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## Efficacy of inhaled corticosteroids in asthma

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Inhaled corticosteroids have now become established as first-line therapy for patients with persistent asthma. Corticosteroids are the only currently available asthma therapy that suppress inflammation in asthmatic airways, and they inhibit almost every aspect of the inflammatory process in asthma. Inhaled corticosteroids are effective in most patients with asthma, irrespective of age or asthma severity. They not only control asthma symptoms and improve lung function but also prevent exacerbations and may reduce asthma mortality and the irreversible changes in airway function that occur in some patients. The dose-response curve to inhaled corticosteroids is relatively flat, and there is increasing evidence that addition of another class of therapy (long-acting inhaled  $\beta_2$ -agonists, low-dose theophylline, or antileukotrienes) may be preferable to increasing the dose of inhaled corticosteroids in patients with moderate-to-severe asthma. Inhaled corticosteroids are convenient to use and are the most cost-effective treatment currently available for long-term asthma control. A small proportion of patients are resistant to the antiinflammatory effects of corticosteroids. Future developments may include inhaled corticosteroids with even fewer systemic effects or more specific anti-inflammatory drugs. (*J Allergy Clin Immunol* 1998;102:531-8.)

**Key words:** Asthma, corticosteroids, airway hyperresponsiveness, inflammation

Corticosteroids are by far the most effective therapy currently available for asthma, and a response to steroids

### Abbreviations used

|                 |                             |
|-----------------|-----------------------------|
| AHR:            | Airway hyperresponsiveness  |
| AP-1:           | Activator protein-1         |
| BDP:            | Beclomethasone dipropionate |
| FP:             | Fluticasone propionate      |
| GR:             | Glucocorticoid receptor     |
| NF- $\kappa$ B: | Nuclear factor- $\kappa$ B  |
| PEF:            | Peak expiratory flow        |

is one of the characteristic clinical features of asthma. Inhaled corticosteroids have revolutionized asthma management and have now become the mainstay of therapy for patients with persistent asthma.<sup>1</sup> There has recently been an enormous increase in our understanding of the molecular and cellular mechanisms whereby corticosteroids suppress inflammation in asthma, and this has led to changes in the way corticosteroids are used and may point the way to the development of more specific therapies in the future.<sup>2</sup> Inhaled corticosteroids are the most carefully studied drugs that are in current clinical use.

### ANTIINFLAMMATORY MECHANISMS

Corticosteroids are very effective at suppressing the eosinophilic inflammation in the airways of patients with asthma. This antiinflammatory effect is through increased transcription and expression of antiinflammatory proteins, such as IL-1 receptor antagonist, IL-10, and neutral endopeptidase. More importantly, this effect is through repression of inflammatory genes, such as cytokines involved in the inflammatory response in asthma (eg, IL-4, IL-5, and chemokines involved in eosinophil recruitment).<sup>2</sup> Corticosteroids are probably so effective in asthma because they inhibit many components of the inflammatory

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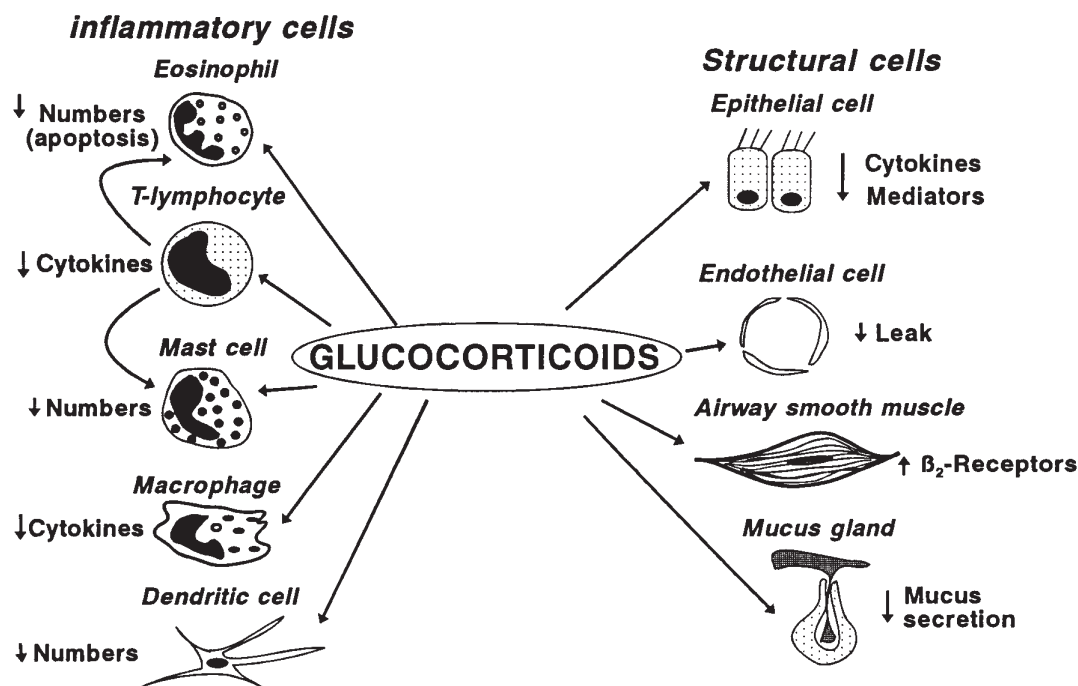


