Editorials

Tissue-Specific Estrogens — The Promise for the Future

As life expectancy continues to increase, women will soon be postmenopausal for one third of their lives. The human and economic costs of this increased longevity in an estrogen-deficient state are substantial. They include a projected increase in cardiovascular events, the leading cause of death among postmenopausal women, and in osteoporotic hip fractures, which are associated with a 20 percent mortality rate within the first year. However, despite the well-established efficacy of estrogens in protecting women against cardiovascular disease and maintaining bone density and reducing fractures, less than one fifth of postmenopausal women ever take them.[1] Furthermore, the proportion who take estrogen for a prolonged period — an important prerequisite for efficacy — is even smaller because of the reluctance of physicians to prescribe estrogens and of women to accept such a prescription. This reluctance is based on the high incidence of side effects: vaginal bleeding, breast swelling and tenderness, and an increased risk of endometrial and breast cancer.[1] Hence the pressing need for "designer estrogens," a growing family of compounds also known as selective estrogen-receptor modulators. These tissue-specific estrogens were designed to preserve the beneficial effects of estrogens, including protection against cardiovascular diseases and osteoporosis, but to have no undesired effects on the reproductive organs.

Raloxifene is one of these compounds. In ovariectomized rats it maintains bone mineral density and improves the serum lipid profile but has little estrogenic action on breast or uterine tissue.[2] In humans, too, it has a favorable effect on bone remodeling and serum lipid concentrations. In this issue of the *Journal,* Delmas et al. report a two-year randomized, placebo-controlled, dose-ranging trial of raloxifene in 601 normal white postmenopausal women.[3] At a dose of 60 mg per day, raloxifene maintained bone mineral density, lowered serum concentrations of total and low-density lipoprotein (LDL) cholesterol, and did not stimulate the endometrium. Specifically, the bone mineral density of the lumbar spine, total hip, femoral neck, and total body increased slightly (1.2 to 1.6 percent) in response to treatment with raloxifene. Serum concentrations of total cholesterol decreased by 6.4 percent and those of LDL cholesterol decreased by 10 percent after three months, with no significant change thereafter. Serum concentrations of triglycerides and high-density lipoprotein (HDL) cholesterol did not change.

These beneficial effects on the skeleton and serum lipid profile are similar to those of tamoxifen[4,5] — which, however, causes endometrial stimulation — but are less strong than those of estrogen. Unlike estrogen, none of the selective estrogen-receptor modulators, including raloxifene, increase the serum concentrations of HDL cholesterol, an independent marker of protection against cardiovascular disease. The protective cardiovascular effect of estrogen is also partially mediated by an estrogen-induced vasodilatory effect and an antioxidant effect on lipoproteins that decreases their atherogenic potential. Similarly, raloxifene also inhibits LDL oxidation[6]; however, its effect on vascular tone is undetermined. The beneficial skeletal effect of raloxifene seems to be due mostly to an antiresorptive action on bone, thus inducing a positive calcium balance when administered over a long period at a dose of 60 mg per day.[7] Like estrogen, tamoxifen decreases plasma antithrombin III and fibrinogen concentrations; the effect of raloxifene on these substances and on the incidence of thrombophlebitis is not known.

The key role of estrogen and its receptor in the normal physiology of the skeleton and the reproductive organs is illustrated in two human syndromes, aromatase deficiency and estrogen-receptor–gene defect. Both are characterized by severe estrogen deficiency, the former because little estrogen is produced and the latter because of resistance to its action. Affected patients have incomplete epiphyseal fusion, with continued linear growth into adulthood, osteoporosis, and lack of sexual development in addition to insulin resistance.[8,9]

The central role of the estrogen receptor in skeletal physiology is further illustrated by studies aimed at elucidating the mechanism (or mechanisms) of action of estrogens and antiestrogens. Estrogens bind to the estrogen receptor, inducing a conformational change that leads to activation of gene transcription through specific estrogen-response elements of target genes. Transcriptional activation of these genes is thought to occur through two distinct domains of the estrogen receptor, AF-1 and AF-2. Differential activation of these two domains by estrogens and antiestrogens explains the tissue selectivity of the latter. Peptide growth factors stimulate estrogen-dependent transcriptional activation of estrogen-response elements and are themselves activated by the estrogen receptor. Indeed, estrogens and raloxifene may partially maintain bone mass through regulation of the gene for transforming growth factor β (TGF-β) by means of the estrogen receptor. Deletion of the ligand-binding domain of the estrogen receptor abolishes both estradiol- and raloxifene-induced activation of the TGF-β promoter. However, deletion of the AF-1 domain of the estrogen receptor abolishes estradiol- but not raloxifene-induced TGF-β activation, and deletion of the AF-2 domain abolishes ral-

oxifene- but not estradiol-induced activation of the TGF-β promoter.[10]

