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News beyond our pages

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Marc E. Rothenberg, MD, PhD, and Harold S. Nelson, MD, Editors

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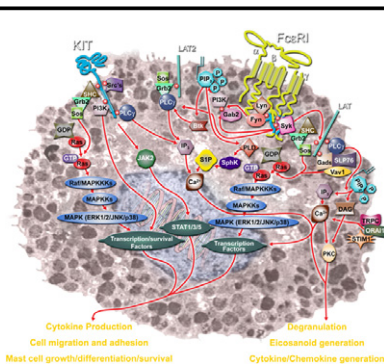
F. Estelle R. Simons, MD, FRCPC, FAAAAI, Winnipeg, Manitoba, Canada

Continuing Medical Education examination: Anaphylaxis: Recent advances in assessment and treatment

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This month's theme: **Anaphylaxis**



About the cover

This month's cover illustrates key signaling events leading to antigen- and KIT-mediated mast cell activation superimposed on an electron micrograph of an LAD2 mast cell (see: Kirshenbaum et al. Characterization of novel stem cell factor responsive human mast cell lines LAD1 and 2 established from a patient with mast cell sarcoma/leukemia; activation following aggregation of FcεRI or FcγRI. *Leukemia Res* 2003;27:677-82). As discussed in the review entitled "Mechanisms of mast cell signaling in anaphylaxis" by Dean D. Metcalfe, Richard D. Peavy, and Alasdair M. Gilfillan (p 639), the mast cell is a crucial player in the generation of anaphylactic responses that are initiated following antigen-dependent, high-affinity IgE receptors (FcεRI) and potentially further enhanced by KIT activation. The use of genetically modified mouse strains and other approaches has allowed the identification of key regulatory steps depicted in the diagram and further discussed in the review article.

The review article by Metcalfe et al is one of several focusing on this month's theme, anaphylaxis. Writing in our Clinical Reviews series, F. Estelle R. Simons (p 625) provides an update on assessing and treating anaphylaxis. In a Current Perspectives article, Scott P. Commins and Thomas A. E. Platts-Mills (p 652) review recent evidence about the role that antibodies to carbohydrate epitopes may play in anaphylactic reactions. Finally, in our Allergy Archives section, Sheldon G. Cohen and Joy C. Mazzullo (p 866) discuss the fascinating history of anaphylaxis and our understanding of it. For additional articles relevant to this theme, look for the red starburst icon in the Table of Contents.

Cover image concept by Drs. Dean Metcalfe, Richard Peavy, and Alasdair Gilfillan. Adapted for the cover by JDI, LLC.



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- Recommendations for appropriate sublingual immunotherapy clinical trials **665**
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Editors' Choice



Online Repository material



Video available online at www.jacionline.org



Theme article



CME activity available online at www.jacionline.org

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Workshop summary

Summary of the 2008 National Institute of Allergy and Infectious Diseases–US Food and Drug Administration Workshop on Food Allergy Clinical Trial Design **671**

Marshall Plaut, MD, Richard T. Sawyer, PhD, and Matthew J. Fenton, PhD, Bethesda, Md

The Editors' choice

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Donald Y. M. Leung, MD, PhD, and Stanley J. Szefler, MD, and the Associate Editors of the JACI

Asthma and lower airway disease

OR

Phenotypic determinants of uncontrolled asthma

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Valérie Siroux, PhD, Anne Boudier, MSc, Jean Bousquet, MD, Jean-Louis Bresson, MD, Jean-Luc Cracowski, MD, Joane Ferran, BSc, Frédéric Gormand, MD, Jocelyne Just, MD, Nicole Le Moual, PhD, Sophie Morange, MD, Rachel Nadif, PhD, Marie-Pierre Oryszczyn, BSc, Christophe Pison, MD, Pierre Scheinmann, MD, Raphaëlle Varraso, PhD, Daniel Vervloet, MD, Isabelle Pin, MD, and Francine Kauffmann, MD, on behalf of the Epidemiological Study on the Genetics and Environment of Asthma, Grenoble, Montpellier, Villejuif, Paris, Lyon, and Marseille, France

This study shows that the lack of asthma control is frequent and is associated with cough/phlegm and female sex in inhaled corticosteroid users and high total IgE and sensitization to molds in inhaled corticosteroid nonusers.