**FIG 1.** Inhaled corticosteroids have effects on many inflammatory and structural cells that are involved in asthmatic inflammation.

ry response in asthma (Fig 1). They inhibit the activation and recruitment of inflammatory cells, particularly eosinophils, T lymphocytes, macrophages, and dendritic cells. Although they do not block mast cell activation, they inhibit the survival of mast cells at the airway surface, thus preventing their activation in challenges such as exercise and fog. Increasingly, it is also recognized that corticosteroids also inhibit the release of mediators from structural cells in the airways, such as epithelial, smooth muscle, and endothelial cells and fibroblasts. Indeed, an inhibitory effect on epithelial cells may be one of the major actions of inhaled corticosteroids (Fig 2).<sup>3</sup>

Many studies have now documented the suppressive effect of inhaled corticosteroids on inflammation in asthmatic airways. This is reflected by a reduced number of inflammatory cells (particularly eosinophils, surface mast cells, and macrophages), and to a lesser extent T lymphocytes, in bronchial biopsy specimens of asthmatic patients. Similar results have been reported in the bronchoalveolar lavage fluid of asthmatic patients. There is also a reduction in other markers of airway inflammation, including eosinophils in induced sputum and in exhaled nitric oxide (NO), a reflection of increased expression of the inflammatory enzyme-inducible NO synthase, which is suppressed by corticosteroids.

### Effects on airway hyperresponsiveness

By reducing airway inflammation, inhaled corticosteroids consistently reduce airway hyperresponsiveness (AHR) in asthmatic adults and children.<sup>4</sup> Chronic treatment with inhaled corticosteroids reduces responsiveness

to histamine, cholinergic agonists, allergen (early and late responses), exercise, fog, cold air, bradykinin, adenosine, and irritants (eg, sulfur dioxide and metabisulfite). The reduction in AHR takes place over several weeks and may not be maximal until after several months of therapy. The magnitude of reduction is variable between patients and is in the order of 1 to 2 doubling dilutions for most challenges; it often fails to return to the normal range. This may reflect suppression of the inflammation but persistence of structural changes that cannot be reversed by corticosteroids. Inhaled corticosteroids not only make the airways less sensitive to spasmogens, but they also limit the maximal airway narrowing in response to spasmogens.

### CLINICAL EFFICACY

Inhaled corticosteroids are very effective in controlling asthma symptoms in asthmatic patients of all ages with asthma of all severities (Table I).<sup>1,5,6</sup> Inhaled corticosteroids improve the quality of life of patients with asthma and may allow patients to lead normal lives, improve lung function, reduce the frequency of exacerbations, and possibly prevent irreversible airway changes. They were first introduced to reduce the requirement for oral corticosteroids in patients with severe asthma, and many studies have confirmed that the majority of patients can be weaned off oral corticosteroids.<sup>6</sup>

### Studies in adults

As experience has been gained with inhaled corticosteroids, they have been introduced in patients with milder asthma, with the recognition that inflammation is

