cal activity, and exposure to ultraviolet light. Another study might examine the effects of various doses of calcium with vitamin D supplements in healthy postmenopausal women who follow a low-fat diet high in fruits and vegetables as compared with women who follow their usual diet. These studies could contribute data on the kinetics and the optimal doses of calcium plus vitamin D supplements in postmenopausal women with and in those without osteopenia. Such data could provide information to bridge the knowledge gap from the current study to the next step, a pooled study evaluating the sex-specific risk of colorectal cancer or, perhaps, a colorectal-cancer trial. Thus, the conclusion of Wactawski-Wende et al. about the role of calcium plus vitamin D supplementation in the prevention of colorectal cancer needs to be interpreted in the light of the complexities of the WHI study and the probability that the doses of these substances may have been too low to achieve the desired effect.

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Inhibition of Tumor Necrosis Factor α for Refractory Asthma

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Tumor necrosis factor (TNF), originally discovered and named on the basis of its tumor regression activity, is an important cytokine that regulates the pathogenetic mechanisms of chronic inflammatory diseases.1,2 The translation of research findings to patient care resulted in the first successful cytokine-specific targeted therapies, the TNF inhibitors. Currently available inhibitors include the monoclonal antibodies against TNF-α, infliximab and adalimumab, and the soluble TNF receptor fused to human IgG, etanercept.1,2 Agents that block TNF-α suppress inflammation, slow disease progression, and in some cases, induce remission in patients with rheumatoid arthritis, ankylosing spondylitis, psoriasis, and Crohn’s disease.3 In this issue of the Journal, Berry and colleagues provide evidence that the soluble TNF inhibitor etanercept may be of benefit in the treatment of another severe chronic inflammatory disease, refractory asthma.3

Although commonly diagnosed with the use of physiological measures of airflow limitation and bronchial hyperreactivity, asthma is a chronic inflammatory disorder of the airways, and management guidelines advocate the use of therapies that decrease inflammation.4 In the majority of cases, therapy with inhaled or oral corticosteroids prevents symptoms and results in normal or near-normal lung function. However, approximately 10 percent of patients have asthma that is refractory to such therapies, with frequent exacerbations and continual symptoms limiting their activity and reducing their quality of life.5-7 These patients account for a substantial proportion of...
complications and deaths related to asthma and for almost half the total health care costs of asthma.\textsuperscript{7}

Extensive genetic, biologic, and physiological evidence indicates that TNF-\(\alpha\) plays a critical role in the initiation and amplification of airway inflammation in patients with asthma\textsuperscript{8-13} (Fig. 1). Preformed TNF-\(\alpha\) is stored by mast cells and rapidly released during IgE-mediated reactions that typify the asthmatic response to allergens.\textsuperscript{8,10,12} TNF-\(\alpha\) perpetuates and amplifies inflammation by up-regulating adhesion molecules, which leads to increased migration of eosinophils and neutrophils into the airways. These key effector cells, as well as resident structural cells such as airway epithelial cells, are activated by TNF-\(\alpha\) to release cytotoxic mediators and reactive nitrogen and oxygen species that result in airway injury. The end result of chronic, unresolved inflammation is a structural change in the airway, termed airway remodeling.\textsuperscript{6} TNF-\(\alpha\) may contribute to all aspects of remodeling, including the proliferation and activation of fibroblasts, the increased production of extracellular-matrix glycoproteins, subepithelial fibrosis, and mucous-cell hyperplasia.\textsuperscript{9} Independent of its effect on inflammation, TNF-\(\alpha\) also has direct effects on bronchial hyperreactivity to methacholine and allergen, as shown in isolated tracheal-ring models.\textsuperscript{11} The administration of aerosolized recombinant human TNF-\(\alpha\) to healthy volunteers or patients with mild asthma induces bronchial hyperreactivity.\textsuperscript{13}

Recently, Howarth and colleagues found that the expression of TNF-\(\alpha\) in the airway was related to the severity of asthma.\textsuperscript{10} The level of expression of the TNF-\(\alpha\) gene and protein was greater in the airways of patients with refractory asthma than in the airways of control subjects or patients with mild asthma, despite the use of high-dose corticosteroid therapy in the patients with refractory asthma.\textsuperscript{10} Open-label use of etanercept for three months in patients with refractory asthma improved airflow measures and symptom scores and reduced bronchial hyperresponsiveness. Berry and colleagues now provide both complimentary evidence that TNF-\(\alpha\) is increased systemically in patients with refractory asthma, as compared with patients with mild asthma or controls, and evidence that etanercept is beneficial in patients with refractory asthma in a double-blind, placebo-controlled trial.

