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Acknowledgements

The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on eczema. Books in this series draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this book. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany Freeman for her excellent editorial support.
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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading." Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with eczema is indexed in search engines, such as www.google.com or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about eczema, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to eczema, from the essentials to the most advanced areas of research. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on eczema. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to eczema, these are noted in the text.

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. NOTE: At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. For readers without access to Internet resources, a directory of medical libraries, that have or can locate references cited here, is given. We hope these resources will prove useful to the widest possible audience seeking information on eczema.

The Editors

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1 From the NIH, National Cancer Institute (NCI): http://www.cancer.gov/cancerinfo/ten-things-to-know.
CHAPTER 1. STUDIES ON ECZEMA

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on eczema.

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and eczema, you will need to use the advanced search options. First, go to http://chid.nih.gov/index.html. From there, select the “Detailed Search” option (or go directly to that page with the following hyperlink: http://chid.nih.gov/detail/detail.html). The trick in extracting studies is found in the drop boxes at the bottom of the search page where “You may refine your search by.” Select the dates and language you prefer, and the format option “Journal Article.” At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display “whole records.” We recommend that you type “eczema” (or synonyms) into the “For these words:” box. Consider using the option “anywhere in record” to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the “Search in these fields” drop box. The following is what you can expect from this type of search:

- **Patient Education for Adults With Chronic Eczema**
  
  
  Summary: This journal article provides health professionals with information on a study that evaluated the effects of patient education on eczema and determined the degree of satisfaction the patients had with the education. Seven patients with severe eczema participated in an individual educational project. The program provided knowledge about self care treatment. Patients completed a nine-item questionnaire before participating in the program, after being accepted as participants, and 2 weeks after the end of the program. Between the first and second individual teaching sessions, the patients were asked to read an informational pamphlet as homework. They were also asked to reflect on their daily activities to determine what their skin was subjected to during a normal day. The second teaching session was oriented toward patient reactions...
to the information presented in the pamphlet. Results of the program evaluation reveal that all patients felt the educational program gave them new knowledge about their disease and provided them with sufficient knowledge about how they should perform their topical treatment and take care of their personal hygiene. Participants also stated that the informational pamphlet was succinct and easy to understand. The article concludes that patient education can be helpful in providing support to patients who have chronic eczema. 1 figure, 2 tables, and 17 references. (AA-M).

- **Recent Developments in the Treatment of Atopic Eczema**
  

  Summary: This journal article for health professionals reports on recent developments in the treatment of atopic dermatitis (AD) or eczema, which is a common, chronically relapsing skin disease with a genetic predisposition and unknown cause. Recent progress in the understanding of the pathophysiologic characteristics of AD has prompted new therapeutic strategies. The article evaluates the effectiveness of phototherapy, cytokines such as interferons and interleukins, and immunosuppressive drugs such as cyclosporine and FK506. In addition, some new and promising but still experimental approaches are discussed, including experimental immunotherapies, Chinese herbal therapy, essential fatty acid supplementation, mast cell stabilizing agents, and topical immunoglobulin G preparations. 154 references and 6 tables. (AA-M).

- **Eczematous Dermatitis: A Practical Review**
  

  Contact: American Academy of Family Physicians. 11400 Tomahawk Creek Parkway, Leawood, KS 66211-2672. (800) 274-2237 or (913) 906-6000. E-mail: fp@aafp.org. Website: www.aafp.org.

  Summary: This journal article for dermatologists discusses various types eczematous dermatitis and their treatment. Eczematous dermatitis can interfere with social function, sleep, and employment, and that its persistence and accompanying pruritus may be stressful and frustrating for patients. The most common and best characterized type of eczema, atopic dermatitis, appears to be increasing in incidence. The authors suggest that other common eczematous dermatoses, particularly allergic dermatitis and irritant contact dermatitis, must be accurately diagnosed, since improvement and resolution rely on appropriate diagnosis and avoidance of pertinent triggering factors. Principles of treatment include general skin care, patient education about avoidance of irritants, skin hydration and the use of topical corticosteroids when necessary. Use of systemic corticosteroids is not generally recommended for the treatment of chronic eczematous dermatitis. (AA-M).