The promising results of the study by Delmas et al. pave the way for important additional investigations. Despite the beneficial effects of raloxifene on bone mineral density and the serum lipid profile, its effect in preventing fractures and cardiovascular events is yet to be determined. The absence of vaginal bleeding and of endometrial or breast stimulation reported by Delmas et al. in women receiving raloxifene, as well as preliminary results demonstrating a decrease in the risk of breast cancer (reported at the National Osteoporosis Foundation Meeting in Washington, D.C., in June 1997), are added benefits that should improve compliance among women taking this new type of hormone-replacement therapy. However, 25 percent of the women in the trial reported by Delmas et al. discontinued therapy. The proportions were similar in all treatment groups, as were the proportions experiencing hot flashes. The absence of an increase in hot flashes among the women given raloxifene is surprising; an increase, such as occurs with tamoxifen, might have been expected.

The favorable effect of raloxifene on bone mineral density and serum lipid concentrations and the absence of any effect on endometrial histology are quite encouraging. The decrease in estrogen-related adverse effects with the selective estrogen-receptor modulators in general and raloxifene in particular should improve compliance and decrease the incidence of cardiovascular events and fractures while not increasing breast cancer. The challenge is to realize this promise.

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EVALUATION OF CHEST PAIN IN THE EMERGENCY DEPARTMENT

EACH year 5 million patients come to emergency departments with chest pain.[1] Some have acute, life-threatening illness, but many others have nothing seriously wrong; some have a history of coronary disease, whereas others have never had a cardiac evaluation. The task of the physician in the emergency department is to sort out the confusing array of patients with chest pain, and to do so rapidly, accurately, and efficiently.

Acute myocardial ischemia as a result of coronary atherosclerosis is the key concern in patients with chest pain. Patients with acute coronary syndromes are at considerable risk for death and serious complications, and outcomes can be improved with appropriate therapy. Patients with acute myocardial infarction associated with ST-segment elevation on the electrocardiogram have significantly lower mortality when treated promptly with either a thrombolytic drug[2] or primary coronary angioplasty.[3] Patients with unstable angina at rest have better outcomes when treated with antiplatelet and anticoagulant drugs.[4] Patients with acute coronary syndromes also benefit from aspirin, beta-blockers, lipid-lowering therapy, and in selected patients, angiotensin-converting–enzyme inhibitors.[5,6]

Thus, the first goal in the emergency department is to identify patients with ST-segment elevation and promptly initiate thrombolytic therapy (or perform angioplasty) for acute myocardial infarction. After the patients with clear-cut acute myocardial infarction have been identified, the remaining patients are more difficult to sort out. The physician must decide whether to admit the patient to the hospital, do further tests in the emergency department, or send the patient home with a plan for outpatient evaluation and management. The decisive factor in this choice is the patient's short-term risk of death or myocardial infarction, since patients at high risk are likely to benefit from in-hospital monitoring and therapy, whereas patients at low risk are not.

Considerable information about short-term risk is conveyed by the medical history, the physical examination, and the electrocardiogram.[4] The most important elements are the patient's description of the chest discomfort and the associated risk factors for coronary disease. Symptoms suggestive of myocardial ischemia at rest that last more than 15 minutes

indicate a relatively high short-term risk, probably because of their association with ruptured coronary plaque. Chest pain associated with ST-segment depression or deep T-wave inversions also indicates a higher short-term risk, in part because it suggests the presence of underlying coronary disease, a larger zone of ischemia, or both. Finally, chest pain associated with heart failure, hypotension, or transient mitral regurgitation also indicates high short-term risk, as well as the need for inpatient therapy.[4] Patients who are determined to be at high risk should generally be admitted to the hospital, since the probability of acute myocardial ischemia requiring monitoring and treatment will be high, even after negative tests in the emergency department.

