingestion of a suspected food, with confirmatory laboratory studies of positive prick skin tests or Radioallergosorbent tests. However, the diagnosis is more complicated when multiple foods are implicated or when chronic

diseases, such as asthma or atopic dermatitis, are evaluated. The diagnosis of food allergy and identification of the particular foods responsible is also more difficult when reactions are not mediated by IgE antibody, as is the case with a number of gastrointestinal food allergies. In these latter circumstances, well-devised elimination diets followed by physician-supervised oral food challenges are critical in the identification and proper treatment of these disorders. Because childhood food allergies to common allergenic foods such as milk, egg, wheat and soy are usually outgrown, oral food challenges are also an integral part of the long-term management of these children.

REVIEW :

Hill DJ, Heine RG, Hosking CS

The diagnostic value of skin prick testing in children with food allergy

Pediatr Allergy Immunol. 2004 Oct;15(5):435-41

The diagnostic accuracy of the skin prick test (SPT) in food allergy is controversial. We have developed diagnostic cut-off levels for SPT in children with allergy to cow milk, egg and peanut. Based on 555 open food challenges in 467 children (median age 3.0 yr) we defined food-specific SPT weal diameters that were '100% diagnostic' for allergy to cow milk (>or=8 mm), egg (>or=7 mm) and peanut (>or=8 mm). In children < 2 yr of age, the corresponding weal diameters were >or=6 mm, >or=5 mm and >or=4 mm, respectively. These SPT cut-off levels were prospectively validated in 90 consecutive children <or=2 yr with challenge-proven food allergy. In young infants under 6 months of age who have not previously been exposed to a particular food item, the SPT were often negative or below the diagnostic cut-off but reached the diagnostic cut-off at the time of challenge in the second year of life. We assessed the diagnostic agreement between food-specific immunoglobulin E (IgE) antibody levels and SPT in a cohort of 820 infants and children under 2 yr of age (median age 13.1 months) with suspected allergy to cow milk, egg or peanut. When applying published 95%-positive predictive CAP values, the diagnostic accuracy of SPT and IgE antibody levels was similar for cow milk, but SPT was more sensitive in diagnosing allergy to egg ($p < 0.0001$) and peanut ($p < 0.0001$). Further studies are required to define age-specific diagnostic IgE antibody and SPT cut-off levels use in infants under 2 yr of age with suspected food allergies.

KEY CLINICAL INVESTIGATION :

Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA.

The relationship of allergen-specific IgE levels and oral food challenge outcome.

J Allergy Clin Immunol 2004;114:144-9.

Background: Oral food challenges remain the gold standard for the diagnosis of food allergy. However, clear clinical and laboratory guidelines have not been firmly established to determine when oral challenges should be performed. Objective: We sought to determine the value of food-specific IgE levels in predicting challenge outcome. Methods: A retrospective chart review of 604 food challenges in 391 children was performed. All children had food-specific IgE levels measured by means of CAP-RAST before challenge. Data were analyzed to determine the relationship between food-specific IgE levels and challenge outcome, as well as the relationship between other clinical parameters and challenge outcome. Results: Forty-five percent of milk challenges were passed compared with 57% for egg, 59% for peanut, 67% for wheat, and 72% for soy. Specific IgE levels were higher among patients who failed challenges than among those who passed (P #.03 for each food). When seeking a specific IgE level at which a 50% pass rate could be expected, a cutoff level of 2 kUA/L was determined for milk, egg, and peanut. Data were less clear for wheat and soy. Coexistent eczema or asthma was associated with failed egg challenges, but other atopic disease was otherwise not associated with challenge outcome. Conclusions: Allergen-specific IgE

concentrations to milk, egg, and peanut and, to a lesser extent, wheat and soy serve as useful predictors of challenge outcome and should be considered when selecting patients for oral challenge to these foods.

KEY CLINICAL INVESTIGATION :
Sampson HA.
Utility of food-specific IgE concentrations

LANDMARK PUBLICATION:

Schwartz LB, Metcalfe DD, Miller JS, et al

Tryptase levels as an indicator of mast cell activation in systemic anaphylaxis and mastocytosis.

N Engl J Med 1987 316:1622-6.

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.

RESEARCH FRONTIER:

Srivastava KD, Kattan JD, Zou ZM, et al

The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy.