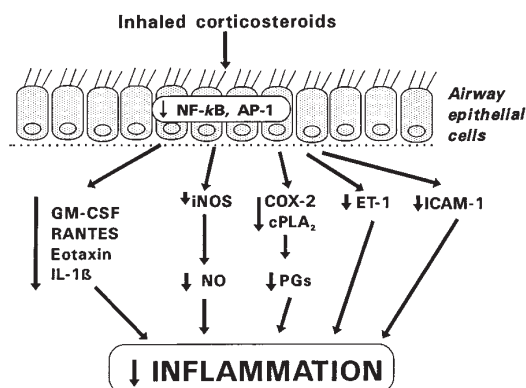


**FIG 2.** Inhaled corticosteroids may inhibit transcription of several inflammatory genes in airway epithelial cells and thus reduce inflammation in airway wall. *iNOS*, Inducible NO synthase; *COX-2*, inducible cyclooxygenase; *cPLA<sub>2</sub>*, cytosolic phospholipase A<sub>2</sub>; *ET-1*, endothelin-1; *ICAM-1*, intercellular adhesion molecule-1.

present even in patients with mild asthma. Inhaled anti-inflammatory drugs have now become first-line therapy in any patient who needs to use a  $\beta_2$ -agonist inhaler more than once a day, and this is reflected in national and international guidelines for the management of chronic asthma.<sup>7-9</sup> In patients with newly diagnosed asthma, inhaled corticosteroids (budesonide 600  $\mu$ g twice daily) reduced symptoms and  $\beta_2$ -agonist inhaler use and improved peak expiratory flows (PEFs). These effects persisted over the 2 years of the study, whereas in a parallel group treated with inhaled  $\beta_2$ -agonists alone there was no significant change in symptoms or lung function.<sup>10</sup> In another study patients with mild asthma treated with a low dose of inhaled corticosteroid (budesonide 200  $\mu$ g twice daily) showed less symptoms and a progressive improvement in lung function over several months, and many patients became completely asymptomatic.<sup>11</sup> There was also a significant reduction in the number of exacerbations. Although the effects of inhaled corticosteroids on AHR may take several months to reach a plateau, the reduction in asthma symptoms occurs more rapidly.<sup>12</sup>

High-dose inhaled corticosteroids have now been introduced in many countries for the control of more severe asthma. This markedly reduces the need for maintenance oral corticosteroids and has revolutionized the management of more severe and unstable asthma. Inhaled corticosteroids are the treatment of choice in nocturnal asthma, which is a manifestation of inflamed airways, reducing nighttime awakening and reducing the diurnal variation in airway function.

High doses of inhaled corticosteroids may also substitute for a course of oral steroids in controlling acute exacerbations of asthma. High-dose fluticasone propionate (FP) (2000  $\mu$ g daily) was as effective as a course of oral prednisolone in controlling acute exacerbations of asthma in general practice.<sup>13</sup>

Inhaled corticosteroids effectively control asthmatic inflammation but must be taken regularly. When inhaled

**TABLE I.** Effects of inhaled corticosteroids in asthma

- Control symptoms
- Improve quality of life
- Improve lung function
- Prevent exacerbations
- Reduce mortality (probably)
- Prevent irreversible airway changes
- Alter natural history of asthma (?)

corticosteroids are discontinued, there is usually a gradual increase in symptoms and airway responsiveness back to pretreatment values,<sup>12</sup> although symptoms may not recur in some patients with mild asthma who have been treated with inhaled corticosteroids for a long time.<sup>14</sup>

### Studies in children

Inhaled corticosteroids are equally effective in children. In an extensive study of children aged 7 to 17 years, there was a significant improvement in symptoms, peak flow variability, and lung function compared with a regular inhaled  $\beta_2$ -agonist, which was maintained over the 22 months of the study.<sup>15</sup> However, asthma deteriorated when the inhaled corticosteroids were withdrawn.<sup>16</sup> There was a high proportion of drop-outs (45%) in the group treated with inhaled  $\beta_2$ -agonist alone. Inhaled corticosteroids are also effective in younger children. Nebulized budesonide reduces the need for oral corticosteroids and also improved lung function in children under the age of 3 years.<sup>17</sup> Inhaled corticosteroids given by means of a large volume spacer improve asthma symptoms and reduce the number of exacerbations in preschool children and in infants.