Further tests in the emergency department can be helpful in the case of patients whose clinical history, physical examination, and standard electrocardiogram do not indicate high risk. Several different types of tests are available,[7] including those that identify myocardial ischemia by detecting a defect in myocardial perfusion (e.g., the technetium-99m sestamibi scan[8]) or abnormalities in left ventricular wall motion (e.g., the echocardiogram[9]), or subtle evidence of myocardial necrosis through sensitive assays of intracellular proteins such as the creatine kinase MB isoenzyme and its subforms,[10] myoglobin,[11] and more recently, troponin I[12] and troponin T.[13] Each type of test assesses a different step in the pathway between coronary occlusion and the resulting myocardial ischemia: impairment of coronary-artery flow, ischemic cardiac dysfunction, and ultimate tissue necrosis. In principle, patients with acute myocardial infarction should have abnormal test results at each step along this causal pathway, whereas patients with unstable angina should have abnormal myocardial perfusion and cardiac dysfunction without evidence of tissue damage. Thus, even a highly sensitive marker of myocardial necrosis will not necessarily be positive in all patients with acute myocardial ischemia.

Troponin I and troponin T are highly sensitive and specific markers of myocardial necrosis, appearing in the serum 3 to 12 hours after the onset of symptoms.[11] Furthermore, elevated troponin levels are powerful, independent predictors of death and serious complications.[12,13] Although normal troponin levels do not rule out acute myocardial ischemia that stops short of infarction, it is reasonable to hypothesize that patients with normal troponin levels may be at such low risk that they can be safely treated as outpatients. This hypothesis was tested by Hamm and coworkers, as reported in this issue of the *Journal*.[14] The authors investigated 773 patients with acute chest pain lasting less than 12 hours. Patients with ST-segment elevation were treated for acute myocardial infarction and excluded from the study. Of the 47 patients in whom an acute myocardial infarction subsequently evolved in the absence of ST-segment elevation, 44 (94 percent) were identified by a rapid troponin T assay and all 47 (100 percent) by a rapid troponin I assay. Many patients classified as having unstable angina in this study (22 to 36 percent) had a positive troponin test, although perhaps these cases should be classified as small myocardial infarctions. The prognosis of patients with normal values for either troponin T or troponin I was quite good — only 1.1 percent and 0.3 percent, respectively, died of cardiac causes or had a nonfatal myocardial infarction during 30 days of follow-up. The authors suggest on the basis of these results that patients with normal troponin levels may safely be discharged from the emergency department.

The results of Hamm and associates are very encouraging, and if the excellent prognosis of troponin-negative patients can be confirmed by others, rapid troponin tests may allow more confident discharge of patients with chest pain from the emergency department. There are several important aspects of their study, however, that if ignored may lead to inappropriate discharge of high-risk patients. First, no details about the chest-pain symptoms were provided, so the risk among patients with a convincing clinical history and a negative troponin test cannot be evaluated. Second, the authors took care to obtain at least two negative samples, with the second at least six hours after the onset of chest pain. False negative troponin tests could result from inadequate sampling. Third, among patients with ST-segment depression on the initial electrocardiogram, the short-term risks among those with negative tests for troponin T (event rate, 2.8 percent) or troponin I (1.4 percent) were not trivial, and the upper confidence limit for their observations is almost 8 percent — a level too high to ignore. Patients with ST-segment depression are at high enough risk on clinical grounds that even a negative troponin test may not lower the risk sufficiently to allow them to be discharged safely from the emergency department.

Patients at low risk can be identified by a careful clinical history, unremarkable electrocardiogram, and negative markers for myocardial necrosis. Although low-risk patients may not need admission to the hospital, they do need further outpatient management. Patients who present for the first time with chest pain usually need further tests to establish the likelihood of underlying coronary disease and to guide appropriate therapy, and patients with established coronary disease may need to have their management plans revised. The evaluation of chest pain in the emergency department should be the first step in an integrated approach to the management of coronary disease.

