tribute to the symptoms. Systemic treatment with an oral drug thus produces what might be considered beneficial side effects. Third, the anti-leukotrienes have a very good safety profile. With usual and correct use, inhaled glucocorticoids and beta-adrenergic bronchodilators also have few side effects, especially in adults; however, when a patient is taking an inhaled glucocorticoid, there will be measurable systemic effects of the glucocorticoid (e.g., inhibition of bone growth in children), which is not the case with montelukast. Furthermore, it makes sense to use LABAs with caution until more data are available regarding their safety.

There is also a mechanistic perspective on these pragmatic, real-life studies by Price et al. Whereas inhaled glucocorticoids act broadly on many targets, the anti-leukotrienes block only one mediator molecule. However, despite this highly focused target, the LTRAs reduce both bronchospasm and the inflammatory reactions caused by the leukotrienes. Moreover, when asthma is induced by an allergen challenge, combining anti-leukotrienes with antihistamines yields additional protection. Likewise, new antagonists of prostanoids or certain cytokines display promising effects in clinical models. We therefore foresee a future generation of combination therapies in asthma in which selective oral medications that block a few key molecules may provide effective and patient-friendly treatments. This scenario would align asthma treatment with that of other diseases, such as hypertension, in which selective interventions are routinely used.

Finally, all current asthma treatments provide only symptomatic relief; they do not modify the underlying condition. Therefore, we treat patients to help them cope with their asthma today. The two studies described by Price et al. show that oral leukotriene modifiers provide an alternative treatment that may help patients pursue their activities of daily life as effectively as inhaled glucocorticoids do. The ease of taking a pill should be particularly attractive in developing parts of the world, where most patients with asthma remain untreated.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Effective Treatment for Early-Stage Prostate Cancer — Possible, Necessary, or Both?

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In 2010, prostate cancer was diagnosed in approximately 217,000 men in the United States. More than 90% of patients with newly diagnosed prostate cancer have localized (clinical stage T1 or T2) disease. Men with early-stage prostate cancer face the treatment dilemma posed by the urologist Dr. Willet Whitmore: “If treatment for cure is necessary, is it possible? If possible, is it necessary?”

The Scandinavian Prostate Cancer Group Study 4 (SPCG-4) has provided important evidence that effective treatment is both necessary and possible for many men with early-stage prostate cancer. In a 2008 report of SPCG-4, radical pros-
that the clinical outcomes are improved when adjuvant radiation therapy is given after prostatectomy in men with pathological stage T3 disease, positive surgical margins, or both. In a Southwest Oncology Group study involving men with pT3N0 prostate cancer, adjuvant radiation therapy was associated with improved metastasis-free and overall survival. The number of men with pT3 disease needed to treat with adjuvant radiation therapy to avert one death at 12.6 years was 9.1, a figure similar to the number needed to treat in SPCG-4.

There are no data from large, randomized, controlled trials regarding the comparative effectiveness of prostatectomy and radiation therapy in patients with early-stage prostate cancer. Although large observational studies are limited by selection bias and other potential confounding factors, they have shown similar long-term rates of disease control with prostatectomy and radiation therapy. The rapid evolution of surgical and radiation-therapy techniques further complicates the comparison of surgery with radiation therapy. Advancements in the accurate delivery of radiation therapy, including conformal and image-guided therapy, have allowed for an escalation in the dose of radiation, with associated improvements in the rates of disease control.

All forms of treatment for prostate cancer have potential adverse effects. Prostatectomy is associated with erectile dysfunction and urinary incontinence. External-beam radiation therapy is associated with erectile dysfunction and bowel symptoms. Watchful waiting also has potential consequences with respect to quality of life. In SPCG-4, 40% of the men assigned to prostatectomy and 63% of men assigned to watchful waiting subsequently received androgen-deprivation therapy. Androgen-deprivation therapy is associated with sexual dysfunction, vasomotor flushing, and fatigue. Androgen-deprivation therapy also increases fat mass, decreases muscle mass, decreases insulin sensitivity, and alters serum lipid profiles. Consistent with these adverse metabolic effects, androgen deprivation has been linked to greater risks for diabetes and coronary heart disease.

Two large, randomized, controlled trials are under way to determine whether treatment will reduce mortality in men with prostate cancers identified through PSA screening. The Prostate Cancer Intervention versus Observation Trial (PIVOT; ClinicalTrials.gov number, NCT0007644) is a randomized trial of prostatectomy versus ob-

catectomy, as compared with watchful waiting, was associated with improved prostate-cancer-specific and overall survival in men with early-stage prostate cancer (clinical stage T1 or T2, well-differentiated or moderately well-differentiated histologic findings, and a prostate-specific antigen [PSA] level of <5 ng per milliliter). In this issue of the Journal, Bill-Axelson et al. update the results of the SPCG-4 study. After a median follow-up of 12.8 years, prostatectomy remained associated with greater prostate-cancer-specific and overall survival. Almost two thirds of the deaths were unrelated to prostate cancer. The survival benefit with prostatectomy was restricted to men younger than 65 years of age and was also evident in a subgroup of men who were categorized as having low-risk disease (Gleason score of the sum of the two most common histologic patterns or grades in a prostate tumor, each of which is graded on a scale of 1 to 5, with 5 indicating the most cytologically aggressive pattern) of <7 and PSA level of <10 ng per milliliter.

The survival benefit with prostatectomy in men with low-risk disease is the most important new finding of SPCG-4 but may not be relevant for men with low-risk early-stage prostate cancers identified by PSA screening. In SPCG-4, the mean age of the patients was 65 years, 88% had palpable tumors, and the cancers were diagnosed by means of screening tests in only 5.2% of the patients. Among men with newly diagnosed prostate cancer in the United States, the median age is 67 years, fewer than 50% have palpable tumors, and most cancers are identified through screening tests. The lead-time bias associated with PSA screening has been estimated to be as long as 10 years. In SPCG-4, the number of men needed to treat with prostatectomy to prevent one death at 15 years was 15. The predicted number needed to treat is substantially greater for contemporary men with low-risk prostate cancers detected by PSA screening because the rates of death from prostate cancer are lower in this group.

Recent studies of radiation therapy provide additional evidence of the importance of local and regional control of the disease in men with prostate cancer. In the Scandinavian Prostate Cancer Group Study 7 (SPCG-7) involving men with high-risk prostate cancer, the addition of radiation therapy to androgen-deprivation therapy, as compared with androgen-deprivation therapy alone, was associated with greater disease-specific and overall survival. Three randomized trials have shown
servation in men with early-stage prostate cancer. PIVOT completed enrollment of 731 men in 2002; the planned follow-up period is 15 years.\textsuperscript{10,11} In contrast to the watchful-waiting group in SPCG-4, patients in the observation group of PIVOT are monitored closely and offered surgery, radiation therapy, or androgen-deprivation therapy at the time of disease progression. The Prostate Testing for Cancer and Treatment trial (ProtecT, NCT00632983) in the United Kingdom is a randomized treatment trial nested within a prostate-cancer screening study.\textsuperscript{11} In the ProtecT study, more than 2500 men with early-stage prostate cancer have been randomly assigned to prostatectomy, radiation therapy, or observation. The results of the PIVOT and ProtecT trials will help inform future decisions about the treatment of low-risk prostate cancer, but many challenges will remain. Management of early-stage prostate cancer will continue to require careful consideration of the severity of the disease, the potential benefits and harms of intervention, and the patient’s age, health status, and individual preferences.

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