Editorial: Sexual dimorphism: Is it relevant to steroid resistance or asthma control? **688**

Gary M. Hunninghake, MD, MPH, and Diane R. Gold, MD, MPH, Boston, Mass

OR

Reports of suicidality in clinical trials of montelukast

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George Philip, MD, Carolyn Hustad, PhD, Gertrude Noonan, BA, Marie-Pierre Malice, PhD, Alan Ezekowitz, MBChB, DPhil, Theodore F. Reiss, MD, and Barbara Knorr, MD, North Wales, Pa, Rahway, NJ, and Brussels, Belgium

Assessed by using 2 complementary methods across large datasets of montelukast clinical trials, there were no completed suicides. Reports of possibly suicidality-related events in patients receiving montelukast were few and comparable with those seen in subjects receiving placebo.

Editorial: Assessing risk: Data from montelukast clinical trials **697**

Kimberly Kelsay, MD, Denver, Colo

OR

Analysis of behavior-related adverse experiences in clinical trials of montelukast

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George Philip, MD, Carolyn M. Hustad, PhD, Marie-Pierre Malice, PhD, Gertrude Noonan, BA, Alan Ezekowitz, MBChB, Theodore F. Reiss, MD, and Barbara Knorr, MD, North Wales, Pa, Brussels, Belgium, and Rahway, NJ

A retrospective analysis of behavior-related adverse experiences (BRAEs) in montelukast clinical trials showed that few BRAEs were reported, serious BRAEs were rare, and frequencies were similar regardless of treatment group.

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- EC** Plasmacytoid dendritic cells during infancy are inversely associated with childhood respiratory tract infections and wheezing **707**

OR

John W. Upham, MBBS, FRACP, PhD, Guicheng Zhang, PhD, Angela Rate, BSc, Stephanie T. Yerkovich, PhD, Merci Kusel, MBBS, PhD, Peter D. Sly, MD, FRACP, DSc, and Patrick G. Holt, DSc, Perth and Brisbane, Australia

Deficiency of circulating plasmacytoid dendritic cells during infancy is correlated with lower respiratory tract infections and an increased risk of subsequent physician-diagnosed asthma by age 5 years.

- EC** Exhaled nitric oxide levels in asthma: Personal best versus reference values **714**

OR

Andrew D. Smith, MRCP(UK), Jan O. Cowan, and D. Robin Taylor, MD, Dunedin, New Zealand

Do optimum exhaled nitric oxide levels correspond to reference values in patients with ongoing asthma? This study showed that personal best fraction of nitric oxide in exhaled air levels are better than predicted values, but are not necessary for asthma control to be adequately achieved.

- OR** The minimally important difference of the Asthma Control Test **719**

Michael Schatz, MD, MS, Mark Kosinski, MS, Aaron S. Yarlas, PhD, Jennifer Hanlon, MPH, Maria E. Watson, PhD, and Priti Jhingran, PhD, San Diego, Calif, Lincoln, RI, and Research Triangle Park, NC

This study identifies the minimally important difference for the Asthma Control Test (ACT), which allows interpretation of the clinical significance of differences in ACT scores between groups or in an individual over time.

Rhinitis, sinusitis, and upper airway disease

- EC** Modulation by aspirin of nuclear phospho–signal transducer and activator of transcription 6 expression: Possible role in therapeutic benefit associated with aspirin desensitization **724**

OR

John W. Steinke, PhD, Jeffrey A. Culp, MD, Elizabeth Kropf, BS, and Larry Borish, MD, Charlottesville, Va

The cysteinyl leukotriene type 1 receptor and leukotriene C₄ synthase promoters have signal transducer and activator of transcription 6 (STAT6)–binding sites that are engaged by IL-4 but inhibited by aspirin. Aspirin desensitization might provide therapy for aspirin-exacerbated respiratory disease through inhibition of STAT6-mediated production and responsiveness to cysteinyl leukotrienes.

