

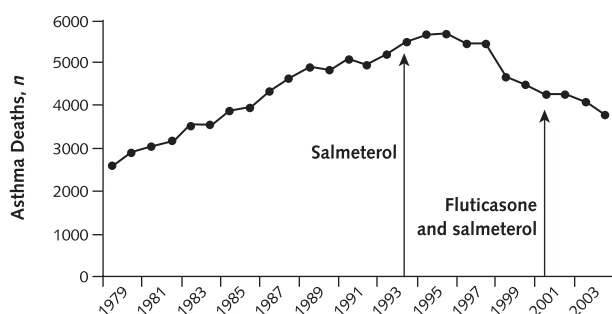
COMMENTS AND RESPONSES

Safety of Long-Acting β -Agonists

TO THE EDITOR: Salpeter and colleagues (1) assert that concomitant use of inhaled corticosteroids does not adequately protect against rare adverse events that are associated with long-acting β -agonist (LABA) use. However, their meta-analysis includes only studies in which patients were randomly assigned to LABAs or placebo and nearly 50% of patients were not receiving concomitant inhaled corticosteroids. The authors attempt to control for this limitation by examining studies that reported concomitant inhaled corticosteroid use in more than 75% of patients, but adherence to unblinded inhaled corticosteroid use in those studies is unknown. In addition, all patients reported using inhaled corticosteroids in addition to study medications in only 1 study; therefore, only that study could potentially assess whether concomitant inhaled corticosteroids affected the outcomes. If Salpeter and colleagues had wished to examine this fully, several studies of patients receiving both inhaled corticosteroids and LABAs were available. In fact, a meta-analysis of 18 studies concluded that asthma exacerbations were infrequent and similar between inhaled corticosteroid and LABA use and inhaled corticosteroid use alone (2). Furthermore, lower exacerbation rates have been reported in other meta-analyses (3–5) of inhaled corticosteroid and LABA use versus double-dose inhaled corticosteroid use alone. A more recent, long-term study in more than 3400 patients found that exacerbations and hospitalizations statistically significantly decreased in patients who were receiving inhaled corticosteroids and LABAs compared with those who were receiving only inhaled corticosteroids (6). These studies contributed to evidence-based guidelines that support the use of inhaled corticosteroids and LABAs as the preferred treatment for symptomatic patients receiving low-dose inhaled corticosteroids.

Salpeter and colleagues also assert that salmeterol may be responsible for 4000 of the 5000 asthma-related deaths that occur in the United States annually. However, when salmeterol was introduced in 1994, more than 5000 asthma-related deaths occurred per year. Since the peak of asthma deaths in 1996, salmeterol sales have increased about 5-fold, while overall asthma mortality rates have

Figure. Asthma deaths in the United States, 1979–2004.



The 1979–1998 rates reflect the International Classification of Diseases, Ninth Revision (ICD-9), code 493, and the 1999–2003 rates reflect the ICD-10 codes. Data are from references 7–9.

decreased by about 25%, despite a continued increase in asthma diagnoses. In fact, according to the most recent data from the National Center for Health Statistics, U.S. asthma mortality rates peaked in 1996 (with 5667 deaths) and have decreased steadily since. The last available data, from 2004, indicate that 3780 deaths occurred. Thus, the suggestion that a vast majority of asthma deaths could be attributable to LABA use is inconsistent with the facts.

Finally, we would like to provide additional information that may be of interest (Figure). The Salmeterol Multi-center Asthma Research Trial (SMART), which contributed nearly 80% of the patients in Salpeter and colleagues' meta-analysis, per protocol did not specify collection of asthma-related hospitalizations as a primary or secondary outcome. Additional data are also not available to conduct such an analysis. However, SMART collected all-cause hospitalizations as a secondary outcome and did not observe statistically significant differences between salmeterol and placebo.