J Allergy Clin Immunol 2005;115:171-178

Background Peanut allergy is potentially life threatening. There is no curative therapy for this disorder. We previously found that an herbal formula, food allergy herbal formula (FAHF)–1, blocked peanut-induced anaphylaxis in a murine model when challenged immediately posttherapy. **Objective** To test whether FAHF-2, an improved herbal formula, from which 2 herbs, Zhi Fu Zi (Radix Lateralis Aconiti Carmichaeli Praeparata) and Xi Xin (Herba Asari), were eliminated, is equally effective to FAHF-1, and if so, whether protection persists after therapy is discontinued. **Methods** Mice allergic to peanut treated with FAHF-2 for 7 weeks were challenged 1, 3, or 5 weeks posttherapy. Anaphylactic scores, core body temperatures, vascular leakage, and plasma histamine levels after peanut challenge were determined. Serum peanutspecific antibody levels and splenocyte cytokine profiles were also measured. **Results** After challenges, all sham-treated mice developed severe anaphylactic signs, significant decrease in rectal temperatures, significantly increased plasma histamine levels, and marked vascular leakage. In contrast, no sign of anaphylactic reactions, decrease in rectal temperatures, or elevation of plasma histamine levels was observed in FAHF-2–treated mice in 5 separate experiments. IgE levels were significantly reduced by FAHF-2 treatment and remained significantly lower as long as 5 weeks posttherapy. Splenocytes from FAHF-2–treated mice showed significantly reduced IL-4, IL-5, and IL- 13, and enhanced IFN- production to recall peanut stimulation in vitro. **Conclusion** FAHF-2 treatment completely eliminated anaphylaxis in mice allergic to peanut challenged as long as 5 weeks posttherapy. This result was associated with downregulation of T_H2 responses. FAHF-2 may be a potentially effective and safe therapy for peanut allergy.

a. Causes (ingestants, exercise, allergy immunotherapy, latex, radiocontrast media) case definition and common presentations.

REVIEW:
Kemp SF. Lockey RF
Anaphylaxis: a review of causes and mechanisms.
Journal of Allergy & Clinical Immunology. 2002;110(3):341-8, 2002
Anaphylaxis is a life-threatening syndrome resulting from the sudden release of mast cell- and basophil-derived mediators into the circulation. Foods and medications cause most **anaphylaxis** for which a cause can be identified, but virtually any agent capable of directly or indirectly activating mast cells or basophils can cause this syndrome. This review discusses the pathophysiologic mechanisms of **anaphylaxis**, its causes, and its treatment.

b. Laboratory evaluation of anaphylactic episode, allergy testing, tryptase

REVIEW:
Schwartz HJ
Anaphylaxis: issues in diagnosis
Curr Opin Allergy & Clin Immunol. 2001;1:357-359.
Although anaphylaxis continues to be recognized as a life-threatening clinical problem, efforts to develop in-vitro methods for diagnosis and verification continue. The results have been interesting but not yet definitive, so that the necessity for clinical diagnosis remains pivotal.

c. Treatment of Anaphylaxis including Cardiopulmonary Resuscitation

i. Acute treatment

REVIEW:
Scott H. Sicherer, F. Estelle R. Simons
Quandaries in prescribing an emergency action plan and self-injectable epinephrine for first-aid management of anaphylaxis in the community.
J Allergy Clin Immunol 2005;115:575 to 583
Anaphylaxis often occurs in the community in the absence of a health care professional. Prompt administration of self-injectable epinephrine as first-aid treatment in the context of a personalized emergency action plan is the key to survival. There is little argument that physicians should prescribe self-injectable epinephrine for individuals who have already experienced anaphylaxis involving respiratory distress or shock triggered by allergens that might be encountered in the community. A quandary faced by physicians is that additional individuals with identified allergy who have no recognized prior history of anaphylaxis or who have a history of mild symptoms after exposure to a known trigger might also be at risk for subsequent life-threatening anaphylaxis and might also warrant prescription of self-injectable epinephrine. Prescribing for the latter individuals requires considerable clinical judgment and has led to controversy regarding possible overprescription or underprescription of self-injectable epinephrine. A second quandary for physicians occurs with regard to the advice they should give to at-risk individuals about actual use

of their self-injectable epinephrine. It is difficult for health care professionals, let alone persons with no health care training, to predict whether anaphylaxis symptoms will occur in an at-risk individual after exposure to a known trigger. Moreover, at the onset of an acute allergic reaction, it is difficult to predict the symptoms that will ultimately develop. We examine these 2 common quandaries and provide examples of clinical scenarios and potential pitfalls in the management of persons identified as being at risk for anaphylaxis in the community. Additional studies of the recognition and treatment of anaphylaxis in the community are needed to develop comprehensive, evidence-based recommendations for its management in this setting.

PRACTICE PARAMETER / GUIDELINE: :
Lieberman, P, Kemp SF, Oppenheimer J, et al.
The diagnosis and management of anaphylaxis: An updated practice parameter.
J Allergy & Clin Immunol. 2005;115:S-491-494.
This section of the Practice Paremeter outlines current recommendations regarding the immediate intervention, subsequent emergency care and resuscitation of 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.

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.

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

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.

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

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

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.

