AllergyWatch®

" 10th Anniversary Edition "

A Synopsis of Allergy and Asthma Literature, Resulting from an Unbiased, Comprehensive Review of Nineteen Major Medical Journals.

A Publication of The American College of Allergy, Asthma & Immunology

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From the Editor

ON behalf of our coeditors, I would like to extend congratulations on our 10th Anniversary to everyone who has worked so hard on this publication over the years. We feel that this effort provides a valuable service to our readers all over the world. I would like to extend a special thanks to Mary Lou Callaghan at the ACAAI who has helped us shepherd this endeavor every step of the way. Since Bud Bardana has been the inspiration for our efforts, I have asked him to commemorate this anniversary by reflecting from the pages of AllergyWatch *10 years ago. I'm sure you'll find his thoughts insightful as always. Enjoy!*

Best Regards, and Happy New Year!

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" In **Allergy Warch** 10 Years Ago..."

'Has Reduced Aspirin Use Led to Increased Prevalence of Childhood Asthma?'

IT is difficult to believe that an inspiration conceived over my kitchen table with then ACAAI President Jean A. Chapman is now a decade old. *AllergyWatch* has evolved in this period and now covers more articles from more journals. Thanks to the diligent work of the new Editor, Tony Montanaro, and his entire editorial staff, the ACAAI executive staff and our generous sponsors, this publication has become an important source of unbiased continuing medical education. I am pleased we have kept *AllergyWatch* free of advertisement.

Our first complete issue, Jan/Feb 1999, featured an article reporting the linkage of aspirin to Reye's syndrome in the early 1980s with a subsequent reduction in aspirin use and a concomitant rise in the prevalence ➤➤

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The following journals have been selected as the primary focus of review in the preparation of materials within "AllergyWatch®".

- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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of childhood asthma (Varner AE, et al: **Ann Allergy Asthma Immunol**. 1998;81:347-351). Varner et al. postulated that aspirin blocks the cyclo-oxygenase-2 pathway and inhibits production of prostaglandin E2. Acetaminophen does not have this effect. Prostaglandin E2 affects the balance between Th1 and Th2 cytokines. In children with an atopic phenotype, acetaminophen causes a shift in the Th1:Th2 balance favoring development of allergic sensitization and asthma.

A decade later, *AllergyWatch* Nov/Dec 2008 highlighted an investigation that implicated acetaminophen as a significant risk factor for asthma and other allergic diseases in children (Beasley R, et al.: **Lancet** 2008;372:1039-1048). These investigators report an impressive dose-response relationship with risk factors extending over 30 countries in a sample of over 200,000 children. The lesson from these observations is that parents should be very cautious dispensing either of these drugs in children under age 7.
E.J.B. ♦♦

Acetaminophen During Pregnancy Linked to Wheezing During Infancy

THE reasons for the recent increase in asthma prevalence in developed countries are unknown. One possible contributor is the shift toward using acetaminophen, rather than aspirin, in pregnant women and young children. Acetaminophen use during pregnancy was evaluated as a risk factor for the development of asthma during the first year of life.

Three hundred forty-five women were followed up from the first trimester of pregnancy through the first year of their child's life. Acetaminophen use during pregnancy was assessed by questionnaire. Associations between prenatal exposure to acetaminophen and the development of wheezing and other respiratory events during the first year of life were sought.

Acetaminophen use during early pregnancy was unrelated to respiratory symptoms in the first year of life. However, infants of women who took acetaminophen in middle to late pregnancy were more likely to develop wheezing, odds ratio 1.8; and wheezing that caused sleep disturbance, odds ratio 2.1. The associations remained significant after adjustment for potential confounders, such as infections during pregnancy.

Acetaminophen use during middle to late pregnancy may be a risk factor for the development of wheezing during the first year of life. This association may be related to depletion of the antioxidant glutathione by acetaminophen. Confirmatory studies in other cohorts could have important public health implications.

COMMENT: *Epidemiologic studies often create more questions than provide answers. Acetaminophen use during pregnancy is another in a long list of factors that potentially increase the risk of developing asthma. The mechanism of action--depletion of glutathione resulting in an increase in oxidative inflammation--provides plausibility. The debate will continue as to the cause of the increase in asthma, but for the time being I will continue to offer acetaminophen for fever or pain.*
D.K.L.
Persky V, Piorkowski J, Hernandez E, et al: Prenatal exposure to acetaminophen and respiratory symptoms in the first year of life.
Ann Allergy Asthma Immunol. 208;101:271-278. ♦♦

WHAT'S NEW IN SLIT?

Grazax Is Cost-Effective in the U.K.

IN the United Kingdom, the sublingual grass pollen tablet Grazax is approved for use in immunotherapy of grass pollen-induced rhinoconjunctivitis, with or without asthma. This study assessed the cost-effectiveness of sublingual immunotherapy using Grazax in patients with rhinoconjunctivitis and co-existing asthma.

Using data from a prospective clinical trial, the pharmacoeconomic analysis included 79 patients assigned to Grazax and 72 to placebo. Both groups had access to symptom-relieving medications, ie, standard care. Information on health resource utilization, missed work time, and quality of life were collected as part of the trial; effects on productivity on the job were estimated from the literature. Cost-effectiveness analysis was performed using the U.K. National Health Service price for Grazax, £2.25 per tablet.

Over a time horizon of 9 years, the gain in quality-adjusted life-years (QALYs) was significantly greater for patients receiving Grazax than in the placebo group. Grazax was associated with a gain of 0.197 QALYs 9 years into the future--equivalent to an extra 72 days of perfect health. Patients in the Grazax group also had increased resource utilization and productivity loss. Immunotherapy with Grazax was highly cost-effective, with a cost of £4,319 per QALY gained. On sensitivity analysis, Grazax would remain cost-effective up to a tablet price of £5.07.

The results support the cost-effectiveness of sublingual immunotherapy for patients with grass pollen-induced rhinoconjunctivitis and asthma. This form of treatment improves quality of life and productivity compared to symptomatic medication only. Cost per QALY is less than that of other accepted treatments.

COMMENT: *Grazax (sublingual grass pollen immunotherapy tablet) is an exciting new monotherapy for grass pollen allergy that is in use in Europe and under active development in the United States. Since the efficacy of sublingual immunotherapy depends on delivering doses over time far in excess of doses required for subcutaneous immunotherapy, the costs of the allergen protein in the product become important. In England, the price of Grazax is about $5 per day. The results of this study suggest that this treatment is cost-effective up to a price of about $10 per day. It remains to be seen how these cutoffs apply to the U.S. market, and how Grazax will be priced if and when it is approved in the United States.*

S.A.T.