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TO THE EDITOR: The meta-analysis by Salpeter and colleagues (1) is interesting and important; however, I have 2 concerns. My first con-

cern is about the trial inclusion in their primary analysis. I have found 2 trials that I think should have been included: Pauwels and colleagues' 1997 trial from the *New England Journal of Medicine* (2) and Woolcock and colleagues' 1996 trial from the *American Journal of Respiratory and Critical Care Medicine* (3). Why weren't these trials included in the primary analysis?

My second concern is about Salpeter and colleagues' separate evaluation of trials in which more than 75% of participants were receiving concomitant inhaled corticosteroids. That analysis should be published in detail, including a discussion of patient adherence to inhaled corticosteroid therapy in the included trials.

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Potential Financial Conflicts of Interest: None disclosed.

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TO THE EDITOR: Salpeter and colleagues (1) seem to suggest that the cause for increased mortality from asthma is the use of LABAs. This class of medication became available in the United Kingdom in 1990 with the advent of salmeterol. Since that time, asthma mortality rates have decreased from approximately 2000 deaths per year to 1300 deaths per year against a context of increased prevalence of asthma. Note that the advice in the United Kingdom is not to prescribe LABAs without a concomitant prescription for inhaled corticosteroids, whereas in Salpeter and colleagues' meta-analysis, only 53% of patients in active or placebo treatment were receiving inhaled corticosteroids.

Another contributing factor to explain increased mortality from asthma in the United States may be structural. In the United Kingdom, everyone has access to free health care, while many U.S. patients, who are largely from at-risk groups, do not.

Inhaled corticosteroids are the mainstay of asthma control, and the main reason for poor control is failure to take the medication (that is, poor adherence). For patients who are adherent and who still have symptoms, both LABAs and leukotriene-receptor antagonists (which are not mentioned by Salpeter and colleagues) may improve symptom control. I fear that Salpeter and colleagues' paper may persuade many physicians to believe that using these excellent medications in conjunction with appropriate doses of inhaled steroids is dangerous, thus depriving patients who need a useful therapeutic option.

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Potential Financial Conflicts of Interest: Dr. Ryan has received sponsorship from, has provided consultancy to, and has lectured for AstraZeneca, Altana Pharma, Boehringer Ingelheim, Pfizer Inc., GlaxoSmithKline, Merck Sharp & Dohme, Schering-Plough, Novartis, Ivax, and Trinity-Chiesi Pharmaceuticals.

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TO THE EDITOR: The citations listed by Salpeter and colleagues (1) to support their recommendations for the use of anticholinergic agents in both acute asthma exacerbations and chronic asthma are, in fact, quoted inaccurately. Rodrigo and Castro-Rodriguez's 2005 meta-analysis clearly states that "inhaled anticholinergic agents with β_2 -agonists lead to a reduction in admission rates of both children and adults of 30%" (2). No published papers support anticholinergics as monotherapy in acute asthma. Also, the addition of anticholinergics to β_2 -agonists treatment provided benefit only to patients with moderate to severe obstruction. Westby and colleagues' 2004 paper (3) did not identify any justification for routinely introducing anticholinergics as add-on treatment for patients whose asthma was not well-controlled with standard therapy. The role of long-term anticholinergics, such as tiotropium bromide, has yet to be established in patients with persistent asthma, and no randomized, controlled trials support this therapy.

Taken together, these papers do not support Salpeter and colleagues' comments recommending the routine use of anticholinergics either in short-term therapy for acute exacerbations or as add-on therapy for chronic asthma.

Inhaled anticholinergic agents do have a bronchodilatory effect in patients with asthma, but in both clinical and physiologic terms, the effect is small.

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TO THE EDITOR: The meta-analysis by Salpeter and colleagues (1) raises concerns over the long-term safety of LABAs in patients with asthma. However, the authors are incorrect in stating that "[i]f long-acting β -agonists were removed from the market, the main treatment options for asthma would be inhaled corticosteroids and anticholinergic agents."