- **Living With Eczema: The Dermatology Patient**
  
  Source: British Journal of Nursing. 5(10):600-604,606-609; 1996.

  Summary: This journal article for health professionals presents an overview of eczema. The prevalence of all forms of eczema is unknown, but there is evidence that atopic eczema is increasing. Types of eczema are identified, including exogenous forms such as contact irritant eczema, contact allergic eczema, and photosensitive eczema; endogenous forms such as atopic eczema, seborrheic eczema, discoid eczema, gravitational eczema, and pompholyx; and unclassified or mixed forms such as asthenotic eczema, lichen
Studies 5

simplex, and juvenile plantar dermatosis. The clinical and histological features of eczema are described. The role of nursing care in the management of eczema is discussed in terms of the nursing assessment; the needs of children, young adults, adults, and the elderly with eczema; and the management of eczema. First-line treatments are discussed, including avoiding provoking factors, bathing, applying emollients, treating bacterial infections, and using topical corticosteroids and occlusive techniques. Other treatment considerations that nurses should discuss with patients are highlighted, including sensitivity to house dust mites, the role of diet in initiating or perpetuating atopic eczema, and the use of systemic treatments. 12 references, 6 figures, and 4 tables. (AA-M).

- **Gastrointestinal Symptoms in Atopic Eczema**


  Summary: This article reports on a study undertaken to determine the prevalence of gastrointestinal symptoms in children with eczema and the association of such symptoms with the extent of eczema or the results of skin prick tests. Sixty-five children with atopic eczema and a control group matched for age and sex were recruited. Their parents completed a questionnaire about the children's gastrointestinal symptoms. The children's skin was examined; their weight, height, and abdominal circumference were measured; and skin prick tests were carried out. Gastrointestinal symptoms, especially diarrhea, vomiting, and regurgitation, were more common in the children with eczema. Diarrhea appeared to be associated with the ingestion of specific foods. Gastrointestinal symptoms were related to diffuse eczema and positive skin prick tests to foods. There were no anthropometric differences between the patient and control groups. The article concludes that a gastrointestinal disorder is common in children with eczema, especially with diffuse distribution. This may be responsible for substantial symptoms and may play a part in the pathogenesis of the disease and in the failure to thrive with which it is sometimes associated. 4 tables. 22 references. (AA-M).

**Federally Funded Research on Eczema**

The U.S. Government supports a variety of research studies relating to eczema. These studies are tracked by the Office of Extramural Research at the National Institutes of Health. CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.

Search the CRISP Web site at [http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen](http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen). You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to eczema.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use

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2 Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).
animals or simulated models to explore eczema. The following is typical of the type of information found when searching the CRISP database for eczema:

- **Project Title: A TWIN STUDY OF CHRONIC FATIGUE SYNDROME IN SWEDEN**  
  Principal Investigator & Institution: Pedersen, Nancy L.; Karolinska Institute Tomtebodavagen 11F Stockholm,  
  Timing: Fiscal Year 2001; Project Start 15-AUG-2001; Project End 31-JUL-2004  
  Summary: Despite considerable research, fundamental questions about CFS remain at best partially answered. These questions include its definition, validity, the degree to which it results from genetic versus environmental factors, the nature of the substantial comorbidity observed with other conditions, and the basis of the female preponderance. The overarching aim of this project is to shed light on a number of basic questions about CFS via a large, population-based classical twin study. First, we will collect data on approximately 32,000 adults aged 42-65 years (13,000 complete twin pairs) who are members of the population-based Swedish Twin Registry for persistent fatigue, several overlapping conditions (fibromyalgia, irritable bowel syndrome, tension headache, allergy/eczema, generalized anxiety disorder, and major depression), and a detailed medical history. Second, the medical records of all twins who appear to have CFS-like illness and a subset of those with "CFS-explained" will be requested via an efficient national retrieval system. Following expert review, these individuals will be classified in regard to the CDC CFS criteria. Obtaining these unique data will allow us to address a set of critical questions regarding CFS. First, we will estimate the prevalence of CFS and its common comorbidities (fibromyalgia, irritable bowel syndrome, tension headache, allergy/eczema, generalized anxiety disorder, and major depression) in one of the largest samples yet studied. Second, we will use a variety of multivariate techniques to derive an empirical typology of prolonged fatigue and to assess how this typology compares to the CFS definition. Third, we will quantify the genetic and environmental sources of variation for CFS and its comorbid conditions. Fourth, critically, we will examine the influence of gender on these sources of variation. Finally, we will analyze the patterns of comorbidity between CFS and fibromyalgia, irritable bowel syndrome, tension headache, allergy/eczema, generalized anxiety disorder, and major depression using multivariate twin analyses and thereby to estimate the extent of overlap between the shared and unique genetic and environmental sources of variation. In concert with other twin studies being conducted by the investigators and their collaborators, we hope to hasten progress in understanding the etiology of CFS by parallel studies in multiple populations. The current proposal has several unique aims and represents a cost-effective means to extend this work in an epidemiological sample that is arguably the best twin registry in the world.  
  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ALLERGIC CONDITION BIOMARKERS AND GLIOMA RISK**  
  Principal Investigator & Institution: Schwartzbaum, Judith A. None; Ohio State University 1800 Cannon Dr, Rm 1210 Columbus, OH 43210  
  Timing: Fiscal Year 2003; Project Start 01-SEP-2003; Project End 31-AUG-2005  
  Summary: (provided by applicant): An inverse association between self-reported allergic conditions (ACs) and glioma has been previously observed in seven case-control and two cohort studies. The mechanism for this association is not known, however, two cytokines that play a central role in ACs (i.e., interleukin (IL)-4, IL-13) also suppress glioma growth. From among genetic polymorphisms that are associated with risk of
ACs, we have identified polymorphisms also involved in normal astrocyte growth or glioma pathogenesis. Gene products of genetic polymorphisms found on the IL-4, IL-13, IL-4Ralpha, IL-13Ralpha1, HLA-DRB1, RANTES, and neuronal nitric oxide synthase (nNOS) play a role in both ACs and the brain. We will examine the case-control distribution of these polymorphisms and haplotypes to: 1) test the hypothesis that polymorphisms associated with ACs reduce glioma risk; 2) identify differential misclassification of serf-reported ACs (unequal measurement of cases and controls); 3) find out whether antihistamine use interferes with protection against glioma afforded by ACs; and 4) determine whether AC polymorphisms affect glioma risk independently of their association with ACs. The innovation in the proposed study is to focus on polymorphisms associated with ACs, an epidemiologic risk factor that reduces glioma risk, rather than on polymorphisms associated with carcinogenesis as has been done in previous studies. Our pilot study will make use of interviews with 260 glioma cases and 450 controls that have already been conducted and blood samples that have been collected in conjunction a population-based case-control study of mobile telephone use and brain tumors in Sweden. Study participants were asked whether they have been diagnosed with asthma, eczema, hay fever or other allergies, continue to have allergies, have symptoms of allergies without a diagnosis, and have used allergy medication. Twenty ml of blood from each participant was collected and stored in a -80 degree freezer and DNA preparation is ongoing. Each participant will be evaluated for the presence AC polymorphisms. Unconditional logistic regression will be used to estimate the association between AC polymorphisms and glioma risk. Assuming a 0.05 significance level and 80 percent power, depending on the polymorphism, the proposed sample is large enough to detect a confounding-adjusted odds ratios of 0.6.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CELLULAR DEFECTS IN THE WISKOTT/ALDRICH SYNDROME**
  
  Principal Investigator & Institution: Remold-O'donnell, Eileen; Cbr Institute for Biomedical Research 800 Huntington Ave Boston, MA 02115
  