Nasser S, Vestenbæk U, Beriot-Mathiot A, Poulsen PB: Cost-effectiveness of specific immunotherapy in allergic rhinitis co-existing with asthma.

Allergy. 2008;63:1624-1629. ♦♦

Some U.S. Allergists Using SLIT

SUBLINGUAL immunotherapy (SLIT) has been rapidly accepted in Europe, but not in the United States. There are few data on the current use of SLIT by American allergists. This study evaluated perceptions and practice of SLIT among practicing allergists in the United States.

An electronic survey regarding perceptions and use of SLIT was sent to practicing allergists who were members of the American College of Allergy, Asthma and Immunology in 2007. A total of 828 responses were received, for a rate of 25.7%. Of the respondents, 766 practiced in the United States.

The main reason for not using SLIT, cited by 61.7% of respondents, was a lack of products approved by the Food and Drug Administration (FDA). When asked what their practice would be if SLIT was approved by the FDA, 65.7% of respondents said they would use it to treat allergic rhinitis, 45.5% to treat children under 5, and 40.9% to treat moderate to severe asthma.

Forty-five allergists reported current SLIT use, a rate of 5.9%. Most SLIT users believed that SLIT was at least as effective as subcutaneous immunotherapy. About two-thirds said their patients paid for SLIT out of pocket. Seventy-nine percent of allergists who used SLIT reported using commercial extracts intended for subcutaneous immunotherapy. The patient was required to take SLIT in the office by 53.5% of clinicians--however, 81.8% did this only with the first dose. In 41.5% of cases, the allergists provided their SLIT patients with epinephrine injectors.

Most U.S. allergists view SLIT as safe and effective and would use it if approved by the FDA. About 6% of U.S. allergists are already using SLIT. The authors call for more research to clarify the optimal dosing and formulation of SLIT.

D.K.L.

Tucker MH, Tankersley MS, on behalf of the ACAAI Immunotherapy and Diagnostics Committee: Perception and practice of sublingual immunotherapy among practicing allergists.

Ann Allergy Asthma Immunol. 2008;101:419-425. ♦♦

German Study Confirms Cost-Effectiveness of SCIT

SUBCUTANEOUS immunotherapy (SCIT) is of confirmed efficacy for allergic rhinitis and asthma. However, there have been few economic evaluations of this widely used therapy. The authors evaluated the cost-effectiveness of SCIT in the German health care system.

A cost-effectiveness analysis was performed using Markov models, with assumptions drawn from the literature or by consensus of a board of experts. The cost-effectiveness of SCIT plus symptomatic therapy, compared to symptomatic therapy alone, was assessed from a societal perspective.

Based on analysis of 15-year costs, adding SCIT to symptomatic therapy produced annual cost savings ➤➤

of €140 per patient. The breakeven point was reached after a 10-year duration of allergic rhinitis or allergic asthma. The incremental cost-effectiveness ratio of SCIT per quality-adjusted life-year (QALY) was about €-20,000 overall, €-22,000 for adults, €-15,000 for adolescents, and €-13,000 for children. Costs were somewhat higher from the third-party payer's perspective, with a ratio of €8,000 per QALY overall. On sensitivity analysis, the cost-effectiveness of SCIT would be greater if treatment duration could be decreased while maintaining clinical benefits.

The results clearly demonstrate the cost-effectiveness of SCIT for patients with allergic rhinitis or asthma. Adding SCIT to symptomatic therapy improves clinical outcomes while reducing costs. The cost reductions arise mainly from prevention of severe disease, thus decreasing demand for medical resources and avoiding lost productivity.

COMMENT: *This paper is another contribution to the literature validating the value of SCIT. This conservative analysis focused on the benefits from a societal perspective and concluded that SCIT is an "indisputable cost-effective treatment." Let's hear it for the Germans.*
D.K.L.
Brüggenjürgen B, Reinhold T, Brehler R, et al: Cost-effectiveness of specific subcutaneous immunotherapy in patients with allergic rhinitis and allergic asthma.
Ann Allergy Asthma Immunol. 2008;101:316-324. ♦♦

Exhaled NO Linked to Atopy in Children

PREVIOUS studies suggest that atopy may mediate the increase in exhaled nitric oxide (eNO) in patients with asthma. However, many factors may affect eNO, so the significance of eNO measurements in epidemiologic studies remains unclear. This study assessed factors influencing eNO levels in schoolchildren with and without respiratory diseases.

The study included a random sample of Italian schoolchildren, aged 10 to 16 years. Asthma and other respiratory symptoms were assessed by questionnaire; spirometry, skin testing, and eNO measurement were performed as well. Variables affecting eNO were analyzed by logistic regression.

Asthma symptoms were reported by 13.7% of children, rhinitis symptoms by 46.9%, and no respiratory symptoms by 39.4%. The ratio of FEV_1 to forced vital capacity in these groups was 87.6%, 90.6%, and 90.4%, respectively. Atopy was present in 52.2% of children with asthma symptoms, 40.1% with rhinitis, and 28.8% without respiratory symptoms. Eighty-two percent of atopic children had a positive skin test for house dust mite.

The median eNO level was 21.2 ppb for children with atopy versus 12.6 ppb for nonatopic children. Among children without respiratory symptoms, eNO was higher for those with atopy. In contrast, among nonatopic children, log-transformed eNO levels were not significantly different for those with asthma, rhinitis, or no symptoms. Log-transformed eNO levels increased with the number of positive skin test results. Independent predictors of increased eNO were atopy, asthma, male sex, and sensitization to indoor allergens.

In this cross-sectional analysis of Italian schoolchildren, atopy is a significant predictor of higher eNO levels. The association is particularly strong for sensitization to indoor and perennial allergens and is enhanced among children reporting asthma symptoms. The findings suggest a role of eNO measurement as a screening test to assess predisposition to allergic disease.

COMMENT: *The value of measuring eNO remains a point of debate in the literature. This survey of children suggests that increases in eNO are an indication of higher probability of sensitivity to perennial allergens and of asthma. Thus this measurement may be of value in large epidemiologic surveys, even if its value in daily asthma management remains controversial.*
D.K.L.
Cibella F, Cuttitta G, La Grutta S, et al: Factors that influence exhaled nitric oxide in Italian schoolchildren.
Ann Allergy Asthma Immunol. 2008;101:407-412. ♦♦

Hygiene Hypothesis Mechanism Revealed: NOT!