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Ultrasonographic Screening for Fetal Aneuploidy

FOR decades, a maternal age of more than 35 years on the expected date of delivery has been an accepted indication for amniocentesis for fetal karyotyping, given the moderate increase in fetal aneuploidy associated with advancing maternal age. More recently, interest has grown in screening tests that might facilitate the diagnosis of fetal aneuploidy in women otherwise at low risk without excessive invasive testing. So-called triple screening is based on an association between fetal aneuploidy and a combination of low concentrations of alpha-fetoprotein and unconjugated estriol and high concentrations of chorionic gonadotropin in maternal serum. The sensitivity of this method for Down's syndrome is nearly 60 percent, with an overall rate of positive results of 5 percent.[1] The estimated risk of fetal aneuploidy based on maternal age, a screening test, or both must be balanced against the risk of pregnancy loss associated with invasive testing, which has been reported to be as high as 1 percent for amniocentesis.[2]

Over the past decade a variety of fetal dysmorphic features detectable by ultrasonography have been proposed as screening markers for the detection of fetal aneuploidy.[3] Features such as short limbs, mild pyelectasis, increased nuchal-skin thickness, choroid-plexus cysts, and unusually echogenic bowel have been associated with an increased risk of aneuploidy. Experience with individual ultrasonographic markers of fetal aneuploidy, however, has repeatedly shown that many yield good results for one investigator and poor results for another.[3] This inconsistency has led to the adoption of multiple-marker scoring systems that generally require the detection of two of these features to justify invasive testing.[3]

The essential nature of any screening test requires that a compromise be struck between the sensitivity of the test and its positive predictive value in selecting the standard for a positive screening result. Furthermore, if a morphologic characteristic detected by ultrasonography and subject to interpretive variability is the basis for the test, then the inherent imprecision of the screening process is amplified. It must be emphasized that a positive predictive value (the probability of disease with a positive screening test) established in a high-prevalence study population cannot be directly transferred to a low-prevalence (screening) population. The lower the prevalence of fetal aneuploidy in the population screened, the lower the positive predictive value (risk of disease) of a positive test result, and the higher the false positive rate, the larger this difference. Therefore, the diagnostic performance of any ultrasonographic screening test for fetal aneuploidy must be confirmed in a low-risk population.

There seems little doubt on the basis of both the report by Taipale et al.[4] in this issue of the *Journal* and other reports[5,6] that there is a substantially greater risk of fetal aneuploidy if ultrasonography reveals increased nuchal translucency (more correctly termed hypoechogenicity or echopenia) between 10 and 15 weeks of gestation. The abnormally wide area of echopenia is thought to result from the accumulation of fluid due to abnormal lymphatic drainage. Taipale et al. found that the sensitivity of a positive screening result (nuchal translucency of 3 mm or more) for Down's syndrome was 54 percent, a result that compares favorably with the sensitivity of maternal serum screening.[1,4] Their overall rate of 0.8 percent for nuchal translucency is remarkably low, as compared with the expected rate of 5 percent for maternal serum screening. These results lead the au-

thors to suggest that if this ultrasonographic screening test were adopted in place of triple screening, fewer amniocenteses would be needed to yield a similar diagnostic sensitivity, and so fewer procedure-related pregnancy losses would result. If the findings of Taipale et al. are confirmed in other large studies of low-risk women, this conclusion will be supported, but widespread acceptance now of ultrasonographic screening for nuchal translucency would be premature.

Taipale et al. adopted a uniform threshold of 3 mm throughout screening for a positive result, whereas other investigators have found that the extent of fetal nuchal translucency normally increases between the 10th and 15th week of gestation and that the use of a uniform biometric standard is inappropriate.[7,8] In another study the differences between the median width of the area of nuchal translucency and the 95th percentile and between the median width and the 99th percentile were only 0.8 and 1.5 mm, respectively, emphasizing the high degree of technical precision required to discriminate normal from abnormal.[6] Minor variations in imaging techniques or measurements might easily lead to diagnostic error. The required degree of technical precision is well within the skills of a well-trained and experienced sonographer, but it is doubtful that such precision can be provided universally. In one study, for example, different examiners classified nearly 20 percent of fetuses differently.[9]

The reported probability of fetal aneuploidy in the presence of increased fetal nuchal translucency has ranged from 18 to 88 percent, arousing concern that the true risk of aneuploidy in association with increased nuchal translucency has not yet been firmly established.[5] Also, the false positive rate is reported to be as high as 6 percent, which is not different from that expected with maternal serum screening.[9] Another group that screened low-risk women for increased fetal nuchal translucency found that it could be measured successfully in only 74 percent of women more than 10 weeks pregnant, and only 20 percent of the aneuploid fetuses were identified on the basis of a finding of nuchal translucency of 3 mm or more.[10] Clearly, if early ultrasonography to detect increased nuchal translucency is added to the prenatal-care plan without the elimination of maternal serum screening, more rather than fewer women will be offered invasive testing, with no assurance of improvement in overall sensitivity.