9. Economic costs of diagnosis and treatment of allergic diseases

REVIEW: ECONOMICS OF ASTHMA
Cleland J, Thomas M, Price D.
Pharmacoeconomics of asthma treatment.
Expert Opin Pharmacother. 2003 Mar;4(3):311-8.
The burden of asthma is increasing in terms of prevalence, severity of symptoms and other markers of asthma control. Poor control of symptoms is a major issue that can result in adverse clinical and economic outcomes. Prescribing costs are the most obvious and visible expense in asthma care but these are but the tip of the iceberg. We need to take all factors into account when considering the overall costs of asthma treatments and recognise that treatment that results in better asthma control may result in lessening of both direct and indirect costs. To assess this accurately, health economic evaluations need to be undertaken in relevant settings, on representative populations. They need to use appropriate measures of asthma outcome. Drug-related costs need to take into account savings made by decreased costs of other prescribed medication and patient factors must be taken into account. We need information that is applicable to the types of patients we see in the real world to make proper cost analyses. Such information can come from 'pragmatic' randomised trials, from retrospective claims analysis from observational studies or using primary care clinical and prescribing databases.

REVIEW: ECONOMICS OF RHINITIS
Blaiss MS.
Cognitive, social, and economic costs of allergic rhinitis.
Allergy Asthma Proc. 2000 Jan-Feb;21(1):7-13.
Allergic rhinitis is a highly prevalent, chronic condition. In addition to physical discomfort, rhinitis symptoms have been associated with detrimental effects on the psychological and social aspects of patients' lives. In allergy-specific questionnaires, subjects with allergic rhinitis consistently report lower quality of life than nonallergic controls. Untreated patients are embarrassed and frustrated by their allergy symptoms. Atopic individuals consistently exhibit significant declines in cognitive processing, psychomotor speed, verbal learning, and memory during allergy season. The discomfort, cognitive impairment, and absenteeism associated with allergic rhinitis exact a significant economic toll on U.S. businesses through decreased productivity. When combined with direct medical expenditures, the economic burden of allergic rhinitis is considerable. The effect of treatment on the economics of allergic rhinitis is highly variable: relatively inexpensive medications (lower direct costs) have central nervous system side effects that can cause somnolence and impair learning, memory, and performance (higher indirect costs). Health outcomes data on the effects of allergic rhinitis and its treatments can help establish, monitor, and improve standards of care; as well as inform priority setting, direct resource allocation, and eliminate unnecessary practices.

10. Psychosocial aspects of allergic disease and chronic illness, failure of adherence to therapy.

REVIEW: PSYCHOSOCIAL ASPECTS OF CHRONIC ILLNESS

Bartlett SJ, Krishnan JA, Riekert KA, Butz AM, Malveaux FJ, Rand CS.

Maternal depressive symptoms and adherence to therapy in inner-city children with asthma.

Pediatrics. 2004 Feb;113(2):229-37.

CONTEXT: Little is known about how depressive symptoms in mothers affects illness management in inner-city children with asthma. OBJECTIVE: Our goal was to determine how maternal depressive symptoms influence child medication adherence, impact of the child's asthma on the mother, and maternal attitudes and beliefs. METHODS: Baseline and 6-month surveys were administered to 177 mothers of young minority children with asthma in inner-city Baltimore, MD and Washington, DC. Medication adherence, disruptiveness of asthma, and select attitudes toward illness and asthma therapy were measured. Six-month data (N = 158) were used to prospectively evaluate long-term symptom control and emergency department use. Independent variables included asthma morbidity, age, depressive symptoms, and other psychosocial data. RESULTS: No difference in child asthma morbidity was observed between mothers high and low in depressive symptoms. However, mothers with high depressive symptoms reported significantly more problems with their child using inhalers properly (odds ratio [OR]:5.0; 95% confidence interval [CI]: 1.3-18.9) and forgetting doses (OR: 4.2; 95% CI: 1.4-12.4). Depressive symptoms were also associated with greater emotional distress and interference with daily activities caused by the child's asthma, along with less confidence in asthma medications, ability to control asthma symptoms, and self-efficacy to cope with acute asthma episodes. In addition, depressed mothers reported less understanding about their child's medications and use (OR: 7.7; 95% CI: 1.7-35.9). Baseline asthma morbidity, maternal depression scores, and family income were independently associated with asthma symptoms 6 months later, whereas medication adherence was not predictive of subsequent asthma morbidity or emergency department use. CONCLUSIONS: Maternal depressive symptoms were not associated with child asthma morbidity but were associated with a constellation of beliefs and attitudes that may significantly influence adherence to asthma medications and illness management. Identifying and addressing poor psychological adjustment in mothers is important when developing a child's asthma treatment and may facilitate parent-provider communication, medication adherence, and asthma management among inner-city children.

REVIEW : PSYCHOSOCIAL ASPECTS OF CHRONIC ILLNESS

Barton C, Clarke D, Sulaiman N, Abramson M.