EARLY childhood exposure to pets has been linked to a reduced risk of wheezing and atopy, but the mechanism of this association remains unclear. One possible explanation is exposure to innate immune stimuli, leading to an altered pattern of immune development. This hypothesis was examined using data from a prospective study of the factors associated with the development of childhood asthma.

The analysis included data on 275 children at high risk of developing allergic diseases, enrolled in the Childhood Origins of ASThma (COAST) study. Pet ownership, cytokine responses, and allergen-specific IgE were assessed up to age 3 years. Samples of settled dust from 101 homes were assessed for the presence of pet allergens and for innate immune stimuli, including endotoxin, a marker of Gram-negative bacteria; muramic acid, a marker of Gram-positive bacteria; and ergosterol, a marker of fungi.

The rate of atopic dermatitis at age 3 was 12% for children exposed to dogs at birth compared to 27% for nonexposed children. Rates of wheezing were 19% versus 36%. Both outcomes were more frequent for children with later exposure to dogs: 23% for atopic dermatitis and 42% for wheezing.

Rates of sensitization to dog ranged from 10% to 12%, and were unrelated to dog exposure. Dust levels of Can f 1 were positively associated with blood cell interleukin (IL)-10, IL-5, and IL-13 responses at age 1 and to IL-5 and IL-13 responses at age 3. Levels of endotoxin in dust were related to interferon-γ responses and IL-13 at age 3 but not age 1; dust muramic acid levels showed a similar pattern of associations. The relationship between dog allergen exposure and cytokine responses was unaffected by adjustment for levels of innate immune stimuli.

Children with early exposure to dogs, particularly in the period soon after birth, have reduced rates of➤➤

wheezing and atopy along with altered patterns of immune development. However, these associations do not result from exposure to innate immune stimuli in settled dust. Further study is needed to explain the protective effect of dog exposure.

COMMENT: *Early exposure to pet dander appears to reduce the risk of developing asthma. This observation has been interpreted as supporting the "hygiene hypothesis," though the mechanisms have been difficult to prove. These authors used the COAST study cohort to assess clinical and immunological differences between infants with and without pet dander exposure. There was also an analysis of household dust for endotoxin, ergosterol, and muramic acid. Dog exposure was associated with a 50% lower incidence of wheezing and atopy, but there was no correlation between this observation and components of household dust that are known to stimulate the innate immune system.*
S.A.T.
Bufford JD, Reardon CL, Li Z, et al: Effects of dog ownership in early childhood on immune development and atopic diseases.
Clin Exp Allergy. 2008;38:1635-1643. ♦♦

Mouse and Cockroach IgE Linked to Allergic Symptoms in Urban Children

EARLY sensitization to indoor allergens is an important predictor of asthma and atopy in children. Little is known about the effects of exposure and/or sensitization to allergens of special importance to asthma in inner-city children--ie, mouse and cockroach. This study evaluated the association between anti-mouse and anti-cockroach IgE and respiratory symptoms and atopy in inner-city children.

A cohort of African American and Dominican children in New York City were prospectively followed up from birth to age 3. Home dust samples were collected for measurement of cockroach and mouse allergen, and levels of anti-mouse and anti-cockroach specific IgE were measured in serum samples. Allergen exposure and sensitization were evaluated as predictors of parent-reported wheezing, rhinitis, and atopic dermatitis.

By 3 years of age, 11% of children tested positive for anti-cockroach IgE, 10% for anti-mouse IgE, and 5% for both. The risk of early wheezing was elevated for all three groups: odds ratio 3.3, 4.6, and 9.7, respectively. For atopic dermatitis, the odds ratios were 3.0 for anti-cockroach IgE, 2.5 for anti-mouse IgE, and 4.7 for both. As IgE class for cockroach and mouse increased, so did the rate of wheezing and atopic dermatitis.

The presence of anti-cockroach and anti-mouse IgE is associated with increased rates of wheezing and atopy among young inner-city children. Analysis of the effects of IgE class suggests a dose-response relationship. Efforts to reduce cockroach and mouse exposure for susceptible children might help to reduce their risk of asthma.

COMMENT: *In this well-designed, prospective birth cohort study, the development of anti-cockroach and anti-mouse IgE by age 3 years was associated with an increased risk of wheeze, rhinitis, and atopic dermatitis. Although there was no direct relationship between measured home allergen levels and sensitization or atopic illness, the authors suggest that interventions to reduce allergen exposure may benefit at-risk children.*
S.M.F.
Donahue KM, Al-alem U, Perzanowski MS, et al: Anti-cockroach and anti-mouse IgE are associated with early wheeze and atopy in an inner-city birth cohort.
J Allergy Clin Immunol. 2008;122:914-920. ♦♦

PASTURE Study Shows in Vitro Production of IgE Antibodies

THERE is interest in the possibility that the process of allergic sensitization may begin in utero, through some process involving the maternal immune system and environmental factors. Maternal exposure to microbial compounds in the farm environment during pregnancy has been linked to a reduced risk of atopic and allergy in offspring. Data from a prospective study of rural pregnant women were used to study factors associated with levels of allergen-specific IgE in umbilical cord blood.

The prospective Protection against Allergy-Study in Rural Environments (PASTURE) study included two groups of pregnant women living in rural areas of Europe: women living on livestock farms and women living in the same region but not on farms. Cord blood samples from 922 newborns were obtained to measure allergen-specific IgE antibodies against 20 common allergens; blood samples from mothers and fathers were evaluated as well. Relationships between cord blood specific IgE levels and parental sensitization, cord blood cytokine responses, and environmental factors were assessed.

Cord blood from 23.9% of infants showed detectable levels of allergen-specific IgE, including rates of 16.4% for any food allergen, 11.2% for any inhalant allergen, and 8.2% for any seasonal allergen. Assessment of IgA antibodies, among other factors, excluded possible contamination with maternal serum. Significant correlations between maternal and cord blood IgE levels were noted only for hen's egg, cow's milk, and soybean allergen. Higher levels of fetal IgE were correlated with reduced production of interferon-γ in cord blood. This was accompanied by a shift in the ratio of interferon-γ to interleukin-5, although fetal IgE was unrelated to interleukin-5 and interleukin-10 production.