- OR** Domestic use of hypochlorite bleach, atopic sensitization, and respiratory symptoms in adults **731**

Jan-Paul Zock, PhD, Estel Plana, MSc, Josep M. Antó, MD, Geza Benke, PhD, Paul D. Blanc, MD, Aurelia Carosso, MD, Anna Dahlman-Högglund, PhD, Joachim Heinrich, PhD, Deborah Jarvis, MD, Hans Kromhout, PhD, Linnéa Lillienberg, PhD, Maria C. Mirabelli, PhD, Dan Norbäck, PhD, Mario Olivieri, MD, Michela Ponzio, PhD, Katja Radon, PhD, Argo Soon, MD, Marc van Sprundel, MD, Jordi Sunyer, MD, Cecilie Svanes, MD, Kjell Torén, MD, Giuseppe Verlato, MD, Simona Villani, PhD, and Manolis Kogevinas, MD, Barcelona, Spain, Victoria, Australia, San Francisco, Calif, Turin, Verona, and Pavia, Italy, Göteborg and Uppsala, Sweden, Neuberberg and Munich, Germany, London, United Kingdom, Utrecht, The Netherlands, Tartu, Estonia, Antwerp, Belgium, Bergen, Norway, and Heraklion, Greece

This epidemiologic study shows that the use of hypochlorite bleach is associated with less atopic sensitization but with more respiratory symptoms in adults who do the cleaning in their homes.

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The LOCAL Study: Local reactions do not predict local reactions in allergen immunotherapy 739

Christopher W. Calabria, MD, Christopher A. Coop, MD, and Michael S. Tankersley, MD, San Antonio, Tex

Local reactions do not predict local reactions at the next immunotherapy injection in a clinic that does not dose-adjust for local reactions.

OR

Cats and dogs and the risk of atopy in childhood and adulthood 745

Piush J. Mandhane, MD, Malcolm R. Sears, MB, Richie Poulton, PhD, Justina M. Greene, DipCompSys, W. Y. Wendy Lou, PhD, D. Robin Taylor, MD, and Robert J. Hancox, MD, Edmonton, Alberta, and Hamilton and Toronto, Ontario, Canada, and Dunedin, New Zealand

Having both a cat and a dog is associated with a lower risk of atopy in childhood and early adulthood. Ownership of either animal alone is not protective.

Editorial: Does exposure to cats and dogs decrease the risk of allergic sensitization and disease? 751

Päivi M. Salo, PhD, and Darryl C. Zeldin, MD, Research Triangle Park, NC

Atopic dermatitis and skin disease

OR

Expression of chemokines and chemokine receptors in lesional and nonlesional upper skin of patients with atopic dermatitis 753

Eva Gros, MSc, Caroline Bussmann, MD, Thomas Bieber, MD, PhD, Irmgard Förster, PhD, and Natalija Novak, MD, Bonn and Düsseldorf, Germany

Disease- and stage-specific changes in the CCR and langerin expressions of dendritic cells and chemokine levels in the skin are important in atopic dermatitis.

EC

Exaggerated IL-17 response to epicutaneous sensitization mediates airway inflammation in the absence of IL-4 and IL-13 761

OR

Rui He, MD, PhD, Hye Young Kim, PhD, Juban Yoon, PhD, Michiko K. Oyoshi, PhD, Andrew MacGinittie, MD, Sho Goya, MD, PhD, Eva-Jasmin Freyschmidt, PhD, Paul Bryce, PhD, Andrew N. J. McKenzie, PhD, Dale T. Umetsu, MD, PhD, Hans C. Oettgen, MD, PhD, and Raif S. Geha, MD, Boston, Mass, and Cambridge, United Kingdom

Blockade of IL-4 and IL-13 promotes the T_H17 response and results in IL-17–mediated airway inflammation and airway hyperresponsiveness after airway challenge in a murine model of allergic skin inflammation elicited by epicutaneous sensitization.

Food, drug, insect sting allergy, and anaphylaxis

OR

Lipid transfer protein (Ara h 9) as a new peanut allergen relevant for a Mediterranean allergic population 771

Susanne Krause, PhD, Gerald Reese, PhD, Stefanie Randow, BTA, Danila Zennaro, MD, Donato Quarantino, MD, Paola Palazzo, BD, Maria Antonietta Ciardiello, PhD, Arnd Petersen, PhD, Wolf-Meinhard Becker, PhD, and Adriano Mari, MD, Borstel and Längen, Germany, and Rome and Naples, Italy

The evaluation of the immunologic properties of peanut lipid transfer protein (Ara h 9) using sera from subjects with peanut and peach allergy from Italy demonstrated that Ara h 9 is an allergen that should be included in peanut component–resolved diagnosis.

