

1. Shepherd J, Cobbe S, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.
2. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCaPS. *JAMA* 1998;279:1615-22.
3. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149-58.
4. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med* 2007;357:1477-86.
5. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;354:1264-72.
6. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol* 1989;129:687-702.
7. Chambless LE, Folsom AR, Sharrett AR, et al. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Epidemiol* 2003;56:880-90.
8. Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in three large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA* 2000;284:311-8.
9. O'Keefe JH Jr, Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. *J Am Coll Cardiol* 2004;43:2142-6.
10. Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *BMJ* 1991;303:276-82.
11. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
12. Eaton SB, Konner M, Shostak M. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. *Am J Med* 1988;84:739-49.
13. Vint F. Post-mortem findings in the natives of Kenya. *E Afr Med J* 1937;13:332-40.
14. Gottmann AW. A report of one hundred three autopsies on Alaskan natives. *Arch Pathol* 1960;70:117-24.
15. Arthaud JB. Cause of death in 339 Alaskan natives as determined by autopsy. *Arch Pathol* 1970;90:433-8.

Copyright © 2007 Massachusetts Medical Society.

Of Attraction and Rejection — Asthma and the Microbial World

Erika von Mutius, M.D., M.Sc.

In the first half of the past century, it was thought that asthma was precipitated or prolonged by infection and that infection with several bacteria, including *Streptococcus pneumoniae* and *Haemophilus influenzae*, had a role in asthma.¹ Some investigators had suggested that bacterial allergy or chronic focal infection could be a cause of asthma.² More recently, population-based studies relating infections with *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* to asthma severity encouraged a resurgent debate, but clinical trials involving various antibiotics failed to demonstrate sustained clinical benefit.¹

To understand this debate we need to consider asthma and wheeze in children. The greatest incidence of wheeze occurs in children under the age of 4 years.³ A significant proportion of infants with wheeze outgrow symptoms between 2 and 3 years of age, and this wheezing phenotype has therefore been referred to as “transient wheeze.” The remaining children with wheeze have repeated episodes of airway obstruction until school age, in about half the cohort in conjunction with allergen sensitization to food and inhalants.⁴ In school-age children, eosinophilic inflammation in the airway is a characteristic feature of asthma, as it is in adults.⁵

Because of the difficulty in performing com-

plex physiological studies in young children, we know very little about the pathogenetic processes occurring in the airways of infants and toddlers with wheeze. Even less is known about the relation between the progression and remission of symptoms and underlying mechanisms. However, some light is shed from studies in which bronchoalveolar lavage was performed in young children with severe wheeze; it is notable that neutrophilic rather than eosinophilic inflammation in the airway has been found at this age.⁶ Whether these findings reflect certain phenotypes of severe wheeze that justify invasive bronchoscopy or whether they reflect features of developing asthma is unknown. In adults, neutrophilic inflammation in the airway is seen in the context of asthma exacerbations due to viral infections and in some patients with severe asthma. Since viral infections are the predominant triggers of wheeze in young children, they may induce neutrophilic inflammation in the airway and thereby contribute to the development of asthma in children up to school age.

In this issue of the *Journal*, Bisgaard and colleagues⁷ propose an alternative explanation; that is, that bacterial colonization of the airways may induce neutrophilic inflammation in the airways and thereby cause asthma. In their prospective

study, in which they followed children at risk of asthma from birth to age 5 years, detection of *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, or a combination of these organisms in aspirates of the hypopharyngeal region at 4 weeks of age was a significant predictor of asthma, reversible airway obstruction, blood eosinophil concentration, and total IgE at age 5 years.