This prospective study demonstrates the presence of allergen-specific IgE antibodies, probably of fetal origin, in cord blood samples. The inverse association between cord blood IgE antibody levels and IFN-γ suggests that fetal production of IgE antibodies is related to suppression of the Th1 response. The effects of maternal farm-related exposures on cord blood IgE are reported separately (Ege MJ, et al: **J Allergy Clin Immunol**. 2008;122:407-412).

COMMENT: *Using data from the large multicenter birth cohort PASTURE study, these researchers found that production of IgE is likely to start in utero. Allergen-specific IgE antibodies were detectable in* ➤➤

cord blood from 23.9% of newborns. Previous studies of cord blood IgE generally demonstrate low sensitivity for predicting future allergic disease. Since the PASTURE project is ongoing, we'll be on alert for future reports about this cohort.
S.M.F.
Pfefferie PE, Sel S, Ege MJ, et al: Cord blood allergen-specific IgE is associated with reduced IFN-γ production by cord blood cells: the Protection against Allergy-Study in Rural Environments (PASTURE) study.
J Allergy Clin Immunol. 2008;122:711-716. ♦♦

Subjective vs Objective Cough Assessments in Asthma

ALTHOUGH cough is an important symptom of asthma, there are few validated measures for assessing cough. Both objective measures, such as cough counts, and subjective measures, such as cough scores, have been reported. This study evaluated agreement between subjective and objective measures of cough.

Objective and subjective assessments of cough were performed in 56 adult asthma patients. The objective assessments included cough reflex sensitivity testing, based on the concentration of citric acid causing 2 and 5 coughs (C2 and C5) and 24-hour ambulatory cough sound recording. Subjective assessments included a cough visual analog scale and 0-to-5 rating scale and the Leicester Cough Questionnaire, a cough-related quality of life scale.

On ambulatory recordings, median frequency of coughing was 2.6 cough sounds per hour (cs/h). Patients spent more time coughing during the day than at night: 3.9 vs 0.3 cs/h. Daytime cough frequency showed a weak inverse association with the $\log_{10}$ C2 value, but not with $\log_{10}$ C5. Objective cough frequency showed only a weak to moderate association with the subjective cough scores and visual analog scale. The Leicester Cough Questionnaire was the subjective assessment most closely related to objective cough frequency.

Subjective assessments are not strongly associated with the objectively assessed frequency of coughing in patients with asthma. When cough is used as an outcome measure in asthma treatment trials, both objective and quality-of-life measures should be included.

COMMENT: *Cough is frequently the chief complaint of our patients with asthma. These British researchers used both subjective and objective measures to document that cough symptoms correlated with quality-of-life reductions, but in general patients are poor reporters of actual cough frequency.*
S.M.F.
Marsden PA, Smith JA, Kelsall AA, et al: A comparison of objective and subjective measures of cough in asthma.
J Allergy Clin Immunol 2008;122:903-907. ♦♦

Does Avoiding Peanuts Increase Peanut Allergy?

RECOMMENDATIONS to avoid peanut exposure during infancy have not led to reductions in the prevalence of peanut allergy. One possible explanation is that tolerance of peanut results from early oral exposure. This hypothesis was addressed by comparing rates of peanut allergy in children with and without early peanut consumption.

The study compared two groups of Jewish schoolchildren: 5,171 in the United Kingdom, where current guidelines recommend peanut avoidance during infancy; and 5,615 in Israel, where peanut is introduced early and consumed frequently and in high amounts. Peanut allergy was assessed using a clinically validated questionnaire. Another questionnaire was used to assess peanut consumption and weaning in 77 U.K. and 99 Israeli infants.

The prevalence of peanut allergy was much higher among the U.K. children: 1.85%, compared to 0.17% in the Israeli children. After adjustment for atopy, the risk ratio for peanut allergy in the British group was 9.8. In the infant study, median peanut consumption was 0 in the U.K. sample, compared with 7.1 g of peanut protein per month in Israel. The Israeli infants consumed peanut a median of 8 times monthly, mainly as roasted peanut butter.

The prevalence of peanut allergy is 10 times higher for Jewish children in the United Kingdom, compared to Israel. This appears to be related to the difference in early peanut consumption by infants between the two countries. It is not explained by other factors, including atopy, social class, genetics, or peanut allergenicity.

COMMENT: *The impressive findings in this study were explained by the fact that children avoiding peanuts in infancy had a 10-fold higher rate of peanut protein allergy, compared to those in a region where peanuts are introduced early. Could recommendations to delay introducing peanut in infant diets actually be abetting the rising prevalence of food allergy?*
S.M.F.
Du Toit G, Katz Y, Sasieni P, et al: Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy.
J Allergy Clin Immunol. 2008;112:984-991. ♦♦

Passive Smoke Interacts with Genes to Increase Early-Onset Asthma Risk

GENOMEWIDE studies have identified single-nucleotide polymorphisms (SNPs) on chromosome 17q21 as genetic risk factors for asthma. Little is known about the age-specific effects of these gene variants, or their interactions with environmental risk factors. Data from a large epidemiologic study of asthma genetics were used to assess the association between 17q21 variants, age at asthma onset, and early exposure to environmental tobacco smoke. ➤➤

The study included data on 1,511 individuals from 372 families enrolled in the Epidemiological Study on the Genetics and Environment of Asthma. Associations with age at asthma onset were assessed for a total of 36 SNPs in the17q21 region; cases occurring at age 4 or younger were considered early onset. Interactions with exposure to environmental tobacco smoke were then assessed.

Significant associations were noted for 11 SNPs, including strong associations with 3 SNPs: rs8069176, rs2305480, and rs4795400. Four SNPs showed a strong association with early-onset asthma, but no association with late-onset asthma. For 6 SNPs, associations with early-onset asthma were significant only for children with a history of early-life exposure to tobacco smoke. For children with a history of smoke exposure, being GG homozygous for the rs8069176 SNP was associated with a 2.9-fold increase in the risk of early-onset asthma, compared to children who were AG or AA.

The asthma-related 17q21 SNPs identified in this study appear specifically associated with early-onset asthma, in interaction with history of early exposure to tobacco smoke. The findings have implications for understanding the function of 17q21 variants in asthma pathophysiology. Because the genetic associations with early-onset asthma and late-onset asthma are different, their mechanisms are likely to differ as well.