Leukotriene-receptor antagonists are advocated as suitable second-line controller therapy in patients with persistent asthma who are already receiving inhaled corticosteroids (2, 3). Indeed, adding a leukotriene-receptor antagonist has been shown to be as effective as LABAs in reducing exacerbation frequency. Moreover, adding a leukotriene-receptor antagonist would confer further beneficial effects on attenuating inflammation and airway hyperresponsiveness (4).

Perhaps future guidelines may err on the side of caution and suggest adding a leukotriene-receptor antagonist instead of a LABA in patients with persistent asthma who are using inhaled corticosteroids.

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Potential Financial Conflicts of Interest: Dr. Currie has received funding from Merck Sharp & Dohme and GlaxoSmithKline for attending international conferences.

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IN RESPONSE: My coauthors and I appreciate the thoughtful comments on our meta-analysis. We would first like to clarify that our analysis included only randomized, placebo-controlled trials to assess the safety of LABAs compared with placebo. The results showed that LABA use in these trials increased asthma hospitalizations, life-threatening attacks, and asthma deaths by 2- to 4-fold compared with placebo.

In response to Dr. Ernst and colleagues' commentary elsewhere in this issue (1), we chose trials of at least 3 months' duration to allow adverse effects associated with continued treatment to develop. Long-acting β -agonists have an initial beneficial effect on asthma control that may last for a few weeks before clinically significant tolerance develops. We analyzed all events that occurred in the trials, even those that occurred in the initial few weeks, and we still found a net increased risk associated with LABA use. It is important to note that in our analysis of hospitalizations, approximately 7% of the participants were African American and all participants had full access to health care.

In response to Drs. Nelson and Dorinsky and Dr. Ernst and colleagues, our study was not designed to assess the protective effect of concomitant inhaled corticosteroids on the adverse effects of LABAs. We estimated that half of the participants in the trials were also using inhaled corticosteroids, which may approximate the degree of use in the general population when the trials were performed. A subgroup analysis of 7 trials (2-8) with more than 75% concomitant inhaled corticosteroid use (an average of 90% use) still demonstrated

a 2-fold increase in asthma hospitalizations for LABA compared with placebo (odds ratio, 2.1 [95% CI, 1.3 to 3.4]). We agree with Drs. Nelson and Dorinsky and Dr. Lindberg that the use of inhaled corticosteroids was not controlled in most of these trials and that the level of adherence is not known.

We attempted to get data from the SMART investigators on asthma hospitalizations in the treatment and placebo groups for those with and without inhaled corticosteroid use (9). Drs. Nelson and Dorinsky and GlaxoSmithKline representatives told us that this information was not available, although they reported a trend toward increased all-cause hospitalizations, life-threatening exacerbations, and asthma deaths for persons taking salmeterol and inhaled corticosteroids compared with those taking inhaled corticosteroids alone. Information on asthma hospitalizations from such a highly powered trial would be helpful in assessing the safety of LABAs with concomitant inhaled corticosteroids. As Dr. Ernst and colleagues suggest, the SMART investigators should provide individual-patient data on asthma hospitalizations in the subgroup of patients taking concomitant inhaled corticosteroids. These data could be combined with individual-patient data from other trials for a more accurate assessment of the safety of LABAs combined with inhaled corticosteroids.

We excluded trials that did not have a placebo control group. Some of these trials, including those cited by Dr. Lindberg (10, 11), evaluated a combination of LABAs and low-dose inhaled corticosteroids compared with low-dose or high-dose inhaled corticosteroids alone, and most were sponsored by pharmaceutical companies. Asthma exacerbations were defined as hospitalizations or asymptomatic drops in peak flow; however, this definition is not used in clinical practice. Using this definition, the 2 Cochrane meta-analyses cited by Dr. Ernst and colleagues showed a reduction in exacerbations for combined treatment compared with inhaled corticosteroids alone (12, 13). However, hospitalizations should be assessed separately from asymptomatic drops in peak flow because LABAs have been shown to improve peak flows while worsening asthma control. Pooled data from these trials, some as short as 1 month in duration, showed that combination treatment with LABAs and inhaled corticosteroids did not statistically significantly affect asthma hospitalizations compared with inhaled corticosteroids alone. Inclusion of the short-duration trials may have biased the results in favor of LABA use. Inhaled corticosteroids may provide clinically significant protection against the adverse effects of LABAs, but this protection may not be complete (14-16). This issue requires additional careful study.