An association between a predictor and a subsequent event can reflect causal mechanisms or merely indicate processes occurring along with the predictor. In the light of this discussion, it is of interest to note that bacterial colonization of the hypopharyngeal region at 1 year of age was no longer a predictor for subsequent wheeze and asthma, which suggests that events in the first weeks of life may be of particular importance in inducing asthma. Children at risk of atopy, including asthma, are born with impairments of innate immune responses. Regulatory T cells, a subgroup of T cells involved in the regulation of immune responses to environmental allergens, have been found to be less effective in neonates born to mothers affected by an allergic illness as compared with offspring of nonatopic mothers.⁸ Furthermore, in neonates at risk of having atopy later in life, impaired type 1 helper T cell (Th1)-mediated immune responses have been shown in a number of studies.⁹

An early colonization of the hypopharyngeal region with *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, or a combination of these organisms may indicate defective clearance of such flora. *S. pneumoniae* colonizes the nasopharynx in healthy subjects, and carriage rates have been shown to decrease from more than 50% in infants to 5 to 10% in adults. In a recent experimental study in mice, effective clearance of colonization with *S. pneumoniae* required a Th1-mediated immune response and toll-like receptor 2 (TLR2) signaling. TLR2 is the microbial pattern-recognition receptor.¹⁰ Genetic variation in TLR2 has in turn been linked to asthma, particularly in environments rich in microbial exposures.¹¹ It is conceivable that defective clearance and subsequent early exposure to low doses of TLR2 ligands such as *S. pneumoniae* induce a risk of asthma in subjects carrying such a genetic background, whereas with high doses of environmental exposures, such as those that might occur in rural farming areas in Europe, the same genetic background might confer protection from disease, because of excessive stimulation.

In my opinion, the data presented by Bisgaard and colleagues may be interpreted to suggest that bacterial colonization of the hypopharynx in the first 4 weeks of life indicates a defective innate immune response very early in life, which promotes the development of asthma. A delayed maturation of Th1-associated immune responses during early postnatal life may increase the risk of sensitization to aeroallergens.⁹ Such impaired innate immunity may also influence a subject's resistance to viruses. It is well recognized that persons with asthma cannot limit viral infections to the upper respiratory tract, and this increased susceptibility has been shown to relate to defective innate immune responses.¹² Repeated viral infections and sensitization at an early age to perennial allergens may induce airway inflammation, thereby promoting the development of asthma in subjects at risk.^{4,9} However, it is also conceivable that colonization of the airways with certain bacterial strains may contribute to the development of asthma by means of the induction of inflammatory responses in the airways of subjects with impaired innate immunity. If this assumption were correct, then treatment with antibiotics in the first months of life should confer protection from the subsequent development of asthma. Although no clinical trial has tested the use of antibiotics in the first weeks of life as a strategy for the prevention of asthma, there is sufficient evidence from a number of population-based cohort studies to suggest that various antibiotic therapies administered early in life do not reduce the risk of asthma.¹³ Therefore, in my view, Bisgaard and colleagues may have found an interesting and new sentinel rather than a causative signal.

No potential conflict of interest relevant to this article was reported.

From the University Children's Hospital, Munich, Germany.

1. Black PN. Antibiotics for the treatment of asthma. *Curr Opin Pharmacol* 2007;7:266-71.
2. Chobot R, Uvitsky IH, Dundy H. The relationship of the etiologic factors in asthma in infants and children. *J Allergy* 1951; 22:106-10.
3. Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172:1253-8.
4. Illi S, von Mutius E, Lau S, Niggemann B, Grüber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006;368:763-70. [Erratum, *Lancet* 2006;368:1154.]
5. Marguet C, Jouen-Boedes F, Dean TP, Warner JO. Bronchoalveolar cell profiles in children with asthma, infantile wheeze, chronic cough, or cystic fibrosis. *Am J Respir Crit Care Med* 1999;159:1533-40.