COMMENT: *Asthma is not one disease; there are multiple phenotypes. Age at onset is one of the most obvious distinctions, and it confers several differential clinical characteristics. This genetic research finds an association between several polymorphisms on chromosome 17 and early-onset asthma (before 4 years of age), an association that is amplified by early life exposure to tobacco smoke. The data support the idea that early- and late-onset asthma are distinct genetically and that this diversity confers different susceptibilities to environmental influences--in this case, tobacco smoke. It is not yet known how this occurs pathobiologically.*
R.J.M.

Bouzigon E, Corda E, Aschard H, et al: Effect of 17q21 variants and smoking exposure in early-onset asthma.
N Engl J Med. 2008;359:1985-1994. ♦♦

Asthma Linked to Serious Pneumococcal Disease

PREVIOUS reports have suggested that asthma patients may be at increased risk of invasive pneumococcal disease. Asthma is not currently considered an indication for pneumococcal vaccine. This study sought to confirm the risk of serious pneumococcal disease (SPD) associated with asthma, using data from before the introduction of pneumococcal vaccine.

Based on review of medical records, the investigators identified 174 cases of SPD occurring in residents of Rochester, Minn., between 1964 and 1983. Criteria-based methods were used to ascertain cases of SPD, defined as invasive pneumococcal disease and/or pneumococcal pneumonia. Each case was matched for age and sex to two controls. Associations with asthma were assessed by merging the cases and controls with the entire database of Rochester residents with and without asthma.

After controlling for high-risk conditions and smoking exposure, SPD was significantly associated with a history of asthma: odds ratio 2.4. The association was even stronger on analysis of adults, odds ratio 6.7. The data suggested that 17% of cases of SPD in the study population were attributable to asthma.

Asthma appears to be a risk factor for SPD, especially in adults. Asthma should be considered an indication for pneumococcal vaccination; further study is needed to clarify the mechanism of this association.

COMMENT: *At present, asthma is not included in the list of indications for pneumococcal vaccination. This retrospective study looked at a database in Rochester, Minn., during the prevaccination years from 1964 to 1983. It found a higher incidence of serious pneumococcal disease in asthmatics, with an odds ratio of about 2.4 for all ages and 6.7 for adults. The researchers couldn't assess the influence of asthma severity on risk of pneumococcal disease. Clinicians should consider vaccinating patients with asthma.*
R.J.M.

Juhn YJ, Kita H, Yawn BP, et al: Increased risk of serious pneumococcal disease in patients with asthma.
J Allergy Clin Immunol. 2008;122:719-723. ♦♦

Exhaled NO Predicts Lung Function Decline in 'Difficult' Asthma

SOME patients have difficult-to-treat asthma, characterized by progressive loss of lung function even on corticosteroids. This study assessed the rate of decline in FEV_1, and the factors associated with accelerated loss of lung function, in patients with difficult-to-treat asthma.

The analysis included 136 nonsmoking patients with difficult-to-treat asthma, recruited over a 2-year period from 10 Dutch hospitals. All met European Respiratory Society criteria for "difficult/therapy resistant asthma," including at least one severe exacerbation per year. Ninety-eight patients were re-evaluated at 5 to 6 years' follow-up. A wide range of clinical factors and inflammatory markers, including the fraction of exhaled nitric oxide, were evaluated as predictors of the rate of decline in FEV_1.

For patients with exhaled NO of 20 ppb or higher, the rate of decline in FEV_1 was 40.3 mL/y faster than in patients with lower levels of exhaled NO. At this cutoff point, high exhaled NO was associated with a twofold increase in the risk of accelerated decline in FEV_1, defined as 25 mL/y or greater: relative risk 1.9. The effect was even stronger for patients whose baseline FEV_1 was less at least 80% of predicted. For this group, accelerated decline in FEV_1 occurred in 90% of patients with high exhaled NO, compared to 29% of those with lower exhaled NO: relative risk 3.1.

Among patients with difficult-to-treat asthma, high exhaled NO is a risk factor for more rapid decline in ➤➤

lung function. This association is strongest for patients with near-normal FEV_1 at baseline. The high levels of exhaled NO likely reflect ongoing damage to the airways.

COMMENT: *The use of exhaled NO to predict future decline in lung function is quite intriguing. This defines a group needing specific therapy in spite of paucity of symptoms or physiologic abnormalities. The appropriate therapeutic intervention to halt this decline is yet to be defined.*
B.E.C.
van Veen IH, ten Brinke A. Sterk PJ, et al: Exhaled nitric oxide predicts lung function decline in difficult-to-treat asthma.
Eur Respir J. 2008;32:344-349. ♦♦

Outdoor Swimming Pools Increase Asthma Risk

STUDIES in elite swimmers suggest that exposure to the chlorine-based disinfectants used in indoor swimming pools may increase the risk of asthma and other respiratory problems. The authors have found similar associations among children using indoor pools, but it is unclear whether outdoor pools also affect risk. Use of outdoor swimming pools was evaluated as a risk factor for asthma and allergies in adolescents.

The study included 857 students at three French secondary schools. Parents provided information on the child's use of residential or nonresidential outdoor swimming pools. The students underwent a physical examination, including measurement of exhaled nitric oxide, measurement of serum IgE, and screening for exercise-induced bronchoconstriction.

Rates of ever or current asthma increased in dose-dependent fashion with lifetime exposure to outdoor pools. This was so for the overall sample as well as for adolescents with a family history of asthma. Among adolescents with low exposure to indoor pools (less than 250 hours), asthma prevalence was substantially increased for those at the highest levels of outdoor pool use (more than 500 hours): four times higher for ever asthma and nine times higher for current asthma. For students with a total IgE greater than 25 kIU/L, the odds for asthma increased by 1 or 2 units for each 100-hour increase in pool use. Using outdoor residential pools was also linked to an increased rate of high exhaled nitric oxide levels and sensitization to cat or house dust mite.

High use of outdoor chlorinated swimming pools is associated with an increased prevalence of asthma among adolescents. Rates of airway inflammation and sensitization to respiratory allergens are also increased. The findings are especially important in light of the increasing popularity of outdoor pools, particularly in warm-weather areas.