### Dose-response studies

Surprisingly, the dose-response curve for the clinical efficacy of inhaled corticosteroids is relatively flat, and although all studies have demonstrated a clinical benefit of inhaled corticosteroids, it has been difficult to demonstrate differences between doses, with most benefit obtained at the lowest doses used.<sup>6</sup> This is in contrast to the steeper dose-response for systemic effects, implying that although there is little clinical benefit from increasing doses of inhaled corticosteroids, the risk of adverse effects is increased. However, the dose-response effect of inhaled corticosteroids may depend on the parameters measured, and although it is difficult to discern a dose-response effect when traditional lung function parameters are measured, there may be a dose-response effect in prevention of asthma exacerbations. Thus in a recent study there was a significantly greater effect of budesonide 800  $\mu$ g daily compared with 200  $\mu$ g daily in preventing severe and mild asthma exacerbations.<sup>18</sup> Normally, a 4-fold or greater difference in dose has been required to detect a statistically significant (but often small) difference in effect on commonly measured outcomes, such as symptoms, PEF, use of rescue  $\beta_2$ -agonist, and lung function, and even such large differences in dose are not always associated with significant differences in response. These

findings suggest that pulmonary function tests or symptoms may have a rather low sensitivity in the assessment of the effects of inhaled corticosteroids. This is obviously important for the interpretation of clinical comparisons between different inhaled corticosteroids or inhalers. It is also important to consider the type of patient included in clinical studies. Patients with relatively mild asthma may have relatively little room for improvement with inhaled corticosteroids, and therefore maximal improvement is obtained with relatively low doses. Patients with more severe asthma or with unstable asthma may have more room for improvement and may therefore show a greater response to increasing doses, but it is often difficult to include such patients in controlled clinical trials.

More studies are needed to assess whether other outcome measures, such as AHR, or more direct measurements of inflammation, such as sputum eosinophils or exhaled NO, may be more sensitive than traditional outcome measures, such as symptoms or lung function tests.

### Prevention of irreversible airway changes

Some patients with asthma experience an element of irreversible airflow obstruction, but the pathophysiologic basis of these changes is not yet understood. It is likely that they are the result of chronic airway inflammation and that they may be prevented by treatment with inhaled corticosteroids. There is some evidence that the annual decline in lung function may be slowed by the introduction of inhaled corticosteroids.<sup>19</sup> Increasing evidence also suggests that delay in starting inhaled corticosteroids may result in less overall improvement in lung function in both adults and children.<sup>20-22</sup> These studies suggest that introduction of inhaled corticosteroids at the time of diagnosis is likely to have the greatest effect.<sup>21,22</sup> Several large studies are now underway to assess the benefit of very early introduction of inhaled corticosteroids in children and adults. So far there is no evidence that early use of inhaled corticosteroids is curative, and even when inhaled corticosteroids are introduced at the time of diagnosis, symptoms and lung function revert to pre-treatment levels when corticosteroids are withdrawn.<sup>20</sup>

### Reduction in mortality

Inhaled corticosteroids may reduce the mortality from asthma, but prospective studies are almost impossible to conduct. In a retrospective review of the risk of mortality and prescribed antiasthma medication, there was a significant apparent protection provided by regular inhaled beclomethasone dipropionate (BDP) therapy (adjusted odds ratio of 0.1), although numbers were small.<sup>23</sup>

### Comparison between inhaled corticosteroids

Several inhaled corticosteroids are currently prescribable in asthma, although their availability varies between countries. There have been relatively few studies comparing efficacy of the different inhaled corticosteroids, and it is important to take into account the delivery system and the type of patient under investigation

when such comparisons are made. Because of the relatively flat dose-response curve for the clinical parameters normally used in comparing doses of inhaled corticosteroids, it may be difficult to see differences in efficacy of inhaled corticosteroids. Furthermore, most comparisons have concentrated on differences in systemic effects at equally efficacious doses, although it has often proved difficult to establish true clinical efficacy. In the UK, BDP, budesonide, and FP are available, whereas in the US, BDP, flunisolide, triamcinolone, FP, and budesonide are available. There are few studies comparing different doses of inhaled corticosteroids in asthmatic patients. Budesonide has been compared with BDP, and it appears to have comparable antiasthma effects at equal doses in adults and children, whereas FP appears to be approximately twice as potent as BDP and budesonide. There do appear to be some differences between inhaled corticosteroids in terms of their systemic effects at comparable antiasthma doses, however, but these are beyond the scope of this review.