6. Krawiec ME, Westcott JY, Chu HW, et al. Persistent wheezing in very young children is associated with lower respiratory inflammation. *Am J Respir Crit Care Med* 2001;163:1338-43.
7. Bisgaard H, Hermansen MN, Buchvald F, et al. Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med* 2007;357:1487-95.
8. Schaub B, Campo M, He H, et al. Neonatal immune responses to TLR2 stimulation: influence of maternal atopy on Foxp3 and IL-10 expression. *Respir Res* 2006;7:40.
9. Holt PG, Upham JW, Sly PD. Contemporaneous maturation of immunologic and respiratory functions during early childhood: implications for development of asthma prevention strategies. *J Allergy Clin Immunol* 2005;116:16-24.
10. van Rossum AM, Lysenko ES, Weiser JN. Host and bacterial factors contributing to the clearance of colonization by *Streptococcus pneumoniae* in a murine model. *Infect Immun* 2005;73:7718-26.
11. Eder W, Klimecki W, Yu L, et al. Toll-like receptor 2 as a major gene for asthma in children of European farmers. *J Allergy Clin Immunol* 2004;113:482-8.
12. Johnston SL. Innate immunity in the pathogenesis of virus-induced asthma exacerbations. *Proc Am Thorac Soc* 2007;4:267-70.
13. Celedón JC, Fuhlbrigge A, Rifas-Shiman S, Weiss ST, Finkelstein JA. Antibiotic use in the first year of life and asthma in early childhood. *Clin Exp Allergy* 2004;34:1011-6.

Copyright © 2007 Massachusetts Medical Society.

Breast-Cancer Therapy — Looking Back to the Future

Anne Moore, M.D.

Adjuvant therapy for breast cancer — treatment after surgical removal of the tumor — is a major therapeutic advance that has had a considerable effect on prolonging disease-free and overall survival. Not all patients benefit from adjuvant therapy, however, and certain types of adjuvant therapy are not appropriate for some patients. For example, adjuvant treatment with tamoxifen, a selective estrogen-receptor modulator, has improved the 15-year survival rate among women with estrogen-receptor–positive breast cancer by 31%, but it does not benefit women with estrogen-receptor–negative disease.¹ Trastuzumab, a monoclonal antibody against the human epidermal growth factor receptor type 2 (HER2), is associated with an improvement of approximately 50% in disease-free survival among the 15 to 20% of women with HER2-positive disease.^{2,3}

In addition to these targeted approaches, adjuvant chemotherapy that includes alkylating agents, antimetabolites, anthracyclines, and taxanes in various combinations has contributed to the overall improvement in outcomes among women with operable breast cancer. As compared with women with estrogen-receptor–positive disease, women with estrogen-receptor–negative breast cancer benefit more from chemotherapy. A recent retrospective analysis of three trials by the Cancer and Leukemia Group B (CALGB) suggests very little overall benefit of adjuvant chemotherapy for women with estrogen-receptor–positive breast cancer who received tamoxifen for 5 years after receiving chemotherapy.⁴

Is it possible to define an optimal adjuvant chemotherapy program for individual patients with either estrogen-receptor–positive or estrogen-receptor–negative breast cancer to maximize the benefit and minimize toxic effects? The article by Hayes et al.⁵ in this issue of the *Journal* addresses this question.

Hayes et al. report their retrospective analysis of an adjuvant-chemotherapy trial, CALGB 9344/INT0148 (referred to below as CALGB 9344), for women with lymph node–positive breast cancer.⁶ The trial began in 1994 to test the benefit of adding four cycles of the taxane paclitaxel after four cycles of doxorubicin plus cyclophosphamide. The trial also investigated whether doxorubicin at higher than standard doses was beneficial, and the answer was that escalating the dose of doxorubicin did not benefit any subgroup of patients. Women with estrogen-receptor–positive breast cancer received tamoxifen for 5 years after chemotherapy. When the results of the trial were first presented at the American Society of Clinical Oncology meeting in May 1998, a small but statistically significant benefit from the addition of four cycles of paclitaxel every 3 weeks after doxorubicin plus cyclophosphamide was reported.⁷ This result changed clinical practice, and the use of adjuvant paclitaxel rose dramatically well before the publication of the results in 2003.

The study by Hayes et al.⁵ was designed to determine whether paclitaxel administered after doxorubicin plus cyclophosphamide was equally beneficial to all subgroups of women enrolled in the CALGB 9344 trial. New information was added by testing the tissue blocks from the original tumors for HER2 positivity with the use of assays for overexpression and gene amplification. The results are noteworthy. There was a significant clinical benefit from the addition of paclitaxel

gen-receptor–negative breast cancer to maximize the benefit and minimize toxic effects? The article by Hayes et al.⁵ in this issue of the *Journal* addresses this question.