Coping as a mediator of psychosocial impediments to optimal management and control of asthma.

Respir Med. 2003 Jul;97(7):747-61.

Adherence to asthma medication regimens by asthma patients is often poor and contributes to the continued and substantial burden of asthma in the community. There is evidence of increased rates of behavioural problems, anxiety and depression in people with moderate-to-severe asthma and these factors may interfere with adherence and contribute to poor asthma control. An alternative explanation is that the relationship between feelings of anxiety and depression, and adherence to the treatment regimen may be more accurately predicted from the coping styles used, rather than the experience of asthma itself. The objective of this paper was to review evidence for associations between coping strategies used by asthma patients, asthma management and health outcomes. The

Medline and PsychInfo databases were searched for articles containing the terms "asthma" and "coping". Patients with asthma tended to use different strategies for coping with stress and illness compared to healthy participants and individuals with other chronic illnesses. Emotion-focussed coping strategies such as denial were commonly used by patients with poor medication adherence, those who attended emergency departments for asthma, were admitted to hospital for asthma, or suffered near-fatal asthma attacks. Interventions to improve coping strategies have been effective in reducing symptoms and psychological distress. The availability of coping resources to patients and/or their caregivers and the coping strategies that are used are likely to mediate the influence of psychosocial factors on the management of asthma. Further studies exploring the ways in which individuals cope with asthma will improve our understanding of the mechanisms linking psychological and social status to asthma morbidity and mortality.

REVIEW :ADHERENCE ISSUES IN ASTHMA
Bender B, Milgrom H, Rand C.
Nonadherence in asthmatic patients: is there a solution to the problem?
Ann Allergy Asthma Immunol. 1997 Sep;79(3):177-85; quiz 185-6.
LEARNING OBJECTIVES: Reading this article will reinforce the reader's awareness of the relationship between adherence and treatment outcome, of the causes of nonadherence, of methods of measurement, and of steps tow ard successful intervention. DATA SOURCES: Articles on adherence to asthma therapy were reviewed. A MEDLINE database using subject keywords was searched from 1990 through 1997. STUDY SELECTION: Pertinent articles were chosen, with preferential presentation of results from controlled studies. RESULTS: There is no evidence of recent improvement in the rates of nonadherence, and patients continue on average to take about 50% of prescribed medication. Nonadherence assessment is most accurate when it can be measured objectively, and relies neither on patient report nor physician estimate. The consequences of nonadherence are measured in patient suffering, financial cost, and serious compromise of clinical trial outcomes. Underlying causes of nonadherence are traced to characteristics of the disease, treatment, patient, and caregiver system.
CONCLUSION: Improved adherence will lead to improved disease control, but only if medical care systems encourage and support the allocation of sufficient resources to allow barriers to self-management to be discussed and solutions negotiated. Attempts to improve adherence outside of the caregiver-patient relationship are less likely to succeed. Special programs for difficult-to-manage patients are necessary to change behavior, although significant illness improvement and cost savings are likely to result.

B. Immunodeficiency Diseases

1. Primary immunodeficiency diseases (including clinical presentation, diagnostic approach, cellular profile, genetic basis, prognostic factors and therapeutic options)

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
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.

REVIEW
Bonilla FA. Geha RS.
Primary immunodeficiency diseases.
J Allergy Clin Immunol 2003;11:S571-81.
Although primary immunodeficiency disorders are relatively rare, intensive investigation of these disorders has yielded a great wealth of understanding of basic immunologic mechanisms in host defense, inflammation, and autoimmunity. These advances have led to important developments for the treatment not only of the primary immunodeficiencies but also for patients with secondary immunocompromised states, autoimmune disorders, hypersensitivity, graft rejection, and graft versus host disease. Correction of a form of severe combined immunodeficiency represents the first true success of human gene therapy. This review introduces the major clinical manifestations of primary immunodeficiency disorders, along with descriptions of essential elements of the pathophysiology of those disorders that have been defined at the molecular level. Key concepts in treatment are also presented. It is critical for the practicing primary care provider and allergist to maintain an index of suspicion for immunodeficiency. Early diagnosis offers the best opportunity for reduced morbidity and survival and is critical for accurate genetic counseling.

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.

a. 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 the presence 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.

b. 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.

c. 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.

REVIEW -SCID

Leonard WJ.

Cytokines and immunodeficiency diseases.

Nat Rev Immunol.2001;1:200-8.

Severe combined immunodeficiency disease (SCID) refers to a spectrum of inherited immunodeficiencies that together represent the most severe forms of primary immunodeficiency in humans. Recent work has shown that many of these diseases, as well as other forms of immunodeficiency, result from defects in cytokine signalling pathways. Such defects can prevent normal development of lymphoid lineages and/or compromise cytokine signalling by these cells. These natural 'experiments' in human genetics have shown the non-redundant role for several cytokines or cytokine signalling molecules. Moreover, a comparison of the phenotypes of humans with SCID to analogous mouse-knockout models has shown not only expected similarities, but also unexpected differences in cytokine signalling between humans and mice.