Collectively, these findings indicate that activation of the TNF-\(\alpha\) axis is fundamental to the process leading to asthma and, particularly, to the development of persistent airflow limitation and bronchial hyperreactivity in patients with refractory asthma despite the use of high-dose corticosteroids.\textsuperscript{5} In spite of the excitement generated by the news of a novel therapeutic approach to patients who have a poor response to standard asthma-control agents, widespread application of this approach would be premature. TNF-\(\alpha\) inhibitors may cause serious adverse effects, such as injection-site reactions, demyelinating disorders, lymphoproliferative diseases, and the reactivation of tuberculosis with dissemination to the miliary form. Of relevance to patients with asthma, recurrent respiratory tract infections are relative contraindications for TNF-\(\alpha\)--inhibitor therapy, and allergic bronchopulmonary aspergillosis would also be a contraindication in such circumstances. Although the incidence of adverse effects was low in the study by Berry et al. and in a recent open-label study,\textsuperscript{3,10} longer studies involving more patients are needed to determine whether TNF-\(\alpha\) inhibitors increase the risk of respiratory tract infections or immunogenic adverse effects in this population.

Irrespective of whether therapies directed against TNF-\(\alpha\) are useful in the management of refractory asthma, study of the effects of selective inhibition of TNF-\(\alpha\) provides unique and valuable insights into the pathobiology of asthma and an ideal opportunity to identify mechanisms contributing to refractory asthma, since our current understanding of these mechanisms is limited. Although in vitro studies, murine models of asthma, evaluations of the TNF-\(\alpha\) levels in humans, and experimental administration of TNF-\(\alpha\) in patients with asthma and control subjects all suggest that TNF-\(\alpha\) plays a role in asthma and resistance to corticosteroids,\textsuperscript{14,15} the fact that other cytokine networks are activated in asthma confounds our ability to distinguish the effects of TNF-\(\alpha\).

The study by Berry et al. reveals that TNF-\(\alpha\) is a major effector of bronchial hyperresponsiveness in patients with asthma that is refractory to corticosteroid therapy. The inhibition of TNF-\(\alpha\) significantly decreased bronchial hyperreactivity and was often accompanied by a progressive decrease in methacholine reactivity during the
The multiple actions of TNF-α contribute to asthma. TNF-α is produced by airway inflammatory cells, in particular, mast cells and macrophages, and resident structural cells such as fibroblasts, smooth-muscle cells, and epithelial cells. Preformed TNF-α along with histamine is immediately released from mast cells during allergic responses. Through paracrine and autocrine effects, TNF-α may perpetuate and amplify inflammation by up-regulating adhesion molecules, which increases the migration of leukocytes that are activated by TNF-α to produce other inflammatory mediators. TNF-α also induces airway epithelial cells to secrete mucin and fibroblasts to increase the production of extracellular-matrix glycoproteins, all of which may contribute to airway remodeling. Independent of its effects on inflammation, TNF-α increases the responsiveness of smooth-muscle cells to contractile agents. The study by Berry et al. reveals that patients with refractory asthma have higher TNF-α levels than do healthy persons or patients with mild asthma and suggests that TNF-α is a critical component in the pathogenesis of the chronic, unremitting bronchial hyperresponsiveness that typifies refractory asthma.
10 weeks of therapy. TNF-α may affect reactivity by acting directly on smooth-muscle cells, recruiting inflammatory cells, or inducing the release of multiple other inflammatory mediators, including mast-cell histamine. In fact, the inhibition of TNF-α decreased levels of histamine in sputum, indicating that it had a primary effect on mast-cell activation. However, the inhibition of TNF-α did not reduce the total cell counts, the percentage of eosinophils, or the levels of eosinophilic cationic protein in sputum, suggesting that other, parallel pathways may be more important in mediating the migration of inflammatory cells into the asthmatic airway. Furthermore, these findings indicate that eosinophilic inflammation of the airway is not linked to bronchial hyperresponsiveness in patients with refractory asthma, which is in contrast to previous correlative evidence suggesting that persistent bronchial hyperresponsiveness in such patients is a consequence of ongoing eosinophilic inflammation of the airway. Similarly, exhaled nitric oxide, a surrogate for airway inflammation that is correlated to the percentage of eosinophils in sputum and methacholine reactivity, was not affected by the inhibition of TNF-α, providing further support for the concept that bronchial hyperresponsiveness is not a direct consequence of nitric oxide levels or eosinophilia.