Drs. Nelson and Dorinsky and Dr. Ernst and colleagues have questioned our estimate that LABA use may be responsible for 4000 of the 5000 asthma deaths in the United States each year. We based our estimate on 3 main assumptions. First, our results, which pooled data from all placebo-controlled trials and found an absolute increased risk for 1 asthma death per 800 persons treated per year, could be extrapolated to the risk associated with LABAs in the general population. The second assumption was that the estimated 3.5 million patients who are prescribed LABAs each year (17, 18) take them with the same adherence as that under trial conditions, which leads to the estimate of 4000 excess deaths due to LABAs each year. If adherence to LABA dosing in the population is less than that in the trials, the number of annual asthma deaths caused by LABAs would be less than 4000. The third assumption is that the published estimate of approximately 5000 asthma-related deaths each year in

the United States is accurate (19). Drs. Nelson and Dorinsky report that the number of annual asthma deaths in the United States is closer to 4000. Because of the variations in collecting population data and uncertainties in the assumptions, we can now estimate that 3000 to 4000 of the 4000 to 5000 asthma deaths in the United States each year are caused by LABAs. However, such calculations are speculative and tenuous: They are limited to the types of patients and conditions included in trials and may not be applicable to the use of LABAs as add-on therapy to inhaled corticosteroids.

Drs. Nelson and Dorinsky and Dr. Ryan question how so many deaths could be caused by LABAs without a marked increase in the asthma mortality rate since their introduction on the market. The asthma mortality rate in the total population is difficult to accurately track. Estimates for the United States since the early 1990s indicate that the rate increased, then stabilized, and recently may be starting to decrease (19–22). One explanation for why we have not seen a dramatic increase in asthma mortality rates over the past 10 years is the widespread use of short-acting β -agonists for many years without concomitant inhaled corticosteroids. These short-acting agents may have been responsible for many asthma deaths in the past. Regular use of short-acting β -agonists causes tolerance to their effects and has been linked to increased fatal and nonfatal asthma attacks (16, 23, 24). Since the risk of these agents became known, guidelines have encouraged that short-acting β -agonists be used sparingly and only on an as-needed basis and that inhaled corticosteroids be used as first-line treatment of asthma.

There is still much to learn about therapeutic options for asthma. Our meta-analysis has verified that LABAs, without consistent use of inhaled corticosteroids, cause an excess of asthma exacerbations and deaths compared with placebo. Further study is needed to reevaluate whether concomitant use of inhaled corticosteroids can completely protect against the adverse effects of LABAs and whether the benefits of LABAs are worth the risks. We must keep in mind that regular short-acting β -agonists also carry a risk for worsening asthma control, especially if they are prescribed without concomitant inhaled corticosteroids. As Dr. Stoloff stated, we referenced an analysis of the short-term benefits of inhaled anticholinergics added to standard therapy with short-acting β -agonists (25). However, other trials of anticholinergics alone show bronchodilator benefits in acute asthma exacerbations, as well as in controlling chronic asthma (26–30). As Dr. Currie and Dr. Ryan pointed out, we failed to mention that leukotriene-receptor antagonists have also been shown to be effective and safe, especially when used in conjunction with inhaled corticosteroids (31, 32).

Dr. Ernst and colleagues' comments (1) might imply to some that we are biased both in our assessment of risk associated with LABAs and in our proposal that LABAs be removed from the market. Please note that I do not have, nor have I ever had, any financial relationship with a pharmaceutical company. I believe that I practice responsible, evidence-based medicine when I do not use β -agonists at all in my clinical practice.