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

Cunningham-Rundles C.

Physiology of IgA and IgA deficiency.

J Clinical Immunol 2001;21:303-9.

Although secretory immunoglobulin A (IgA) is important in mucosal immunity. selective IgA deficiency is the most common primary immunodeficiency of humans. In most cases this defect is not associated with any illness. The reasons for this are unknown, but other immunological compensations might provide sufficient or complete restitution. Alternatively, it is possible that IgA deficiency alone may not predispose to disease, but additional immunological abnormalities might be present in symptomatic individuals. Some IgA-deficient individuals have a reduced antibody response to immunizations (even with normal IgG and IgM levels) and others have deficient responses to bacterial polysaccharides when IgG subclass levels are normal. The physiological role of IgA, the frequency and causes of IgA deficiency, the diseases associated with its absence, and current limited understanding of the pathogenesis of selective IgA deficiency will be reviewed.

d. 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

Cugno M. Nussberger J. Cicardi M. Agostoni A.
Bradykinin and the pathophysiology of angioedema.
Internat Immunopharm 2003;3:311-7

Angioedema has different causes and different clinical presentations. Some types of angioedema may be mediated by bradykinin. We measured plasma levels of bradykinin-(1-9)nonapeptide by radioimmunoassay after high-performance liquid chromatography in patients with different types of angioedema during acute attacks and/or in remission, i.e. hereditary C1-inhibitor deficiency, angiotensin converting enzyme (ACE) inhibitor treatment, idiopathic non histaminergic and responders to antihistamines. Eleven patients with the deficiency of C1-inhibitor had very high levels of bradykinin during acute attacks of angioedema (18.0-90.0 pM) (normal range 0.2-7.1 pM).In three patients with history of ACE inhibitor-related angioedema, plasma bradykinin was

high during ACE inhibitor treatment (62.0, 8.9 and 27.0 pM) and in a fourth patient was 47.0 pM during an acute attack and decreased by 93% to 3.2 pM after withdrawal of the ACE inhibitor. The patient with idiopathic angioedema, during an acute attack involving the right arm, had high levels of bradykinin in the venous blood refluent from the angioedematous arm (20.0 pM) while in the contralateral arm bradykinin levels were normal (6.6 pM), similarly to what we previously observed in cases of brachial angioedema due to C1-inhibitor deficiency. The four patients with angioedema responsive to antihistamines had normal levels of bradykinin even during acute attacks (5.7, 3.4, 4.7 and 1.2 pM). In one of these patients who had a brachial angioedema, bradykinin levels were normal in the venous blood refluent from both arms. Bradykinin is involved in hereditary C1-inhibitor deficiency angioedema, in ACE inhibitor-related angioedema, and in idiopathic nonhistaminergic angioedema, while bradykinin is not related to allergen-dependent or idiopathic angioedema that are responsive to antihistamines.

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.

e. 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 - Leukocyte Adhesion Deficiency

Bunting M. Harris ES. McIntyre TM. Prescott SM. Zimmerman GA.
Leukocyte adhesion deficiency syndromes: adhesion and tethering defects involving beta 2 integrins and selectin ligands.
Curr Opin Hematol 2002;.9:30-5.

Leukocyte adhesion deficiency (LAD) syndromes are failures of innate host defenses against bacteria, fungi, and other microorganisms resulting from defective tethering, adhesion, and targetingof myeloid leukocytes to sites of microbial invasion. LAD I and variant LAD I syndromes are caused by mutations that impair expression or function of integrins of the beta 2 class (CD11/CD18 integrins, or "leukocyte" integrins). In contrast, subjects with LAD II have similar clinical features but intact leukocyte integrin expression and function. The molecular basis for LAD II is defective glycosylation of ligands on leukocytes recognized by the selectin family of adhesion molecules as well as defective glycosylation of other glycoconjugates. The defect has recently been attributed to mutations in a novel fucose transporter localized to the Golgi apparatus. Establishing the molecular basis for LAD syndromes has generated insights into mechanisms of leukocyte accumulationrelevant to a broad variety of immunodeficiency syndromes as well as to diseases and disorders of unregulated inflammation that result in tissue damage.

REVIEW IgE & Immunodeficiency

Grimbacher B. Belohradsky BH. Holland SM.
Immunoglobulin E in primary immunodeficiency diseases.
Allergy. 2002;57:995-1007.