Thus, the findings of Berry et al. provide support for the notion that TNF-α plays a pivotal role in corticosteroid-resistant bronchial hyperreactivity and that this effect may be mediated by direct effects on smooth-muscle cells and mast cells. Although TNF-α also induces the proliferation and activation of myofibroblasts and fibroblasts, the authors did not evaluate the effect of TNF-α inhibition on airway remodeling. Longer studies that assess the architecture of endobronchial tissue will be required to determine whether airway remodeling results from actions mediated by TNF-α. In addition, although the actions of TNF-α account for much of the bronchial hyperreactivity in patients with refractory asthma, it may not do so in all types of asthma, especially since patients with mild asthma, unlike those with refractory asthma, have levels of TNF-α similar to those of controls.

Given that the total cost of asthma in the United States is approximately 10 billion dollars per year, with the majority of the economic impact related to the use of emergency rooms and hospitalization, effective therapy for the patients with refractory asthma who use these resources is greatly needed and bound to have an enormous effect on health care costs. Despite the promise of early studies of antinflammatory therapy for asthma, it is prudent to await results of large, multicenter studies before applying such findings to individual patient care. Studies of TNF-α inhibitors in patients with asthma are ongoing, ensuring that we will not have to wait long for results. However, even if the results of larger trials are favorable, TNF-α–inhibitor therapy will likely be used in combination with, not as a replacement for, standard treatment of refractory asthma, which includes close and careful monitoring by a health care provider, the exclusion of diseases that mimic asthma during the initial evaluation, the treatment of exacerbating conditions, educating patients regarding asthma care, and adherence to a regimen of therapies that control asthma.

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Autoimmunity and Immunotherapy for Cancer
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Adjuvant treatment for patients after resection of high-risk and regionally metastatic melanoma remains suboptimal. Despite the Food and Drug Administration’s approval of high-dose interferon alfa-2b, the substantial toxicity of the therapy and the fact that its benefit is limited to 20 to 30 percent of patients at risk have hindered its general acceptance.

Attempts to identify patients who benefit from adjuvant treatment with interferon alfa-2b have been disappointing to date. Although analyses of individual studies suggest that the benefit of high-dose interferon alfa-2b might be restricted to certain subgroups of patients, on the basis of the number of melanoma-involved lymph nodes, no consistent overall pattern was observed. In addition, no other features have been identified that predict either responsiveness of the tumor among patients with advanced melanoma or the likelihood of freedom from relapse in the adjuvant setting among patients who receive interferon alfa-2b. Consequently, adjuvant treatment with this agent has been proposed for all patients with intermediate- and high-risk melanoma for whom the likelihood of reducing the risk of relapse outweighs the anticipated toxic effects of the treatment.1

The principal mechanism underlying the beneficial effect of interferon alfa-2b in patients with melanoma is unclear. Proposed mechanisms include enhanced antigen presentation as a result of the up-regulation of the expression of major-histocompatibility-complex molecules, promotion of dendritic-cell development, increases in the function of immune effector cells, antiangiogenic effects, and direct antiproliferative effects on the tumor. In this issue of the Journal, Gogas et al. report a strong association between the development of autoimmunity during or after treatment with adjuvant interferon alfa-2b and a favorable outcome in patients with high-risk melanoma.2 The results of this prospective trial suggest a mechanistic connection between autoimmunity and the benefit from interferon alfa-2b in patients with melanoma.

The link between type 1 interferons, which include interferon alfa-2b, and autoimmunity is well established. Autoimmune disorders, including thyroiditis and vitiligo, have been reported to develop in 15 to 30 percent of patients who receive interferon alfa therapy. Patients with systemic lupus erythematosus have elevated levels of interferon alfa, and their lymphocytes have a gene-expression signature that is indicative of activation of the interferon gene.3 In mouse models of systemic lupus erythematosus, lupus does not develop as frequently or as rapidly in mice that lack the type 1 interferon receptor as it does in mice that have the receptor.3 Similar mouse genetic models suggest that the interferons have a role in type 1 diabetes mellitus and other autoimmune conditions.

Given the ability of type 1 interferons to induce an immune response against autoantigens, it is not surprising that they also have a role in inducing an immune response against tumors. An association between autoimmunity and a favorable antitumor effect has been reported for several forms of immunotherapy, particularly in patients with melanoma. The development of auto-