COMMENT: *The increased incidence of asthma in patients exposed to swimming pools is an evolving concern. This appears to be related to airway damage from chlorine oxidants. This observation has also been made in Olympic swimmers. It appears patients with an allergic diathesis have increased susceptibility.*
B.E.C.
Bernard A, Nickmilder M, Voisin C: Outdoor swimming pools and the risks of asthma and allergies during adolescence.
Eur Respir J. 2008;32:979-988. ♦♦

Early Rhinovirus-Induced Wheezing Predicts Later Childhood Asthma

EPISODES of viral wheezing in infancy are often the first manifestation of childhood asthma. It remains unclear whether this risk is affected by the specific virus involved; most studies of this issue have focused on respiratory syncytial virus (RSV). Associations between the timing and cause of early viral infections and the subsequent risk of childhood asthma were assessed in a cohort of high-risk children.

The prospective follow-up study included 289 infants with a parental history of respiratory allergies or asthma, drawn from the Childhood Origins of ASThma (COAST) cohort. Wheezing respiratory illnesses occurring in early childhood were investigated using nasal lavage, culture, and multiplex reverse transcriptase-polymerase chain reaction. Specific viral causes of wheezing were analyzed as predictors of childhood asthma at age 6, along with other risk factors.

A specific viral cause was identified in 90% of wheezing illnesses. Significant associations with asthma at age 6 were noted for early wheezing from birth to age 3 caused by RSV, odds ratio (OR) 2.6; and both RSV and rhinovirus (RV), OR 10.0. Wheezing caused by RV during the first year of life was an independent predictor of asthma, OR 2.8; as was aeroallergen sensitization, OR 3.6. Wheezing caused by RV occurring from birth to age 3 was a very strong risk factor for later asthma: OR 25.6, compared to an OR of 3.4 for aeroallergen sensitization by age 3. Overall, asthma developed in 86.7% of children who had wheezing caused by RV at age 3.

In children at high genetic risk, early childhood wheezing caused by RV infection is a strong risk factor for the development of asthma later in childhood. When outpatient illnesses are considered, wheezing caused by RV is a much stronger risk factor than that caused by RSV. Further studies are needed to identify factors associated with RV wheezing illness in early childhood, as well as the resulting asthma phenotypes.

COMMENT: *Persistent wheezing associated with early-onset RV infection appears to be a more dominant predictor of asthma than RSV infection. It does not appear to be related to the allergic diathesis. This research group has also published studies defining a group of patients who have persistent RV protein isolation and RV in the lower airway. As the COAST study continues, it will be interesting to see if this effect of RV persists after puberty or if it disappears, like the RSV effect does.*
B.E.C.
Jackson DJ, Gangnon RE, Evens MD, et al: Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children.
Am J Respir Crit Care Med. 178:667-672, 2008. ♦♦

More Data on Variable Course of Childhood Wheezing

THERE is considerable variation in the course and management of childhood asthma. Atopy and asthma risk factors may have differing effects on the natural history of wheezing in children, depending on the child's propensity to wheeze. The incidence, course, and risk factors for wheezing in children from birth to adolescence were investigated using German birth cohort data.

The analysis included 1,314 children enrolled at birth in the Multicentre Allergy Study (MAS). The children underwent regular follow-up to age 13, including assessment of atopic diseases, IgE measurements, and pulmonary function testing. The incidence and longitudinal patterns of childhood wheezing were analyzed, along with predictors of wheezing risk at age 11 to 13.

Complete data on the course of wheezing were available for 441 children. Twenty-nine percent were early wheezers, having their first episode of wheezing at age 3 or before. Late wheezing (age 3 to 6) and very late wheezing (after age 6) each occurred in 9% of children. Risk factors for wheezing at age 13 included parental atopy, atopic sensitization to common allergens, high total IgE levels, and high exposure to indoor allergens in early childhood. All of these risk factors were much stronger among early wheezers than in late or very late wheezers. Three-fourths of children with early wheezing and sensitization to indoor allergens would still have wheezing at age 13.

The findings demonstrate the variable course of childhood wheezing. Early wheezing, before age 3, carries an increased risk of continued wheezing into adolescence, especially when other risk factors are present. The results add to the growing evidence that childhood asthma is a syndrome rather than a single, uniform disease.

COMMENT: *This study reinforces the previous reports from the MAS study cohort and reaffirms the value of the modified asthma predictive index. Earlier emergence of an IgE-mediated diathesis defines a population with a more persistent course. This reinforces the need for early application of disease-modification strategies such as allergy immunotherapy and possibly omalizumab.*
B.E.C.

Matricardi PM, Illi S, Grüber C, et al: Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence.
Eur Respir J. 2008;32:585-592. ♦♦

In Utero Farm Exposure Has Protective Effects

THE farm environment has protective effects against the development of atopy and allergies; the mechanisms of this effect are unclear, but innate immune responses are likely involved. Recent studies have suggested that farm exposure during pregnancy may affect immune responses, potentially reducing allergic disease risk in offspring. The effects of the timing of farming exposures on allergic disease risks in children were assessed.

The cross-sectional study included two groups of children, aged 5 to 17 years, living in rural areas of New Zealand: 1,333 children of farmers and 566 nonfarmers' children. Parents provided data on various farming-related exposures in the mother during pregnancy, as well as current and lifetime exposures in the children. Symptoms of asthma, hay fever, and eczema were the outcomes of interest.

The prevalence of asthma and eczema symptoms was significantly lower for the children of farmers, especially livestock farmers. Certain farming exposures were related to a reduction in asthma, hay fever, and eczema symptoms, including current and in utero exposure to animals and/or grain and hay. In most cases, there was no clear exposure-response relationship for in utero exposures. The effects of maternal exposures during pregnancy remained significant on adjusted analyses. In contrast, the protective effects of current exposure were significant only for some outcomes (asthma medications, lifetime asthma, and hay fever).

After controlling for prenatal exposure, farming exposures during the first 2 years of life no longer had a significant protective effect. In combination, prenatal and current exposures had the strongest associations with wheezing, odds ratio (OR) 0.48; asthma medication, OR 0.47; and eczema, OR 0.46.

In utero exposure may account for some of the reduced risk of asthma, hay fever, and eczema in the children of farmers. However, the protective effects appear strongest when exposure continues into childhood. As in other studies, contact with animals seems to be an important protective factor.

COMMENT: *In utero exposure to allergens has been an area of controversy. The immunologic mechanism that is operative in rearranging the Th1/Th2 imbalance is yet to be defined. This study continues to add support to the hygiene hypothesis.*
B.E.C.