  Timing: Fiscal Year 2001; Project Start 01-JUN-1997; Project End 31-MAY-2004
  
  Summary: The Wiskott-Aldrich (WAS) is a severe X-linked blood cell disease caused by mutations of the WASP (Wiskott-Aldrich syndrome protein) gene. The most common manifestations of this disease are thrombocytopenia and T lymphocyte based immune defects (eczema etc.). To define the molecular event(s) in Wiskott-Aldrich cells with respect to the role of WASP we intend to undertake biochemical and cell-biological approaches to characterize the pathology of WAS. We will identify blood cell populations from healthy individuals and from WASP- and WASP-defective patients that express WASP. We will determine whether WASP interacts with blood cell components such as CD43, GPIb, actin filaments, ezrin, moesin, Ca++ ions and the protease calpain. We will characterize interacting molecules by immune precipitation and by binding studies with GST fusion proteins of WASP and domains of WASP. We will investigate the effect of WASP depletion in T cells on cytoarchitecture, structure of microvilli, and density and distribution of CD43, ezrin, radixin, moesin and calpain. The relevance of WASP-depletion in Jurkatt cells will be evaluated by comparison with T-cells from WASP patients. We will define defective biochemical event(s) by studying pairs of WASP+ and WASP- T-cells to identify biochemical and morphological events responsible for the nonresponsiveness to immobilized anti-CD3. We will identify neo-epitopes of WAS-patient platelets and lymphocytes responsible for premature loss of the cells from circulation. These studies will allow us to define the molecular events leading to platelet and T lymphocyte defects and loss in the WAS. We hope to contribute to a
better understanding of his disease and to establishing a basis for the development of new rational therapeutic modalities. We anticipate that these studies will also contribute to the understanding of mechanisms that regulate the function and lifespan of T lymphocytes and platelets in normal individuals and their respective disregulation in immunodeficiency diseases.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DEVELOPMENT OF A SAFER SMALLPOX VACCINE**
  Principal Investigator & Institution: Cho, Michael W. Medicine; Case Western Reserve University 10900 Euclid Ave Cleveland, OH 44106
  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-AUG-2004
  Summary: (provided by applicant): Smallpox, which is caused by variola virus, is a highly contagious disease with a high fatality rate. A successful, worldwide vaccination campaign during the 1950s-1970s, using live vaccinia virus, resulted in eradication of smallpox. However, there remains a remote, but distinct possibility that large stockpiles of the virus may have been produced and stored as a part of bioweapons program in some countries or by terrorist organizations that are presently hostile to the United States. Smallpox poses a grave danger as an agent of biological weapon because of its highly contagious nature. Since vaccination against the disease stopped during early 1970s in the U.S., a large number of the young generation is unvaccinated and vulnerable to possible bioterrorist attacks. Although existing smallpox vaccine is relatively safe, it is not without serious medical complications including eczema vaccinatum, vaccinia necrosum, and encephalitis. Given the high frequency of AIDS patients who are immunodeficient, use of the current vaccine could result in a serious public health disaster. Therefore, it is imperative to consider developing a second-generation smallpox vaccine that is safer, yet as effective as the existing vaccine. Presently, variola virus is not available to perform additional research and the immune correlate of protection against either variola or vaccinia virus is largely unknown. Given these circumstances, a study is proposed with a long-term goal of developing a safer smallpox vaccine, with the following specific aims: (1) to characterize humoral and cellular immune responses against vaccinia virus in macaques previously immunized with the virus; (2) to evaluate immunogenicity and degree of attenuation of three recombinant vaccinia viruses derived from two different vaccinia strains (Western Reserve and Wyeth) in mice; and (3) to compare immunogenicity and safety of the newly generated vaccinia virus(es) with those of currently licensed smallpox vaccine strain in macaques previously infected with chimeric SIV/HIV-1 (SHIV). A successful completion of the proposed projects would allow better understanding of immune correlates of protection against vaccinia virus and could facilitate development of a safer smallpox vaccine.
  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DEVELOPMENTAL MECHANISMS OF EARLY LIFE ECZEMA**
  Principal Investigator & Institution: Halonen, Marilyn J. Professor; University of Arizona P O Box 3308 Tucson, AZ 857223308
  Timing: Fiscal Year 2001; Project Start 30-SEP-2001; Project End 31-AUG-2006
  Summary: (Applicant's Abstract) The long term goal of this project is to characterize the immune status of infants at birth and to determine directly in human infants the susceptibility factors and antecedent pathway(s) that lead to eczema in the first two years of life. Early life eczema is a major risk factor for asthma. We will focus on
clarifying the relative roles and identifying the participants of the innate and the adaptive immune system in the development of eczema. Preliminary data lead us to discard the current concept that infants at birth have a Th2 "default" status in favor of a more general state of limited cytokine production in cord blood cells. The hypothetical scenario proposed and tested here is that the immune system at birth has a limited capacity for producing many immune cytokines compared to the adult. This limited capacity may be a result of T cell naivete, immune cell immaturity or active suppression possibly via IL-10 (or some combination of these events). Eczema (we hypothesize) develops in children via complex gene by environment interactions, with an important role for a delayed capacity to produce IFN-gamma that provides a window of opportunity for allergen sensitization. We predict that with full maturation of the response, new sensitization will be reduced but sensitization that has occurred during this window will then be facilitated by LPS. The nature of the fully matured response will be influenced by gene variants in CD14, IL-10 and IL-13. Three specific aims are proposed. 1. Establish the main cellular mechanisms for the limited capacity of cytokine production of the immune cells of human infants at birth and assess the role of IL-10 in inducing and/or maintaining that status. 2. Test the hypothesis that the development of the response to pattern recognition molecules like LPS is delayed in infants who develop eczema and the delay permits enhanced allergen sensitization. 3. Determine the influence of IL-10, IL-13 and CD14 gene polymorphisms on the mechanism of overcoming the decreased capacity to produce IFN-gamma and on allergic sensitization. This project is a cell biology oriented project that focuses on dissecting immune development in early life in both normal infants and infants at risk for asthma and in doing so interfaces with each of the other projects mainly through providing a biologic context for testing in vivo the impact of genetic polymorphisms and the molecular mechanisms identified.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: FUNCTION OF FCERI ON EPIDERMAL LANGERHANS CELLS**