Immunoglobulin E (IgE) was discovered in the late 1960s (1,2). Since then, aberrations of IgE synthesis have been noted in allergic diseases, in certain bacterial, fungal and parasitic infections, in graft-versus-host disease, and in certain acquired and primary immunodeficiency disorders (PID). However, the exact biological role of IgE under these conditions is unclear. This review will focus on IgE abnormalities in PID in which either deficiency or excess of IgE production is associated with increased susceptibility to infection. Particular emphasis will be put on the hyper-IgE syndrome, the Wiskott–Aldrich syndrome, the Omenn syndrome and the Comèl–Netherton syndrome

f. 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 thefield.

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 timeconsuming, which results in misdiagnosis of a substantial percentage of such disorders. Hence, the bprevalence 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

Ballow M.

Intravenous immunoglobulins: clinical experience and viral safety.

J Am Pharm Assoc 2002;42:449-58.

OBJECTIVES: To discuss the current procedures and processes by which viral safety is ensured for intravenous immunoglobulins (IVIGs), to place in context the current increase in clinical indications for IVIGs, and to describe the safety issues that have led to product shortages. DATA SOURCES: Articles on viral safety retrieved from MEDLINE using the search terms gamma globulin, intravenous, adverse reaction, and infection and information from the manufacturers' literature and Food and Drug Administration package inserts. STUDY SELECTION AND DATA EXTRACTION: Studies that specifically addressed the areas of major concern or advancement in viral safety of IVIGs, including donor selection, plasma screening, and other quality control procedures to ensure safety of source plasma; detection of viruses that may have escaped antibody screening tests through the use of polymerase chain reaction-based assays, which are capable of detecting small amounts of viral genomic material (e.g., hepatitis C virus, hepatitis B virus, and human immunodeficiency virus [HIV]) in small plasma pools; and industrial-scale, validated viral inactivation methods, such as pasteurization and solvent/detergent treatment, that have been incorporated into the manufacturing processes of immunoglobulins to further minimize the risk of viral transmission. DATA SYNTHESIS: In addition to the treatment of primary immunodeficiency disorders, the clinical uses of IVIGs have expanded to include treatment of Kawasaki's syndrome, idiopathic thrombocytopenic purpura, infection following bone marrow transplantation, secondary immunologic disorders (e.g., pediatric HIV infection), hematologic disorders (e.g., chronic lymphocytic leukemia), and neurologic indications (e.g., Guillain-Barre syndrome). Although IVIG preparations are derived from human plasma, they have a long safety record and a low risk for transmitting viral infections. CONCLUSION: Viral validation studies demonstrated that the processes discussed herein differ in their capabilities to inactivate lipid-enveloped and nonlipidenveloped viruses.

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 administrationof 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.

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 heath 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

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.

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.

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.

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
Tangsinmankong N, Bahna S L, Good R A
The immunologic workup of the child suspected of immunodeficiency.
Annals Allergy, Asthma Immunol 2001;87:362-9
OBJECTIVE: 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 / 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 organizecurrent knowledge and practice in the diagnosis and managementof primary immunodeficiency diseases. Preparation of this Practice Parameter included a review of the medicalliterature, mainly via the PubMed database. Published clinicalstudies or reports were rated by category of evidence andused to establish the strength of a clinical recommendation. There are few randomized trials in the diagnosisand 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
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 – 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
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.

FRONTIER REVIEW
Chan A T, Flossmann O, Mukhtyar C, et al.
The role of biologic therapies in the management of systemic vasculitis
Autoimmun Rev. 2006 5:273-8
The recent development of biologic therapies capable of selectively targeting components of the immune system has revolutionised the treatment of inflammatory arthritides. The steady increase in use of biologic agents coupled with the expansion in the knowledge of the pathogenesis of vascular inflammation has led to their application in the treatment of primary systemic vasculitis. These agents may have a role in addition to or in place of conventional immunosuppression and also be effective when the latter fails to induce remission. The use of biologics as targeted therapies has

also, in reverse, improved our understanding of the pathophysiology of vascular inflammation. While the advent of biologics heralds a new era in the management of the systemic vasculitis, evidence for their efficacy is still in its infancy and has yet to match that of conventional immunosuppressants. In this review, we examine the up-to-date evidence for the use of biologics in systemic vasculitis, including TNF-alpha inhibitors, and highlight the challenges facing their use. We examine the rationale for using biologics based on the pathophysiology of vasculitis. Issues of toxicity and pharmacovigilance with the use of biologics are also discussed. Finally, future directions and predictions are presented.

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 restorehomeostasis to the immune system. Consequently, lifelong treatment with such agents is necessary, whichentails 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.

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 hypothalamus-pituitarythyroid axis. Although thyroid-stimulating hormone (TSH) can be produced by many 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.

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 cell-stimulatory 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+ Tr 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.

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),auto-immune 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, auto-antibodies 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.

RESEARCH FRONTIER

Dahlke MH, Loi R, Warren A et al.