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Yuki Hitomi, PhD, Motohiro Ebisawa, MD, PhD, Morimitsu Tomikawa, MD, Takanori Imai, MD, PhD, Takatsugu Komata, MD, Tomomitsu Hirota, DDS, PhD, Michishige Harada, PhD, Masafumi Sakashita, MD, Yoichi Suzuki, MD, PhD, Naoki Shimojo, MD, PhD, Yoichi Kohno, MD, PhD, Kimie Fujita, MD, PhD, Akihiko Miyatake, MD, PhD, Satoru Doi, MD, PhD, Tadao Enomoto, MD, PhD, Masami Taniguchi, MD, PhD, Noritaka Higashi, MD, PhD, Yusuke Nakamura, MD, PhD, and Mayumi Tamari, MD, PhD, Kanagawa, Sagamihara, Chiba, Shiga, Osaka, Wakayama, and Tokyo, Japan

NLRP3 polymorphisms are significantly associated with susceptibility to food-induced anaphylaxis and aspirin-induced asthma through their functional effects on higher expression of *NLRP3* transcripts.



- Elevated serum cytokines during human anaphylaxis: Identification of potential mediators of acute allergic reactions 786



Shelley F. Stone, PhD, Claire Cotterell, BSc (Hons), Geoffrey K. Isbister, MBBS, MD, FACEM, Anna Holdgate, MBBS, MMED, FACEM, and Simon G. A. Brown, MBBS, PhD, FACEM, Perth, Darwin, Newcastle, Sydney, and Fremantle, Australia

IL-6, IL-10, TNF receptor I, histamine, and mast cell tryptase were elevated in severe anaphylaxis compared with moderate allergic reactions and correlated with hypotension, but not hypoxemia or other respiratory features.

Immune deficiencies, infection, and systemic immune disorders



- Reduced central tolerance in Omenn syndrome leads to immature self-reactive oligoclonal T cells 793

Raz Somech, MD, PhD, Amos J. Simon, PhD, Atar Lev, MSc, Ilan Dalal, MD, Zvi Spierer, MD, Itamar Goldstein, MD, Meital Nagar, MSc, Ninette Amariglio, PhD, Gideon Rechavi, MD, PhD, and Chaim M. Roifman, MD, Tel Aviv and Holon, Israel, and Toronto, Ontario, Canada

T-cell oligoclonal expansion in Omenn syndrome emanates from an incomplete block before the maturation stage of negative selection, where the autoimmune regulator plays a critical role. These cells show a pattern of gene expression compatible with autoimmunity.

- Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks 801

Timothy J. Craig, MD, Robyn J. Levy, MD, Richard L. Wasserman, PhD, MD, Agaiandra K. Bewtra, MD, David Hurewitz, MD, Krystyna Obtulowicz, MD, Avner Reshef, MD, Bruce Ritchie, MD, Dumitru Moldovan, MD, Todor Shirou, MD, Vesna Griucheva-Panovska, MD, Peter C. Kiessling, PhD, Heinz-Otto Keinecke, MS, and Jonathan A. Bernstein, MD, Hershey, Pa, Atlanta, Ga, Dallas, Tex, Omaha, Neb, Tulsa, Okla, Krakow, Poland, Tel Hashomer, Israel, Edmonton, Alberta, Canada, Tirgu Mures, Romania, Sofia, Bulgaria, Skopje, Republic of Macedonia, Marburg, Germany, and Cincinnati, Ohio

Compared with placebo, C1 esterase inhibitor at a dose of 20 U/kg, but not 10 U/kg, significantly shortened the time to onset of symptom relief in acute hereditary angioedema attacks, providing a statistically secure dosing recommendation.