### CLINICAL USE OF INHALED CORTICOSTEROIDS

Inhaled corticosteroids are now recommended as first-line therapy for all patients with persistent symptoms.<sup>1</sup> Inhaled corticosteroids should be started in any patient who needs to use a  $\beta_2$ -agonist inhaler for symptom control more than once daily (or possibly 3 times weekly). It is conventional to start with a low dose of inhaled corticosteroid and to increase the dose until asthma control is achieved. However, this may take time, and a preferable approach is to start with a dose of corticosteroids in the middle of the dose range (400  $\mu$ g twice daily) to establish control of asthma more rapidly.<sup>24</sup> Once control is achieved (defined as normal or best possible lung function and infrequent need to use an inhaled  $\beta_2$ -agonist), the dose of inhaled corticosteroid should be reduced in a step-wise manner to the lowest dose needed for optimal control. It may take as long as 3 months to reach a plateau in response, and any changes in dose should be made at intervals of 3 months or more. This strategy ("start high - go low") is emphasized in the most recent US and UK guidelines.<sup>8,9</sup> When daily doses of 800  $\mu$ g or greater are needed, a large volume spacer device should be used with a metered-dose inhaler and mouth washing with a dry powder inhaler to reduce local and systemic side effects. Inhaled corticosteroids are usually given as a twice daily dose to increase compliance. When asthma is more unstable, 4 times daily dosage is preferable.<sup>25</sup> For patients who require 400  $\mu$ g or less daily, once daily dosing appears to be as effective as twice daily dosing, at least for budesonide.<sup>26</sup>

The dose of inhaled corticosteroid should be increased to 2000  $\mu$ g daily if necessary, but higher doses may result in systemic effects, and it may be preferable to add a low dose of oral corticosteroid because higher doses of inhaled corticosteroids are expensive and have a high incidence of local side effects. Nebulized budesonide has been advocated to

give an increased dose of inhaled corticosteroid and to reduce the requirement for oral corticosteroids,<sup>27</sup> but this treatment is expensive and may achieve its effects largely by means of systemic absorption.

### Additional bronchodilators

Conventional advice was to increase the dose of inhaled corticosteroids if asthma was not controlled on the assumption that there was residual inflammation of the airways. However, it is now apparent that the dose-response effect of inhaled corticosteroids is relatively flat, so that there is little improvement in lung function after doubling the dose of inhaled corticosteroids. An alternative strategy is to add some other class of controller drug. In patients in general practice whose symptoms were not controlled by BDP 200 µg twice daily, addition of salmeterol 50 µg twice daily was more effective than increasing the dose of inhaled corticosteroid to 500 µg twice daily in terms of lung function improvement, rescue  $\beta_2$ -agonist use, and symptom control.<sup>28</sup> This surprising result was confirmed in a group of patients with more severe asthma whose symptoms were not controlled on 800 to 1000 µg BDP daily.<sup>29</sup> Similar results have been found with another long-acting inhaled  $\beta_2$ -agonist, formoterol, which in addition reduced the frequency of mild and severe asthma exacerbations.<sup>18</sup> Recent studies have also shown that addition of low doses of theophylline (giving plasma concentrations of <10 mg/L) were more effective than doubling the dose of inhaled budesonide, either in mild or severe asthma.<sup>30,31</sup> Similar data are now emerging with antileukotrienes.<sup>32</sup> The reason why these alternative treatments are more effective than higher doses of inhaled corticosteroids remains to be elucidated, but it does suggest that there is a reversible component of asthma that may not be steroid-sensitive inflammation. It is possible that this may be an abnormality in airway smooth muscle itself (as a result of remodeling), edematous swelling of the airway, or production of cysteinyl-leukotrienes that is not sensitive to inhibition by inhaled corticosteroids.<sup>33</sup>

### Cost effectiveness

Although inhaled corticosteroids may be more expensive than short-acting inhaled  $\beta_2$ -agonists, they are the most cost-effective way of controlling asthma because reducing the frequency of asthma attacks will save on total costs.<sup>34</sup> Inhaled corticosteroids also improve the quality of life of patients with asthma and allow many patients a normal lifestyle, thus saving costs indirectly.<sup>35</sup>

### Oral corticosteroid-sparing therapy

In patients who have serious side effects with maintenance oral corticosteroid therapy, there are several treatments that have been shown to reduce corticosteroid requirements.<sup>36</sup> These treatments are commonly termed corticosteroid-sparing, although this is a misleading description that could be applied to any additional asthma therapy (including bronchodilators). The

amount of corticosteroid sparing with these therapies is not impressive.