Immune-mediated hepatitis drives low-level fusion between hepatocytes and adult bone marrow cells.

J Hepatology 2006;44:334-41.

BACKGROUND/AIMS: The role of adult bone marrow-derived cells (BMC) in hepatic regeneration is controversial. Both transdifferentiation of BMC as well as fusion with hepatocytes have been suggested in toxin-based and genetic selection models. METHODS: We have developed a transgenic mouse model of immune-mediated hepatitis to clarify the role of BMC in liver regeneration following injury mediated by T cells. RESULTS: Repeated adoptive transfer of transgenic T cells into bone marrow chimeras resulted in multiple waves of hepatitis. Hepatocytes derived from donor bone marrow were identified using a self-protein that does not interfere with hepatocyte function and proliferation in recipient animals. Some cells contained one recipient nucleus and another independent donor bone marrow-derived nucleus, suggesting that cellular fusion plays some role in liver repair after immune hepatitis. However, despite pronounced infiltration by myeloid cells, the frequency of fusion was extremely low. CONCLUSIONS: This study provides a unique, clinically relevant model in which fusion hepatocytes can be purified and characterized by the expression of donor MHC antigen. It demonstrates that although fusion between BMC and hepatocytes occurs under conditions of inflammation that correspond to human disease, its frequency needs to be increased to be of any therapeutic value.

7. Immune neurologic and neuromuscular disorders

REVIEW

Zipp F, Aktas O.

The brain as a target of inflammation: common pathways link inflammatory and neurogenerative diseases.

Trends in Neurosciences 2006;29:518-27.

Classical knowledge distinguishes between inflammatory and non-inflammatory diseases of the brain. Either the immune system acts on the CNS and initiates a damage cascade, as in autoimmune (e.g. multiple sclerosis) and infectious conditions, or the primary insult is not inflammation but ischemia or degeneration, as in stroke and Alzheimer's disease, respectively. However, as we review here, recent advances have blurred this distinction. On the one hand, the classical inflammatory diseases of the brain also exhibit profound and early neurodegenerative features - remarkably, it has been known for more than a century that neuronal damage is a key feature of multiple sclerosis pathology, yet this was neglected until very recently. On the other hand, immune mechanisms might set the pace of progressive CNS damage in primary neurodegeneration. Despite differing initial events, increasing evidence indicates that even in clinically heterogeneous diseases, there might be common immunological pathways that result in neurotoxicity and reveal targets for more efficient therapies.

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).

8. Immune hematologic disorders

REVIEW

Zola H, Swart B, Nicholson I et al.

CD molecules 2005: human cell differentiation molecules.

Blood 2005;106:3123-6.

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 cellsurface 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.

REVIEW

Shanafelt TD, Madueme HL, Wolf RC et al. Rituximab for immune cytopenias in adults: idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia and Evans syndrome. Mayo Clin Proceedings 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, bcomorbid 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.

RESEARCH FRONTIER

Solomou EE, Keyvanfar K, Young NS. T-bet, a Th1 transcription factor is upregulated in T cellsfrom patients with aplastic anemia.
Blood 2006;107:3983-91.

In aplastic anemia, immune destruction of hematopoietic cells results in bone marrow failure. Type 1 cytokines, especially IFN-gamma, have been implicated in the pathophysiology of T-cell mediated, Fas-mediated stem cell apoptosis of hematopoietic cells. Here, we show that the transcription factor Tbet (T-box expressed in T cells) is increased in T cells from patients with aplastic anemia. Patients' Tbet bound directly to the proximal site of the IFN-gamma promoter without any prior stimulation, in contrast to healthy controls. Increased levels of Itk kinase participated in T-bet up-regulation and active transcription of the IFN-gamma gene observed in these patients. Blocking PKC-, a kinase that lies downstream of Itk kinase, decreased T-bet protein and IFN-gamma intracellular levels. These data suggest that the increased IFN-gamma levels observed in aplastic anemia patients are the result of active transcription of the IFN-gamma gene by T-bet. Blocking the transcription of the IFN-gamma gene with kinase inhibitors might lead to the development of novel therapeutic agents for patients with aplastic anemia and other autoimmune diseases.

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

RESEARCH FRONTIER

Dullforce PA, Seitz GW, Garman KL, et al.

Antigen-specific accumulation of naïve, memory and effector CD4 cells during anterior uveitis monitored by intravital microscopy.

Cellular Immunol 2006;239:49-60.