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Mechanisms of allergy and clinical immunology

- OR** Prostaglandin E₂–EP₃ signaling suppresses skin inflammation in murine contact hypersensitivity **809**
Tetsuya Honda, MD, PhD, Toshiyuki Matsuoka, MD, PhD, Mayumi Ueta, MD, PhD, Kenji Kabashima, MD, PhD, Yoshiki Miyachi, MD, PhD, and Shuh Narumiya, MD, PhD, Kyoto, Japan
Prostaglandin E receptor subtype EP₃ signaling suppresses skin allergic inflammation through modulation of keratinocyte function.
- EC** Induction of long-lived allergen-specific plasma cells by mucosal allergen challenge **819**
OR *Elke O. Luger, PhD, Verena Fokuhl, MSc, Michael Wegmann, PhD, Melanie Abram, MSc, Kati Tillack, MSc, Gernot Achatz, PhD, Rudolf A. Manz, PhD, Margitta Worm, MD, Andreas Radbruch, PhD, and Harald Renz, MD, Berlin and Marburg, Germany, and Salzburg, Austria*
Inhalation of allergen induces short-lived allergen-specific plasma cells locally in the lungs; these cells survive in the bone marrow and spleen and are resistant to conventional cyclophosphamide treatment. Prospectively, targeting of IgE-mediated allergies will therefore require different therapeutic strategies.
- OR** Critical role of IgE-dependent mast cell activation in a murine model of allergic conjunctivitis **827**
Ken Fukuda, MD, PhD, Masabaru Ohbayashi, PhD, Kei Morohoshi, MD, PhD, Lane Zhang, BS, Fu-Tong Liu, MD, PhD, and Santa J. Ono, PhD, Atlanta, Ga, and Sacramento, Calif
Connective tissue–type mast cells were successfully reconstituted in conjunctiva of *Kit^{W^{-sh}/W^{-sh}}* mice. The authors demonstrated a direct contribution of IgE-activated mast cells to both the early-phase reaction and late-phase inflammation during ocular allergy.
- OR** The occupant as a source of house dust bacteria **834**
Martin Täubel, PhD, Helena Rintala, PhD, Miia Pitkäranta, MSc, Lars Paulin, MSc, Sirpa Laitinen, PhD, Juha Pekkanen, MD, Anne Hyvärinen, PhD, and Aino Nevalainen, PhD, Kuopio and Helsinki, Finland
This study detected a strong presence of human-derived bacteria in mattress and floor dust. The health relevance of human-derived versus nonhuman-derived microbial exposures in relation to asthma and allergy needs to be established.


Letters to the Editor

-  Anaphylactic reaction to (mixed) fruit juice containing dragon fruit **841**
Andreas Kleinheinz, MD, Ute Lepp, MD, Björn M. Hausen, MD, Arnd Petersen, PhD, and Wolf-Meinhard Becker, PhD, Buxtehude and Borstel, Germany
Dragon fruit (pitaya), a novel ingredient of popular beverages, is described as a source of allergen. A nonspecific lipid transfer protein, which shows no cross-reactivity to peach lipid transfer protein (Pru p 3), is identified as the causative allergen.

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-  Induction of IL-10–producing regulatory T cells with TCR diversity by epitope-specific immunotherapy in pollinosis **842**

Kei-ichi Yamanaka, MD, Atsushi Yuta, MD, Masato Kakeda, MD, Ryogen Sasaki, MD, Hiroshi Kitagawa, MD, Esteban C. Gabazza, MD, Kimihiro Okubo, MD, Ichiro Kurokawa, MD, and Hitoshi Mizutani, MD, Kawasaki, Japan

This is the first report showing upregulation of an IL-10–producing regulatory T-cell population with a highly diverse T-cell receptor repertoire in patients receiving allergen-specific immunotherapy.

- Serum tryptase levels in atopic and nonatopic children **845**


Hirsh D. Komarow, MD, Zonghui Hu, PhD, Erica Brittain, PhD, Ashraf Uzzaman, MD, Donna Gaskins, RN, and Dean D. Metcalfe, MD, Bethesda, Md

This study establishes normative serum reference tryptase values in atopic and nonatopic children. Among atopic subjects, a statistically significant association with tryptase was found for sex and race but not for ethnicity, total IgE levels, weight/weight percentile, and eczema status.

