All kinds of nostrums and contraptions have been used to treat asthma over the centuries and some have actually helped. Although he did not know what actually caused his own breathing difficulty, Dr. Henry Hyde Salter back in the 19th century prescribed strong coffee to stem an attack. The caffeine in coffee is a mild bronchodilator and is similar to theophylline, a recognized therapy for asthma.

Asthma cigarettes were popular in the 19th and into the 20th century. Smoking for asthma now seems crazy, but asthma cigarettes were made with herbs and material from plants like jimsonweed, which also contain substances that act as bronchodilators.

Sir William Osler, often tagged with the “father of modern medicine” sobriquet, described asthma as having the following components: spasm of the bronchial muscles; swelling of the bronchial mucous membrane; inflammation of the smaller bronchioles; a familial tendency, with the problem often beginning in childhood and persisting into old age; and a predilection to strike due to a wide variety of initiating circumstances such as dust, exposure to cats, emotion, diet, and infections.

Osler wasn’t that far off. More up-to-date definitions describe asthma as a collection of phenotypes of lung disease that lead to inflammation of the airways. The inflammation results in bronchoconstriction. These newer descriptions bring in the initiating event, as well as the biomarkers.

The primary goals of treatment, according to the NIH, are to reduce impairment and the risk of exacerbations. Treatment has had two prongs: reversing the bronchoconstriction with beta agonists and quelling inflammation with inhaled and oral corticosteroids. Over the past several decades, elucidation of some of the pathways underlying inflammation, such as the leukotriene pathway, has led to some new treatments. In the ’20s, researchers discovered immunoglobulin E (IgE). Severe asthma is often accompanied by high levels of IgE. That discovery led to omalizumab (sold as Xolair), a monoclonal antibody that treats asthma by binding to IgE.

Asthma is also characterized by the infiltration of eosinophils into the small airways. This infiltration is mediated—at least in part—by interleukin-5 (IL-5).

The term interleukin was coined by Dr. Vern Paetkau at a time when it was thought that these proteins were produced by leukocytes and acted on leukocytes, hence the term “interleukin.” It is now known that interleukins act on a wide variety of cells, but the name stuck. The various interleukins can act to increase as well as decrease the inflammatory or immune response of the human body.

There are at least 35 different varieties of interleukins, and they are named by number. As maestro of the eosinophils, IL-5 seems to be one of the most important ones, and it has a hand in orchestrating their growth, differentiation, recruitment, activation, and survival.

An Investigational New Drug application was opened in 1997 for mepolizumab, which blocks IL-5. Initial studies focused on a general “moderate asthma” population. Although mepolizumab produced a profound decrease in eosinophils, it did not demonstrate a clinical benefit. Working with the FDA, the drug’s developers chose a more restricted study group...
reflecting a readily identifiable “real world” population for trials conducted in the 2000s. It wasn’t until two months ago that mepolizumab finally made it to market. Sold as Nucala and marketed by GlaxoSmithKline, it is the first approved IL-5 antibody.

Mepolizumab keeps IL-5 from binding to a specific IL-5 receptor on the eosinophil cell surface and inhibits the overexpression of serum and tissue eosinophils. By neutralizing the effect of IL-5, mepolizumab reduces eosinophilic inflammation in the lung and reduces exacerbations and improves asthma control.

The FDA approved mepolizumab as an add-on maintenance treatment for patients aged 12 and older who have severe asthma with an eosinophilic phenotype. It is injected in 100 mg doses subcutaneously in the upper arm, thigh, or abdomen every four weeks. It is not indicated for relief of acute bronchospasm or status asthmaticus. It was studied in a population treated with high-dose inhaled corticosteroids plus a second controller drug.

Mepolizumab’s approval was based on three randomized, placebo-controlled, multicenter trials that enrolled 1,327 people. All study volunteers had markers of eosinophilic airway inflammation. In the first trial, the markers included blood eosinophil count ≥300 cells/mcL, sputum eosinophil count ≥3%, exhaled nitric oxide concentration of 50 ppb or deterioration of asthma control after ≤25% reduction in regular maintenance inhaled corticosteroids/oral corticosteroids. For the other two trials, the enrollment criteria included an elevated blood eosinophil count of >150 cells/mcL within 6 weeks of dosing or >300 cells/mcL within 12 months of dosing.

Of the study volunteers, 59% were female, 85% white, and ranged in ages from 12 to 82. They were long-time asthma sufferers (an average of 19 to 20 years), and their asthma was severe (mean percentage of predicted FEV1 was 60%). The vast majority had never smoked.

Adverse events were most often related to headache, injection site reaction, back pain, and fatigue. Researchers counted 263 adverse reactions among those taking mepolizumab compared with 257 taking a placebo, so the drug emerged from clinical trials with a good safety profile.

Efficacy measures were exacerbations that resulted in an emergency department visit, hospitalization, or both. The drug was studied in both 75- and 100 mg doses. Both were effective, but 100 mg was superior, which is why it is the approved dose. The 100 mg dose was significantly better than placebo, and not just in the narrow P value sense of the word. Hospitalizations were reduced by 39% to 69% compared with placebo, and exacerbations fell by 48% to 53%.

One confirmatory trial focused on reducing the dose of oral corticosteroids; the primary endpoint was the reduction of oral corticosteroids 20 to 24 weeks after starting therapy while maintaining asthma control. The results showed 23% of those taking mepolizumab reduced their oral corticosteroid use by 90 to 100%, compared with 11% of those taking a placebo. One exception to the hands-down good results was FEV1. It was measured in all three trials, and the improvements from mepolizumab were inconsistent.

Managed care implications
After nearly two decades of clinical development, mepolizumab offers new hope to those with asthma. All the work that countless researchers have done to crack open the mysteries of inflammation and delineate its complexities has paid off with the identification of IL-5 and a therapy that stifles its pro-inflammatory activity.

The announced wholesale acquisition price (WAC) is $2,500 per dose, which works out to about $32,500 a year (there are 13 doses per year). That is roughly double the price of omalizumab, the anti-IgE drug. So it seems like mepolizumab is another in the growing list of expensive medications testing the payer wallets.

Soon, though, it may face some competition from other drugs that target interleukins. The one most likely to reach the market first is another anti–IL-5 agent, Teva’s reslizumab, which got a thumbs up from an FDA advisory committee in December. But will reslizumab and the others compete on price?

The FDA does not seem inclined to demand comparative effectiveness trials, so perhaps payers and providers can team up in some way to use “big data” including genomic traits, biomarkers, patient administered respiratory functions, and aggregated claim data to determine a rational prior authorization pecking order for these increasingly expensive medications. But that is a discussion for another day in Tomorrow’s Medicine! MCG