Uveitis is an immune-mediated ocular disease and a leading cause of blindness. We characterized a novel model of uveitis with intravital microscopy. Transfer of ovalbumin-specific T cells from DO11.10 spleen to BALB/c recipients and subsequent challenge with ovalbumin in the anterior chamber of the eye resulted in anterior uveitis. Antigen-specificity was verified by injection of irrelevant antigen and transfer of T cells with a different specificity. Subsets of CD4 T cells, including naive (DO11.10 RAG(-/-)) and in vitro-activated Th2 effector CD4 T cells, infiltrated anterior segment tissues early in the inflammation. Memory-like CD44(high) CD4 T cells from unprimed transgenic mice and in vitro-activated Th1 effector CD4 T cells accumulated to larger numbers than naive or Th2 effector cells at 48 and 72 h. Of these, the alpha(2)-integrin+CD4 unprimed T cells entered the eye more efficiently, and antibody to alpha(2)-integrin markedly inhibited the inflammatory response. Intravital microscopy revealed the early arrival and antigen-specific accumulation of CD4 T cells in inflamed tissue and should be helpful in understanding T cell migration to other organs.

10. Immune skin disorders

REVIEW

Ong PY, Leung DY.

Immune dysregulation in atopic dermatitis.

Curr Allergy Asthma Reports. 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.

RESEARCH FRONTIER

Satoh T, Moroi R, Aritake K, Urade Y, Kanai Y et al.

Prostaglandin D2 plays an essential role in chronic allergic inflammation of the skin via CRTH2 receptor.

J Immunol 2006;177:2621-9

PGD(2) plays roles in allergic inflammation via specific receptors, the PGD receptor designated DP and CRTH2 (chemoattractant receptor homologous molecule expressed on Th2 cells). We generated mutant mice carrying a targeted disruption of the CRTH2 gene to investigate the functional roles of CRTH2 in cutaneous inflammatory responses. CRTH2-deficent mice were fertile and grew normally. Ear-swelling responses induced by hapten-specific IgE were less pronounced in mutant mice, giving 35-55% of the responses of normal mice. Similar results were seen in mice treated with a hemopoietic PGD synthase inhibitor, HQL-79, or a CRTH2 antagonist, ramatroban. The reduction in cutaneous responses was associated with decreased infiltration of lymphocytes, eosinophils, and basophils and decreased production of macrophage-derived chemokine and RANTES at inflammatory sites. In models of chronic contact hypersensitivity induced by repeated hapten application, CRTH2 deficiency resulted in a reduction by approximately half of skin responses and low levels (63% of control) of serum IgE production, although in vivo migration of Langerhans cells and dendritic cells to regional lymph nodes was not impaired in CRTH2-deficient mice. In contrast, delayed-type hypersensitivity to SRBC and irritation dermatitis in mutant mice were the same as in wild-type mice. These findingsindicate that the PGD(2)-CRTH2 system plays a significant role in chronic allergic skin inflammation.CRTH2 may represent a novel therapeutic target for treatment of human allergic disorders, includingatopic dermatitis.

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

a. Hyperacute

b. Acute

c. Chronic

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

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

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 May;19(5):351-9.

Many studies have shown a strong association between initial graft injury and poor long-term 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 to support clinical application of these strategies.

c. Methods to induce allograft host tolerance

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 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 treatment of hematologic malignancies. Twenty patients aged 31 to 50 years were prepared for transplantation with cyclophosphamide (120 mg/kg) and fractionated total body irradiation (12.0 or 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 HLAidentical allogeneic 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 as a 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 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 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 and treatment of chronic GVHD.

b. Treatment

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 lymphocytes. 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.

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 1percent, 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
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 transducer 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 Mg^{2+} over Mn^{2+}, distinct from the characteristics of cellular DNA 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 $NaDodSO_4$/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: 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.

4. Mast Cell Dyscrasias

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 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 mastcell- 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

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

Approaches to the treatment of hypereosinophilic syndromes: A workshop summary report

Klion, AD, Bochner, BS, Gleich GJ, et al

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.

RESEARCH FRONTIER

Cools J, DeAngelo DJ, Gotlib J, et al.

A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome.

N Engl J Med. 2003;348:1201-14

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
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.

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 reactiveor 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 ofthese 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)
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.

F. Established and Evolving Immune-based Treatment Modalities

1. Glucocorticoids and Immunosuppressants (also see Section III.A.)

REVIEW:
Nelson RP, Ballow M.
Immunomodulation and immunotherapy:
Drugs, cytokines, cytokine receptors and antibodies.
J Allergy ClinImmunol 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 discussedin terms of general principles, molecular targets, major indications, and adverse effects.

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.
This article reviews alternate, nonsteroidal agents including methotrexate, gold, cyclosporine, and azathioprine and the available evidence behind their use in difficult-to-control asthmatics

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

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
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

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:
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)

REVIEWS

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 PUBLICATIONS

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- – converting 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 (FEV_1) (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 FEV_1 (95 percent confidence interval, 0.08 to 0.55; P=0.01).

7. Recombinant molecules and humanized monoclonal antibodies (imatinib, infliximab, omaluzimab, rituximab)

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

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

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
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.