- Polyethylene glycol–modified adenosine deaminase improved lung disease but not liver disease in partial adenosine deaminase deficiency **848**

Raz Somech, MD, Yew Hon Lai, MD, Eyal Grunebaum, MD, Nicole Le Saux, MD, Ernest Cutz, MD, and Chaim M. Roifman, MD, Toronto and Ottawa, Ontario, Canada

Partial adenosine deaminase (ADA) deficiency can be associated with severe lung and liver disease. Lung disease improved promptly on treatment with PEG-ADA, suggesting tissue damage had been caused by nucleoside metabolites. In contrast, liver disease did not improve unless corticosteroid treatment was introduced, suggesting autoimmune-mediated tissue damage.

-  Higher incidence of pediatric anaphylaxis in northern areas of the United States **850**

William J. Sheehan, MD, Dionne Graham, PhD, Lin Ma, MS, Sachin Baxi, MD, and Wanda Phipatanakul, MD, MS, Boston, Mass



The authors queried a nationwide billing database of US pediatric hospitals. When evaluating cases of anaphylaxis, they found higher rates of pediatric anaphylaxis in northern areas than in southern areas of the United States.

- Associations between prenatal pesticide exposure and cough, wheeze, and IgE in early childhood **852**

Ann Marie Reardon, MA, Matthew S. Perzanowski, PhD, Robin M. Whyatt, DrPH, Ginger L. Chew, ScD, Frederica P. Perera, DrPH, and Rachel L. Miller, MD, New York, NY

This study compares prenatal urban residential pesticide levels with subsequent pediatric asthma symptoms and IgE production. Significant associations between diazinon and cis-permethrin levels and early cough were found.

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A pilot study of equal doses of 10% IGIV given intravenously or subcutaneously **854**

Shilpa H. Desai, BS, MD, Akhil Chouksey, MD, John Poll, RN, and Melvin Berger, MD, PhD, Cleveland, Ohio

A pilot study in subjects with primary immunodeficiency compared the same dose of 10% IGIV given subcutaneously and intravenously. Both were efficacious, and 10 of 11 subjects preferred the subcutaneous route. Dosing requirements for subcutaneous IgG warrant further study.

Cyclosporin A reduces CD4⁺CD25⁺ regulatory T-cell numbers in patients with atopic dermatitis **856**

DirkJan Hijnen, MD, PhD, Inge Haeck, MD, Annemieke A. van Kraats, MSc, Evert Nijhuis, PhD, Marjolein S. de Bruin-Weller, MD, PhD, Carla A. F. M. Bruijnzeel-Koomen, MD, PhD, and Edward F. Knol, PhD, Utrecht, The Netherlands

Cyclosporin A is increasingly being used in the treatment of severe atopic dermatitis. The authors observed that cyclosporin A reduces the number of peripheral blood regulatory T cells in patients with atopic dermatitis.

Correspondence

Vitamin C for the common cold should not be rejected on the basis of old and erroneous articles **859**

Harri Hemilä, MD, PhD, Helsinki, Finland

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Timothy Mainardi, MD, Simi Kapoor, MD, and Leonard Bielory, MD, Springfield, NJ

Natural killer T cells in bronchial biopsies from human allergen challenge model of allergic asthma **860**

Catherine Reynolds, PhD, Julia Barkans, BSc, Peter Clark, PhD, Harsha Kariyawasam, MD, PhD, Daniel Altmann, PhD, Barry Kay, MD, PhD, and Rosemary Boyton, MD, PhD, London, United Kingdom

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Ponpan Matangkasombut, MD, SD, Rosemarie H. DeKruyff, PhD, and Dale T. Umetsu, MD, PhD, Boston, Mass

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Bettina Seidl, BSci, Behnam Kalali, PhD, Markus Gerhard, MD, Johannes Ring, MD, Markus Ollert, MD, and Martin Mempel, MD, Munich, Germany

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Toshiro Takai, PhD, Anh Tuan Vu, MD, Tuan Anh Le, MD, PhD, Hirokazu Kinoshita, MD, PhD, Hiroko Ushio, DVM, PhD, Shigaku Ikeda, MD, PhD, Hideoki Ogawa, MD, PhD, and Ko Okumura, MD, PhD, Tokyo, Japan

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Sheldon G. Cohen, MD, and Joy C. Mazzullo, Bethesda, Md



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