Douwes J, Cheng S, Travier N, et al: Farm exposure in utero *may protect against asthma, hay fever and eczema.*
Eur Respir J. 2008;32:603-611. ♦♦

CLINICAL TIDBITS

'Tis the Season (for Influenza Vaccine)

THE American Academy has issued updated recommendations for influenza immunization in children. Annual immunization is now recommended for all children aged 6 months through 18 years. Children at increased risk of influenza complications and healthy children aged 6 through 59 months should be immunized this season. Older children and adolescents should also be immunized this year, if feasible; if not, immunization should be routine as of the 2009-10 influenza season.

In addition to reducing the high burden of➤➤

influenza in children, the expanded recommendations will reduce disease transmission at home and in the community. Immunization is further recommended for household contacts and out-of-home care providers of children with high-risk conditions and of healthy children younger than 5. Women who will be pregnant during influenza season should be immunized, as should health care professionals. The recommendations include information on vaccines and dosing, contraindications and precautions, and future needs.

COMMENT: *Unless we have an unusually early flu season, which thus far hasn't occurred (at the time of this submission, anyway), we'll likely experience the typical midwinter seasonal increase in influenza cases. Immunization of at-risk individuals reduces the burden of the illness and its sequelae in specific groups; immunization of a broader population expands the benefit and yields herd immunity.*

The American Academy of Pediatrics, in its current policy statement, is recommending all children beginning at age 6 months receive an annual flu vaccine. One has the distinct sense that universal population immunization is the ultimate goal. Unfortunately, the goal of even immunizing the highest risk groups has fallen short each year, as noted. A broader influenza immunization campaign in children, despite the imperfect antigenic match between vaccine and circulating strain(s) in some years, will ultimately benefit patients of all ages with asthma.

K.R.M.

Committee on Infectious Diseases: Prevention of influenza: recommendations for influenza immunization of children, 2008-2009.

Pediatrics. 2008;122:1135-1141. ♦♦

Rapid Onset of Action with Ciclesonide

CICLESONIDE has shown clinical efficacy at least as good as other inhaled corticosteroids. More information is needed on the onset of this new drug's effects on airway hyperresponsiveness (AHR) and other measures. In a randomized crossover study, 21 patients with mild asthma received inhaled ciclesonide, 320 or 640 µg bid, or placebo for 7 days. Compared to placebo, both doses of ciclesonide led to improvement in the provocative concentration of adenosine monophosphate producing a 20% reduction in FEV_1. This improvement was apparent within 2.5 hours and was still present on days 3 and 7, associated with significant reductions in exhaled nitric oxide. There was a trend toward decreased eosinophil numbers at 7 days, especially at the higher dose of ciclesonide.

In patients with mild asthma, inhaled ciclesonide improves airway hyperresponsiveness within a few hours, followed by improvement in exhaled NO. The data suggest an earlier onset of action with ciclesonide than has previously been reported.

COMMENT: *Inhaled steroids are generally thought to have a dose response measured in days. However, it depends what measure is used. Onset of effect of inhaled ciclesonide demonstrated improvement in airway reactivity within 2.5 hours. Nitric oxide demonstrated decrease within 3 days. The mechanisms involved in this rapid effect are probably vascular but have yet to be elucidated. Interestingly, there was no dose response at between 320 and 1,280 µg of ciclesonide. Even though these subjects had mild asthma (FEV_1 greater than 90% predicted) there was statistical improvement in FEV_1.*

S.F.W.

Erin EW, Zacharasiewicz AS, Nicholson GC, et al: Rapid effect of inhaled ciclesonide in asthma: a randomized, placebo-controlled study.

Chest. 2008;134:740-745. ♦♦

Atopic Characteristics Affect Airway in Infants

FAMILY history of atopy is a clear risk factor for asthma in infants. However, the timing of airway involvement in the atopic process is unclear, as is the relationship between the airway function and the infant's atopic characteristics.

These issues were addressed in a study of 114 infants with eczema, median age 10.7 months. On pulmonary function testing, forced expiratory flow at 75% exhaled volume was 336 mL/s for infants sensitized to egg or milk, compared to 285 mL/s for those not sensitized to these allergens. Airway reactivity to inhaled methacholine, measured in sedated infants, was also higher in infants sensitized to egg or milk, but there was no difference in exhaled nitric oxide. Exhaled NO was higher in infants with total serum IgE levels greater than 20 IU/mL, but there was no difference in forced flows or airway reactivity.

In infants with eczema, atopic characteristics may have important effects on airway physiology, reactivity, and inflammation. Before any wheezing has occurred, airway function is lower and airway reactivity is higher among infants sensitized to egg or milk.

COMMENT: *This study suggests that the "allergic march" is an important consideration in infants with eczema, food allergy and high IgE levels. The finding that elevated exhaled NO was a significant predictor of airway reactivity only when correlated to serum IgE is of interest for predicting airway reactivity in children with eczema.*

S.M.F.

Tepper RS, Llapur CJ, Jones MH, et al: Expired nitric oxide and airway reactivity in infants at risk for asthma.

J Allergy Clin Immunol. 2008;122:760-765. ♦♦

Home Heating Affects Childhood Asthma

INDOOR pollutants, including combustion byproducts from home heating systems, may affect asthma symptoms. This randomized trial from New Zealand evaluated the effects of upgraded home heating sys-➤➤

tems on the clinical outcomes of asthmatic children.

The study included 409 children with asthma; at baseline, all lived in homes with inefficient heaters. Intervention households received one of three types of non-polluting, more effective heaters; control homes received new heaters after the end of the study winter. At that time, there was no significant change in FEV_1 or other pulmonary function measures.

However, children whose homes received the new heaters missed 1.8 fewer school days. They also had reductions in asthma-related health visits and parent-reported poor health. Wheezing symptoms decreased, as did disturbed sleep, nighttime coughing, and lower respiratory tract symptoms. Home temperatures increased while nitrogen dioxide levels decreased.

Installing a more effective, non-polluting home heater may improve symptoms and other outcomes in children with asthma. The effects of this type of environmental modification in colder climates are unclear.

COMMENT: *These New Zealand researchers assessed the effect of non-polluting, more efficient home heating systems on the outcomes of children with asthma. There were significant improvements in reduction of asthma symptoms, missed school days and health-care utilization in the intervention group. Although the pulmonary function test improvement did not achieve statistical significance, this may be explained by the use of a small portable testing device, which could have been susceptible to poor technique and inconsistent readings. Improved home heating systems can have a positive impact on children's asthma.*
S.M.F.