  Principal Investigator & Institution: Borkowski, Teresa A. Professor; Pediatrics; Johns Hopkins University 3400 N Charles St Baltimore, MD 21218

  Timing: Fiscal Year 2001; Project Start 01-SEP-1997; Project End 31-AUG-2002

  Summary: (provided by applicant): The candidate is an assistant professor of dermatology at Johns Hopkins and has commenced the fourth year of this KO8 research program. This application constitutes a request for the fifth year of funding. Langerhans cells (LC) are the principal antigen presenting cells in the skin and part of the network of professional antigen presenting cells. They are responsible for primary and secondary immune T cell responses. Recently the high affinity receptor of IgE (FcERI) has been identified on LC. FcERI complex plays a central role in allergic inflammation. While the function of FcERI in the degranulation of mast cells and basophils is well documented, little is known about the function of this receptor on antigen presenting cells. The aims of this proposal are: 1) To create a model system to study the role of FcERI on Langerhans cells and dendritic cells. 2) To determine the phenotype and changes induced in epidermal Langerhans cells following the ligation of FcERI, and 3) To determine in vivo and in vitro the functional changes induced in epidermal Langerhans cells following the ligation of FcERI. Related studies will determine if FcERI on LC plays a role in the polarization of T cells towards a Th2 phenotype. The studies proposed will be conducted in vitro, and in vivo using a unique transgenic murine model. Unlike human epidermal LC, FcERI is not expressed on murine epidermal LC. However, the mouse that is transgenic for human FcERI alpha (developed by the sponsor) expresses
Eczema

FcERI on epidermal LC. Thus, this mouse is uniquely suited for the study of FcERI on epidermal Langerhans cells in a murine system. Since LC occur in small numbers in human epidermis, a murine model may be the only meaningful way to study this receptor. This transgenic mouse is exclusively available in the Laboratory of Jean-Pierre Kinet M.D., the candidate's sponsor. For this reason, the performance site of this grant is The Laboratory of Allergy and Immunology, Beth Israel Deaconess Medical Center, Boston MA. Preliminary studies of phenotype have determined that IgE regulates the expression of FcER on Langerhans cells and that up-regulation is independent of transcriptional regulation or signaling. The studies proposed here will further explore the mechanisms of upregulation. Preliminary functional studies indicated a need to cross the human alpha transgenic mouse onto a murine alpha knock-out background. Mice are now backcrossed 9 generations, and studies of function may proceed. A fifth year is requested to complete the specific aims indicated above.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

• Project Title: HOUSE DUST MITE ANTIGEN ON SKIN OF PATIENTS WITH ATOPIC DERMATITIS
  Principal Investigator & Institution: Platts-Mills, Thomas A.; University of Virginia Charlottesville Box 400195 Charlottesville, VA 22904
  Timing: Fiscal Year 2001
  Summary: This abstract is not available.
  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