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Potential Financial Conflicts of Interest: Dr. Salpeter has consulted on legal cases involving β -agonists but has never given expert testimony and has no contracts with law firms.

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Use of Long-Acting β -Agonists and Inhaled Corticosteroids

TO THE EDITOR: Dr. Ernst and colleagues (1) and I agree that inhaled corticosteroids are the appropriate first-line agent for chronic asthma management and that long-acting β -agonists (LABAs) are a valuable next level of treatment for many patients. We seem to disagree on exactly how best to use LABAs. Dr. Ernst and colleagues note that the “greatest benefit from inhaled corticosteroids occurs with low doses” and imply that the need for higher doses will be obviated by early addition of LABAs. In fact, the Gaining Optimal Asthma Control (GOAL) study found that while asthma control could be attained more rapidly and at a lower dose of inhaled corticosteroids by adding LABAs, most study patients were receiving the highest dose of salmeterol–fluticasone or fluticasone by the end of 1 year (2). Martinez (3) subsequently noted that only an additional 10% to 15% of GOAL patients achieved control with intermediate doses of inhaled corticosteroids by adding LABAs. Ernst and colleagues also note that higher doses of inhaled corticosteroid are associated with a “small increase in serious adverse events, such as fractures and cataracts.” Upon examination of their reference on this point, only the use of more than 2000 μ g of beclomethasone-equivalent units of inhaled corticosteroids per day for an average of 6 years was associated with an elevated risk for hip fracture (relative risk,

1.61 [compared with age-matched patients in a control group]). Moreover, the log-linear analysis, a measure of dose–response, showed no definite increase (relative risk, 1.03) (4). When all of these data are considered, I believe that the recommendation of ensuring that inhaled corticosteroids have been used to the maximum benefit before considering LABAs is reasonable. At the bottom line, however, we agree on the most important point: Asthma is a serious condition and it should be treated until controlled.

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Potential Financial Conflicts of Interest: None disclosed.

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CLINICAL OBSERVATIONS

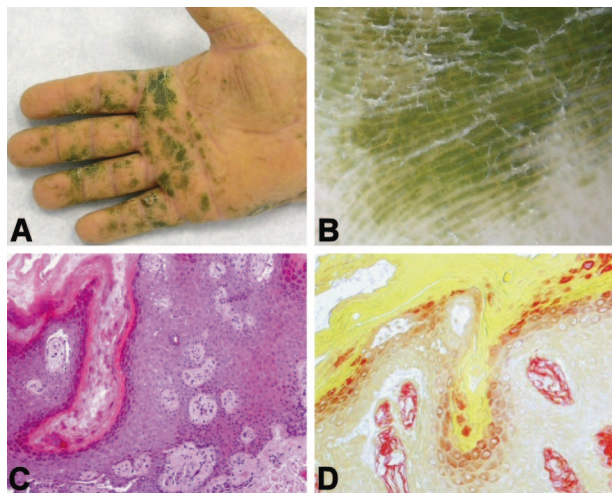
Green Sweating Spots on Hands and Feet: Unusual Expression of Hyperbilirubinemia

Background: Liver disease may cause cutaneous manifestations, including jaundice, purpurae, diffuse erythema, spider nevi, telangiectasia, atrophy, hyperpigmentation, gynecomastia, thin hair, and white nails.

Objective: To describe a patient with cholestatic hyperbilirubinemia who presented with green discoloration of the hands and feet.