Howden-Chapman P, Pierse N, Nicholls S, et al: Effects of improved home heating on asthma in community dwelling children: randomized controlled trial.
BMJ. 2008;337:a1411. ♦♦

New Equation Affects Interpretation of Spirometry

INTERPRETATION of spirometry data relies on the reference equations used. In 2005, the American Thoracic Society and the European Respiratory Society (ATS/ERS) published new guidelines recommending the use of reference values derived from the National Health and Nutrition Examination Survey (NHANES) III data set.

The investigators compared the effects of the NHANES equation with previous reference equations for the interpretation of spirometric data. The analysis included 8,733 patients tested from 2000 to 2007. The other equations used were the Crapo, Knudson, and Morris equations. The Knudson and Morris equations had high rates of discordance from the NHANES III equation: 45.5% and 35.3%, respectively. Diagnostic recategorization was less common on comparison with the Crapo equation: 15.9%. All three previous equations tended to overclassify obstruction while underclassifying restriction.

Using the NHANES III equation to interpret spirometric results may lead to diagnostic reclassification of many patients. This effect of the new ATS/ERS guidelines should be borne in mind when interpreting the results of pulmonary function tests.

COMMENT: *The ATS/ERS spirometry normals were changed to NHANES III data in 2005. There are significant discrepancies between previous standardized normals and NHANES. Implications are important for researchers and practitioners. Reclassification of severity according to percent of predicted normals using NHANES may generate unnecessary treatment, inappropriate referrals, and a different cohort of asthmatic volunteers in clinical trials.*
S.F.W.

Collen J, Greenburg D, Holley A, et al: Discordance in spirometric interpretations using three commonly used reference equations vs National Health and Nutrition Examination Study III.
Chest. 2008;134;1009-1016. ♦♦

Don't Overdo SABAs!

ALTHOUGH short-acting β_2-agonists (SABAs) are widely used for the treatment of asthma symptoms, there is significant variability in response. Population pharmacokinetic/pharmacodynamic modeling was used to characterize the albuterol dose/response relationship.

The study included 81 pediatric and adult asthma patients, 24% of them African American. Based on cumulative dose-response data, the albuterol dose required to produce 50% of the maximum effect (ED_{50}) was 141 µg, while the maximum effect of albuterol (Emax) was 24.0%. The coefficient of variation was 40% for ED_{50} and 56% for Emax. There was significant racial variation, with 180 µg of albuterol by metered-dose inhaler (MDI) producing a 17.5% increase in percentage of predicted FEV_1 in white patients vs 11.7% in African Americans. A 2.5 mg dose of nebulized albuterol increased FEV_1 to 200 mL or higher in 21% of patients.

This pharmacodynamic population model suggests that most patients with stable asthma will achieve a 12% increase in percentage of predicted FEV_1 with two to four doses of albuterol via MDI. The maximum improvement achieved with additional doses varies significantly; African American patients may need more aggressive treatment to ensure adequate relief of bronchconstriction.

COMMENT: *Dose response to albuterol is an important criterion in asthma diagnosis and management. This study demonstrated a flat dose response curve, with ED_{50} at just 180 µg for albuterol by MDI. There was no added bronchodilation with nebulized albuterol after three sequential doses of albuterol 180 µg by MDI. African-Americans had a significant blunting of dose response. Genotyping was not available.*
S.F.W.

Blake K, Madabushi R, Derendorf H, Lima J: Population pharmacodynamic model of bronchodilator response to inhaled albuterol in children and adults with asthma.
Chest. 2008;134;1009-1016. ♦♦

REVIEWS OF NOTE

COMMENT: *Although technically a review article, this is a very thorough analysis of the published literature that addresses the cost-effectiveness of asthma interventions. The authors detail the shortcomings of studies, such as a lack of assessment of asthma control and lack of inclusion of long term outcomes. It is encouraging that the literature overwhelmingly supports the use of inhaled corticosteroids as a cost-effective intervention. The jury on omalizumab is still out.*
S.A.T.
Campbell JD, Spackman DE, Sullivan SD: Health economics of asthma interventions.
Allergy.2008;63:1581-1592. ♦♦

COMMENT: *Eosinophilic gastrointestinal diseases (EGD) are important and more common than previously thought, and many of us struggle with how to diagnose and manage them. This review discusses "off-label" uses of immunomodulatory agents, including good data supporting their use for EGD.*
S.A.T.
Stone KD, Prussin C: Immunomodulatory therapy of eosinophil-associated gastrointestinal diseases.
Clin Exp Allergy. 2008;38:1858-1865. ♦♦

COMMENT: *This is a practical review by an author with extensive personal experience in use of formulas in allergic infants. The tables are particularly useful as they summarize the various categories of formulas. This article will help you with the next child with severe eczema, as you advise as to the best new formula choice.*
D.K.L.
Bahna SL: Hypoallergenic formulas: optimal choices for treatment versus prevention.
Ann Allergy Asthma Immunol. 2008;101:453-459. ♦♦

COMMENT: *I can remember the 1970s, when pulmonologists and allergists hotly debated the role of allergy in asthma. The former hardly recognized allergy as a valid concept. Thirty short years later, allergy has been firmly established in everyone's mind as a major contributor to the development of asthma. At the same time, viral processes are undoubtedly also contributing. As in most dichotomies, there is much to recommend a middle path. This review article describes some recent data on the possible roles of virus-induced invariant natural killer cells and interleukin-13 in the pathogenesis of asthma.*
R.J.M.
Djukanović R, Gadola SD: Virus infection, asthma, and chronic obstructive pulmonary disease.
N Engl J Med. 2008;359:2062-2064. ♦♦

COMMENT: *Atopic dermatitis is a fascinating disease, one which has typically been seen as a systemic allergic process (notably food allergies) rising to the outer surface of the body: a centrifugal process, if you will. But data on disturbances of the natural barrier functions of the skin warrant a concept of centripetal pathogenesis, in which defective natural barriers (structural proteins in the epidermal envelope, like filaggrin, and natural immunity defects) allow environmental substances to enter and inflame the patient's skin. Thus, when patients expect you to cure their eczema by eliminating food allergies, you can explain that it's the inherently defective skin barrier that prevents cure. Treatment emphasis should be on supporting the barrier every day, as much as on allergies.*
R.J.M.
O'Regan G, Sandilands A, McLean WHI, Irvine AD: Filaggrin in atopic dermatitis.
J Allergy Clin Immunol. 2008;122:689-693. ♦♦

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