• Project Title: IMMUNOLOGIC BASIS OF COW MILK INDUCED HYPERSENSITIVITIES
  Principal Investigator & Institution: Sampson, Hugh A. Professor; Pediatrics; Mount Sinai School of Medicine of New York University New York, NY 10029
  Timing: Fiscal Year 2001; Project Start 01-AUG-1999; Project End 31-JUL-2003
  Summary: Cow mil is one of the major causes of food hypersensitivity in children. Based on 4 prospective studies, 2.5% of infants develop cow milk allergy in the first year of life [100,000 babies/year in the U.S.] Although exclusive breast feeding reduces the incidence of cow milk allergy, 0.5% of infants exclusively breast fed through the first 6 months of life develop cow milk allergy due to cow milk antigen passed in maternal breast milk. Long-term follow-up indicates that about 80% of these infants "outgrow" their milk allergy by 3 years. However, 15% of infants with milk-specific IgE antibodies at 1 year of age remained milk allergic at 10 years of age and 35% were allergic to other foods at the age of 10 years. Cow milk allergy is associated with a broad spectrum of both IgE- and non-IgE-hypersensitivity disorders: IgE-mediated [urticaria, eczema, rhinoconjunctivitis, asthma, colic, vomiting, diarrhea and hypotension; and non-IgE-mediated [milk-induced enterocolitis syndrome, benign eosinophilic proctocolitis, enteropathy syndrome, allergic eosinophilic gastroenteritis, eosinophilic eosaphagitis, and gastroesopha-geal reflux]. The immunologic mechanisms responsible for these hypersensitivities, and the subsequent development of tolerance are poorly understood, and will be addressed in this program project. The combined resources of this program project provide a unique opportunity to define the immunologic bases for four common forms of cow milk hypersensitivity. The first project will identify four distinct patient groups with cow milk allergy [both IgE- and non-IgE-mediated] and non-allergic control group, establish the relative allergenicity of cow milk proteins and map allergenic epitopes [B cell and/or T cell] in these four forms
of milk hypersensitivity, investigate basic immunologic mechanisms associated with these hypersensitivities and determine the changes that occur when milk allergy is "outgrown". The second project will seek to define whether pathway(s) employed by intestinal epithelial cells [IELs] to handle cow milk proteins differ from those of non-allergens [e.g. tetanus toxoid] and whether IECs from milk allergic patients handle antigen differently compared to normal controls. Since most patients "outgrow" their milk allergy, IEC function will be re-evaluated once clinical tolerance has developed to determine whether antigen processing of cow milk protein changed [normalized], contributing to the loss of hypersensitivity. The third project provides a unique opportunity to address the issue of oral tolerance induction in normal children and those with distinct forms of cow milk hypersensitivity. Finally the fourth project provides an opportunity to dissect basic immunologic mechanisms of IgE-mediated food hypersensitivity not possible in man.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title:** INTERACTIONS BETWEEN PERCEPTUAL AND CONCEPTUAL LEARNING

Principal Investigator & Institution: Goldstone, Robert L. Professor; Psychology; Indiana University Bloomington P.O. Box 1847 Bloomington, IN 47402

Timing: Fiscal Year 2001; Project Start 30-SEP-1999; Project End 31-MAY-2003

Summary: People show a remarkable ability to learn new concepts. Children learn to classify some animals as dogs, some foods as candy, and some people as relatives. Specialized experts learn to classify some mushrooms as poisonous, some tumors as malignant, and some wines as Bordeauxs. The proposed experiments and model explore how people learn new concepts. The central thesis is that concept learning often changes how objects are organized into features. We may build our concepts from the perceptual features of objects, but the concepts that we build in turn influence what we see as the features. The aim of the proposal is to provide a formal account of the interactions between conceptual and perceptual learning. The first series of experiments explores the mechanisms by which concept learning alters descriptions of the objects to be categorized. Particular emphasis is given to selective attention, unitization (integrating originally separate sources of information), and dimensionalization (isolating originally fused sources of information). The second series of experiments uses established and new operational definitions of features to quantify the influence of concept learning on object organization. A neural network model of concept learning is proposed. In this model, the concepts to be acquired alter the perceptual features used for categorization. Rather than assuming that fixed perceptual features are combined to determine categorization rules, this model allows for a mutual and simultaneous influence between concepts and perception. Medical professionals are often required to learn new concepts (e.g., malignant tumor, eczema, and Parkinson's disease). Many of these concepts have a strongly perceptual basis. An understanding of how perceptual concepts are learned, and how perceptual adaptation supports concept learning, could help to more effectively train medical professionals. More generally, the experimental results provide a framework for understanding expert/novice differences, for applying results on neural plasticity to behavior, for establishing training regimes for improving perceptual abilities, and for refining educational procedures that involve teaching concepts with a strong perceptual component.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen
• **Project Title: INTERNATIONAL SYMPOSIUM ON ATOPIC DERMATITIS**