Several immunosuppressive agents have been shown to have oral corticosteroid-sparing effects, including methotrexate, oral gold, and cyclosporin A. These therapies all have side effects that may be more troublesome than those of oral corticosteroids and are therefore only indicated as an additional therapy to reduce the requirement of oral corticosteroids. None of these treatments is uniformly effective in all patients, but there are occasional patients who appear to show a good response. Because of side effects, these treatments cannot be considered as a way to reduce the requirement for inhaled corticosteroids. Several other therapies, including azathioprine, dapson, and hydroxychloroquine, have not been found to be beneficial. The macrolide antibiotic troleandomycin is also reported to have corticosteroid-sparing effects, but this is only seen with methylprednisolone and is due to reduced metabolism of this corticosteroid. Therefore there is little therapeutic gain.<sup>37</sup>

### CORTICOSTEROID-RESISTANT ASTHMA

Although glucocorticoids are highly effective in the control of asthma and other chronic inflammatory or immune diseases, a small proportion of patients with asthma fail to respond even to high doses of oral glucocorticoids.<sup>38,39</sup> Resistance to the therapeutic effects of glucocorticoids is also recognized in other inflammatory and immune diseases, including rheumatoid arthritis and inflammatory bowel disease. Corticosteroid-resistant patients, although uncommon, present considerable management problems. Recently, new insights into the mechanisms whereby corticosteroids suppress chronic inflammation has shed new light on the molecular basis of corticosteroid-resistant asthma.

Corticosteroid-resistant asthma is defined as a failure to improve FEV<sub>1</sub> or PEF by greater than 15% after treatment with oral prednisolone 30 to 40 mg daily for 2 weeks, providing the oral steroid is taken (verified by plasma prednisolone level or a reduction in early morning cortisol level). These patients do not have Addison's disease, and they do not have the abnormalities in sex hormones described in the very rare familial glucocorticoid resistance. Plasma cortisol and adrenal suppression in response to exogenous cortisol is normal in these patients, and therefore they experience the side effects of corticosteroids.

Complete corticosteroid resistance in asthma is very rare, with a prevalence of less than 1 in 1000 asthmatic patients. Much more common is a reduced responsiveness to corticosteroids, such that large inhaled or oral doses are needed to control asthma adequately (corticosteroid-dependent asthma). It is likely that there is a range of responsiveness to corticosteroids and that corticosteroid resistance is at one extreme of this range.

It is important to establish that the patient has asthma, rather than chronic obstructive pulmonary disease, "pseudoasthma" (a hysterical conversion syndrome involving vocal cord dysfunction), left ventricular fail-

ure, or cystic fibrosis, which do not respond to corticosteroids. Asthmatic patients are characterized by a variability in PEF and, in particular, a diurnal variability of greater than 15% with episodic symptoms. It is also important to identify provoking factors (allergens, drugs, or psychologic problems) that may increase the severity of asthma and its resistance to therapy. Biopsy studies have demonstrated the typical eosinophilic inflammation of asthma in these patients.<sup>39</sup>

### Mechanisms of corticosteroid resistance

There may be several mechanisms for resistance to the effects of glucocorticoids. Certain cytokines (particularly IL-2, IL-4, and IL-13) may induce a reduction in affinity of glucocorticoid receptors in inflammatory cells, such as T lymphocytes and monocytes, by increasing expression of glucocorticoid receptor- $\beta$ , an endogenous inhibitor of corticosteroid action, resulting in local resistance to the antiinflammatory actions of corticosteroids.<sup>39,40</sup> Another mechanism is an increased activation of the transcription factor activator protein (AP)-1 by inflammatory cytokines, such that AP-1 may consume activated glucocorticoid receptors and thus reduce their availability for suppression of inflammation at inflamed sites.<sup>41</sup> The reasons for this excessive activation of AP-1 by activating enzymes is currently unknown but might be genetically determined.