Case Report: A 56-year-old man, hospitalized for recurrent fever, latent jaundice, and epigastric pain, progressively developed macules on his hands and feet. The macules were deep green; were partly coalescing; and were preferentially located on the volar and lateral sides of the fingers, palms, and soles (**Figure, A**). He also had mild keratoderma in the affected areas. Examination with a hand-held dermatoscope revealed a linear distribution of green-colored pigment along the dermatoglyphic ridges with partial sparing of the furrows (**Figure, B**). A 3-mm incisional cutaneous biopsy was performed. Histopathologic examination showed a hyperkeratotic scale containing accumulation of an amorphous substance within the stratum corneum and in dilated adnexal pores (**Figure, C**). With the Hall method of staining (1), the amorphous substance showed a selective intense yellowish-green hue, suggestive of bilirubin deposition (**Figure, D**). Increased levels of total (206.45 μ mol/L [12.07 mg/dL]) and conjugated bilirubin (136.32 μ mol/L [7.97 mg/dL]), aspartate aminotransferase (137 U/L), alanine aminotransferase (290 U/L), alkaline phosphatase (124 U/L), and γ -glutamyltransferase (692 U/L) were the main findings of laboratory tests. Cholelithiasis was

Figure. Green sweating spots as sign of cutaneous bilirubin excretion.



A. Clinical image of several deep-green macules coalescing into diffuse patches that are mainly located on the volar and lateral side of the fingers and on the palms. The skin was hyperkeratotic, and in some exfoliated areas, a normal-colored underlying skin was exposed. **B.** Dermoscopic image showing a linear distribution of the green pigment, mainly arranged at the level of the dermatoglyphic ridges with a partial sparing of the furrows (DermLite Foto, 3Gen, Dana Point, California; original magnification, $\times 10$). **C.** Microscopic examination of palm skin biopsy specimen reveals an hyperkeratotic scale containing amorphous substance within the stratum corneum and in dilated adnexal pores (hematoxylin-eosin stain; original magnification, $\times 250$). **D.** Microscopic examination of palm skin biopsy specimen shows a selective intense yellowish-green hue, suggestive of bilirubin deposition (Hall staining method; original magnification, $\times 250$).

diagnosed by endoscopic retrograde cholangiopancreatography, and a surgical cholecystectomy normalized the abnormal laboratory values. The cutaneous green discoloration cleared over the following 3 weeks.

Discussion: Green skin pigmentation has been reported with *Pseudomonas aeruginosa* nail infection, resolution of ecchymosis, cutaneous absorption of exogenous pigment, copper deposition, poisoning, sweat gland chromhidrosis or pseudo-chromhidrosis, acute pancreatitis, intraabdominal hemorrhagic diseases, and eosinophilic cellulitis (2). Increased levels of bilirubin in the skin usually cause jaundice, because bilirubin is confined within peripheral cutaneous blood vessels. However, an increased level of bilirubin may cause a

rare transient green discoloration when it is excreted through eccrine sweat glands. We found evidence of this event in our patient by dermoscopy, which detected green pigment mainly along the skin ridges where the eccrine sweat glands open (Figure, B), and by biopsy, which showed the amorphous accumulation of bilirubin pigment within the stratum corneum surrounding dilated adnexal ducts (Figure, C and D). The green color observed is attributable to the switch from brown-colored bilirubin to green-colored biliverdin by oxidative processes. Bilirubin excretion through eccrine sweating could be considered an exceptional variant of eccrine chromhidrosis (2–4). Chromhidrosis, inclusive of eccrine or apocrine forms, is an uncommon condition characterized by production of variously colored sweat. In apocrine glands, oxidation of lipofuscin pigment may cause yellow, green, blue, or black sweat. In eccrine glands, chromhidrosis may follow the ingestion of certain dyes or drugs. Pseudo-chromhidrosis refers to the coloring of sweat when exogenous chemicals, such as extrinsic dyes and paints, or chromogenic bacteria react on the skin surface (5). Although hyperbilirubinemia is a very common feature of liver disorders, green discoloration has been described in only 3 reports (2–4). This unusual variant of eccrine chromhidrosis could be added to the list of cutaneous signs of liver diseases, such as jaundice, purpura, diffuse erythema, spider nevi, telangiectasia, atrophy, hyperpigmentation, gynecomastia, thin hair, and white nails.

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