Overall, the evidence is compelling that the risk of fetal aneuploidy is substantially increased if increased nuchal translucency is noted during ultrasonography between 10 and 15 weeks of gestation, and therefore, consideration should be given to fetal-karyotype analysis. Personally, I perform a careful search for increased nuchal translucency as well as the other ultrasonographic markers of fetal aneuploidy as part of every obstetrical ultrasonographic examination, but I do not consider this a standard feature of the examination. I do not believe that there is yet sufficient experience with screening for increased fetal nuchal translucency in low-risk women to justify the adoption of this technique.

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CHOOSING THERAPY FOR CHILDHOOD ASTHMA

FOR over a century asthma has been recognized as a disorder in which the airways are irritable and narrow too easily and too much in response to a variety of nonspecific stimuli. This view of asthma as a disorder of bronchial hyperresponsiveness led to the use of short-acting β_2-adrenergic–receptor agonists by inhalation for the rapid relief of symptoms. Over the past decade, the emphasis has moved from understanding the physiology of airway dysfunction and bronchial hyperresponsiveness in asthma to determining why the impairments occur.

In adults, allergic, occupational, and intrinsic asthma are all characterized by the involvement of activated mast cells and eosinophils as sources of the mediators of inflammation, which leads to bronchi-

al hyperresponsiveness, airway obstruction, and the symptoms of asthma.[1] Application of molecular techniques to bronchial-biopsy specimens and lavage cells has provided strong evidence that this inflammatory response is orchestrated by a subgroup of helper T cells, designated Th2-like cells. These cells preferentially secrete cytokines encoded in the interleukin-4 gene cluster on chromosome 5q that is responsible for mast-cell and eosinophil engagement and for isotype switching of B lymphocytes to generate IgE. The close association between asthma and atopic allergy suggests the important role of environmental allergens, which can activate specific Th2-like cells through epithelial dendritic cells. This process involves antigen presentation on major-histocompatibility-complex class II molecules and the engagement of costimulatory molecules, especially CD28 and B7.[1]

This understanding provides a rationale for the use of inhaled corticosteroids, which by acting on multiple steps of the inflammatory cascade, can suppress the inflammatory response and restore airway function.[2] With the recent introduction of the long-acting inhaled β_2-adrenoceptor agonists, salmeterol and formoterol, there are additional options for the long-term management of asthma. These agents are highly effective in relieving the symptoms of asthma. Nonetheless, concern about the masking of progressive underlying airway inflammation and the acquisition of drug tolerance has led to the recommendation that these agents not be given alone but instead be used as supplementary therapy in patients already receiving inhaled corticosteroids.

Although most adults with asthma can control their disease with moderate doses of inhaled corticosteroids and short-acting inhaled β_2-agonists as required, some cannot. Such patients may have persistent inflammation,[3] tissue injury, and airway-wall remodeling, with proliferation of airway smooth muscle and deposition of matrix proteins.[4] Altered airway structure, combined with greater airway responsiveness, helps explain why, in symptomatic patients taking moderate doses of inhaled corticosteroids, the addition of an inhaled long-acting β_2-agonist provides greater improvement in lung function and symptom control than an increase in the dose of the inhaled corticosteroid.[5,6] These findings reinforce the concept that chronic asthma is a dynamic disorder of inflammation and tissue injury and repair and helps explain both the complex clinical picture and the variable response to treatments.

Most cases of asthma begin in childhood. In genetically susceptible children, prenatal and early postnatal environmental exposures are important factors. A strong maternal influence in the development of asthma may be explained in part by the combination of a reduced capacity to generate interferon-γ (which removes an important means to down-regulate Th2 cytokines), impaired lung growth, and prenatal allergen sensitization. These factors may lead to a persistent Th2 response, which may be augmented by heavy exposure to allergens and reduced infections in early postnatal life.[7]

Until recently, little was known about the immunopathology of childhood asthma. Bronchoalveolar lavage and mucosal biopsies in children between 1 and 15 years of age have revealed bronchial inflammation and collagen deposition below the basement membrane — findings that are similar to those in adults and indicate that inflammation and remodeling occur early in life.[8,9] These discoveries have coincided with more intensive early treatment of childhood asthma, an approach that is designed to suppress bronchial inflammation and reduce or prevent subsequent airway remodeling and chronic airflow limitation.