### FUTURE DIRECTIONS

Inhaled corticosteroids are now used as first-line therapy for the treatment of persistent asthma in adults and children in many countries because they are the most effective treatments for asthma currently available. The recent trend to start with a relatively high dose of inhaled corticosteroids to achieve more rapid control of asthma before the dose is reduced to the minimum needed to maintain control may lead to lower overall maintenance doses.<sup>6</sup> Although many patients, particularly those with more severe asthma, remain undertreated, there is also a danger of overtreatment, and many patients with mild asthma who may require very low doses of inhaled corticosteroids are inappropriately treated with high doses. It is essential that inhaled corticosteroids are slowly reduced to the minimal dose required to control asthma, and this dose should then be maintained. An important clinical development is the recognition that asthma is better controlled by addition of an alternative class of treatment (long-acting inhaled  $\beta_2$ -agonists, low dose theophylline, and antileukotrienes) than by increasing the dose of inhaled steroid. Although there may be some patients who are better treated with a higher dose of inhaled corticosteroid, at present it is not possible to identify such patients clinically. Improvement in techniques for the noninvasive monitoring of airway inflammation may be valuable in the future for assessing the requirement for inhaled corticosteroids.<sup>42</sup>

### New corticosteroids

Budesonide and FP have been important advances in inhaled corticosteroid therapy. They have reduced systemic effects because of greater first-pass hepatic metabolism than BDP. There are other inhaled corticosteroids in development, such as mometasone, that show a similar improved profile. However, all currently available corticosteroids are absorbed from the lungs into the systemic circulation and therefore inevitably have some systemic component. A class of steroids was developed that was metabolized in the lung, but such so called *soft* steroids, such as tipredane and butixocort, did not prove to be clinically effective, probably because they were metabolized too rapidly in the airways. Steroids that are metabolized by enzymes in the circulation may be the safest type of inhaled corticosteroid. However, it is still not certain whether the antiinflammatory effects of inhaled corticosteroids in asthma are mediated entirely by local antiinflammatory effects in the airways, and it is possible that there is a systemic component (eg, on bone marrow eosinophil precursors). Furthermore, it is not clear whether inhaled corticosteroids are distributed from their point of deposition in the airways to more peripheral airways by means of the local circulation. If this is the case, then corticosteroids that are degraded by enzymes in the circulation may not reach small airways, which are known to be inflamed in asthma.

Understanding the molecular mechanisms of action of corticosteroids has led to the development of a new generation of corticosteroids. As discussed above, a major mechanism of the antiinflammatory effect of corticosteroids appears to be direct inhibition of transcription factors, such as nuclear factor (NF)- $\kappa$ B and AP-1, that are activated by proinflammatory cytokines (transrepression). By contrast, the endocrine and metabolic effects of steroids, which are responsible for the systemic side effects of corticosteroids, are likely to be mediated by means of DNA binding (transactivation). This has led to a search for novel corticosteroids that selectively transrepress, thus reducing the potential risk of systemic side effects. Because corticosteroids bind to the same glucocorticoid receptor (GR), this seems at first to be an unlikely possibility, but although DNA binding involved a GR homodimer, interaction with transcription factors AP-1 and NF- $\kappa$ B involves only a single GR. A separation of transactivation and transrepression has been demonstrated by using reporter gene constructs in transfected cells with selective mutations of the glucocorticoid receptor. Furthermore, some steroids, such as the antagonist RU486, have a greater transrepression than transactivation effect. Indeed, the topical steroids used in asthma therapy today, such as FP and budesonide, appear to have more potent transrepression than transactivation effects, which may account for their selection as potent antiinflammatory agents.<sup>43</sup> Recently, a novel class of steroids has been described in which there is potent transrepression with relatively little transactivation. These *dissociated* steroids, including RU24858 and RU40066, have antiinflammatory effects *in vivo*.<sup>44</sup> This suggests that the

development of steroids with a greater margin of safety is possible and may even lead to the development of oral steroids that do not have significant adverse effects.

## New antiinflammatory drugs

There has been a concerted effort to find novel antiinflammatory drugs that might replace corticosteroids in the future.<sup>45</sup> However, it has proved very difficult to find classes of drug that are as safe and efficacious as inhaled corticosteroids. More specific antiinflammatory drugs that selectively inhibit eosinophilic inflammation, such as anti-IL-5 drugs, chemokine receptor (CCR3) inhibitors, and adhesion molecule blockers (such as very late antigen-4 inhibitors), are currently in clinical development, but whether these more specific drugs will have the efficacy of corticosteroids is not yet known. Drugs that inhibit NF- $\kappa$ B are also in early development but may prove to be too toxic for use in asthma. More generalized antiinflammatory drugs, such as phosphodiesterase 4 inhibitors, have proved to be disappointing because of side effects, and immunomodulators, such as cyclosporin A, lack uniform clinical efficacy and have a high degree of toxicity. Thus it is likely that inhaled corticosteroids will remain the mainstay of asthma therapy for many years to come.

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