Principal Investigator & Institution: Hanifin, Jon M. Professor; National Eczema Assn for Science & Educ for Science and Education Portland, OR 97205

Timing: Fiscal Year 2001; Project Start 01-MAY-2001; Project End 30-APR-2002

Summary: This conference is being convened to bring together an international group of investigators in the field of atopic dermatitis. The objectives of the Symposium are to: 1) Provide a forum for presenting and discussing important research on atopic dermatitis (AD); 2) Assemble a cadre of recognized international experts from the fields of dermatology, allergy, molecular genetics, epidemiology and immunobiology to develop a comprehensive overview of the condition at the molecular, cellular, tissue, and population levels; 3) Encourage agreement on definitions and criteria for future genetic, epidemiologic and clinical investigations; 4) Identify a list of key research topics that deserve priority consideration by NIH Institutes, investigators, and public/private sector funders; 5) Examine the impact of atopic disease on the prevalence, incidence, and costs of occupational dermatoses, specifically allergic contact dermatitis/hand eczema; 6) Improve the public awareness regarding the scope and prevalence of AD and the range of therapeutic options that are currently available to treat the condition in all of its clinical manifestations. Provide particular emphasis on the special problems faced by non-Caucasian populations with eczema/atopic dermatitis.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

• **Project Title: MECHANISMS OF WASP FUNCTION IN T CELL RESPONSES**

Principal Investigator & Institution: Geha, Raif S. Professor; Beth Israel Deaconess Medical Center St 1005 Boston, MA 02215

Timing: Fiscal Year 2003; Project Start 01-AUG-2003; Project End 31-JUL-2008

Summary: The Wiskott Aldrich syndrome (WAS), an X-linked primary immunodeficiency characterized by deficient T cell function, thrombocytopenia and eczema, is caused by mutations in the WASP gene. WASP is recruited to the immune synapse (IS) where it is thought to be activated by the small GTPase Cdc42 to initiate Arp2/3 mediated actin polymerization. Actin polymerization is important for formation, IL-2 secretion and proliferation by T cells in response to TCR ligation. T cells from patients and mice deficient in WASP fail to increase their cellular F-actin, secrete IL-2 and proliferate following TCR ligation. This suggests that WASP plays a critical role in actin dependent changes that are essential for T cell activation. Our preliminary data suggests that following TCR ligation WASP can be recruited to lipid rafts and the IS by phosphorylated ZAP-70 and that this is mediated by the adapter protein CrkL which bridges p-ZAP-70 to the WASP partner WIP. Interestingly the majority of WASP missense point mutations in WAS are located in the WIP binding WH1 domain. Furthermore, there is data to suggest that the proline rich region of WASP which interacts with SH3 domain containing protein may also be involved in localization of WASP to the IS. We hypothesize that WASP recruitment to GEMs and the IS is mediated by WIP and by the polyproline rich region of WAS, and that it plays a critical role in T cell activation and in the dynamic actin changes in T cells following TCR ligation. To test this hypothesis, we propose to: 1. Analyze the ability of WASP-/- T cells to form an immune synapse and to undergo actin based cytoskeletal changes following TCR ligation by a) examining IS formation with anti-CD3 coated beads, MHC class II-peptide bilayers and antigen presenting cells, b) analyzing reorganization of cellular F-actin, actin cytoskeleton architecture changes and cell motility following engagement of the TCR/CD3 complex. 2. Examine the ability of WASP-/- T cells to form lipid rafts in