In this issue of the *Journal,* Simons and colleagues confirm the efficacy of inhaled beclomethasone dipropionate in children with mild asthma.[10] In a one-year study, the clinical benefit of beclomethasone dipropionate was somewhat greater than that of salmeterol alone. Beclomethasone dipropionate was certainly superior in reducing bronchial hyperresponsiveness, an index of airway inflammation. However, the nature of the treatment is suppressive rather than curative, as indicated by the return of bronchial hyperresponsiveness within two weeks after the treatment was stopped.

It is of some concern that regular use of beclomethasone dipropionate resulted in reduced growth in height, as compared with that in the salmeterol and placebo groups. The effect of inhaled corticosteroids on growth and bone mineralization is a complex issue, because asthma itself may impair growth. In children with severe perennial asthma, inhaled corticosteroids given over prolonged periods do not impair growth or pituitary–adrenal function, possibly because of a greater effect of poorly controlled disease on these endocrine factors.[11] There is some evidence that the lost growth may eventually be recovered. Children with asthma typically have delayed puberty and hence delayed epiphyseal fusion, which may account for the attainment of normal (or nearly normal) final height despite reduced growth rates. A meta-analysis of 21 studies involving 810 children showed no overall effect of beclomethasone dipropionate on growth at doses of up to 800 μg daily.[12] Nevertheless, in addition to the study by Simons et al., three other well-controlled studies have reported a retardation in growth of up to 1 cm per year in children with mild asthma treated with inhaled corticosteroids.[13-15] In a study performed by our group,[14] catch-up growth did not occur over a follow-up period of five months.

Weighing the risk of side effects against the benefits of long-term treatment is especially critical for children with relatively mild disease. For children

with symptomatic disease and an impaired quality of life, inhaled corticosteroids are — and should remain — the mainstay of asthma control. In children with milder asthma, the jury remains out on the questions of when and how to use corticosteroids. We await the results of longer-term studies addressing the effects of treatment on the natural history of asthma and on growth to make these judgments. A reasonable approach, according to the latest guidelines of the National Institutes of Health,[16] is to use cromolyn sodium or nedocromil sodium and to monitor the clinical response over a period of four to six weeks. If symptoms persist and pulmonary function remains impaired, an inhaled corticosteroid should be given at a medium dose and then gradually reduced to the lowest dose that maintains good control of symptoms.

Since the swallowed portion of an inhaled dose of corticosteroids accounts for a high proportion of the drug that reaches the circulation, it seems sensible to minimize oropharyngeal deposition with the use of large-volume spacers and mouth rinsing. Use of a large-volume spacer with a metered-dose inhaler abolishes the inertial effect of the aerosol, allows large particles to settle out, eliminates the need to coordinate activation of the inhaler with inhalation, and greatly increases the fraction of the inhaled dose that reaches the lungs. Small-volume spacers decrease the velocity of the inhaled particles but are less efficient in increasing the fraction of the drug that reaches the lungs. The use of second-generation inhaled corticosteroids, such as budesonide and fluticasone, which undergo extensive first-pass metabolism, should also reduce the systemic effects of the swallowed portion. However, if this reduction is accompanied by an increase in the potency of the drug, the amount absorbed from the lungs will become more important.

Although some authors recommend using inhaled corticosteroids early in the course of childhood asthma, other options should not be forgotten, including environmental interventions and medications such as cromolyn sodium, nedocromil sodium, and the recently introduced leukotriene modifiers. Examples of environmental interventions include reducing exposure to dust mites by encasing bedding (mattress, pillows, and comforters) in allergen-impermeable covers, washing sheets and blankets in hot water (>54.4°C [130°F]), exterminating cockroaches, removing household pets from living quarters, eliminating or reducing exposure to environmental tobacco smoke, and reducing indoor humidity in order to minimize exposure to mold.[16]

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