Efficacy and Safety of Inhaled Corticosteroids
New Developments

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Inhaled corticosteroids have revolutionized the treatment of asthma and have now become the mainstay of therapy for patients with chronic disease (1). In a supplement to this journal published 5 yr ago the currently available data on efficacy and safety of inhaled corticosteroids was reviewed (2). Since then there have been many important developments in our understanding about how inhaled corticosteroids work in asthma, and much more data on the efficacy and safety of inhaled corticosteroids have been published. In addition, there are now many more studies comparing different inhaled corticosteroids, so that inhaled corticosteroids are now among the most carefully studied drugs in clinical use. The new information about inhaled corticosteroids has reflected an enormous increase in their prescription for use in asthma, including earlier introduction in adults and children. In order to discuss and evaluate this new information, we organized an international meeting of leading investigators in this field. Their contributions to the meeting and the ensuing discussions have formed the basis for this review.

This supplement concentrates on developments occurring since the previous review in 1993. Where necessary, we have included some older studies in order to provide a balanced and comprehensive picture.

MOLECULAR MECHANISMS

There has recently been an enormous increase in our understanding of the molecular mechanisms whereby glucocorticoids suppress inflammation in asthma. This has shed new light on the molecular mechanisms of asthma and may point the way to the development of more specific therapies in the future (3, 4).

Glucocorticoid Receptors

Corticosteroids exert their effects by binding to glucocorticoid receptors (GRs), which are localized to the cytoplasm of target cells. The affinity of cortisol binding to GR is approximately 30 nM, which falls within the normal range for plasma concentrations of free hormone. There is a single class of GR that binds corticosteroids, with no evidence for subtypes of differing affinity in different tissues. Glucocorticoid receptors are widely distributed within human lung; immunocytochemical localization studies and *in situ* hybridization indicate the greatest levels of expression in airway epithelial cells and bronchial vascular endothelial cells (5).

Recently a splice variant of GR, termed GR-β, has been identified that does not bind corticosteroids, but binds to DNA, and may therefore interfere with the action of steroids (6). The structure of GR has been elucidated using site-directed mutagenesis, which has revealed distinct domains (7, 8). The glucocorticoid binding domain is at the C-terminal end of the molecule, and in the middle of the molecule are two finger-like projections that interact with DNA. Each of these "zinc fingers" is formed by a zinc molecule bound to four cysteine residues (Figure 1). An N-terminal domain (τ_1) is involved in transcriptional *trans*-activation of genes once binding to DNA has occurred, and this region may also be involved in binding to other transcription factors (9). This is the least conserved part of the molecule. Deletion analysis has demonstrated a 41 amino acid core at the C-terminal end of the τ_1 domain that is critical for *trans*-activation. In human GR there is another *trans*-activating domain (τ_2) adjacent to the steroid-binding domain, and this region is also important for the nuclear translocation of the receptor. Glucocorticoid receptor is phosphorylated (predominantly on serine residues at the N-terminal), but the role of phosphorylation in steroid actions is not yet certain (10).

The inactivated GR is bound to a protein complex ($\sim$ 300 kilodaltons [kD]) that includes two molecules of 90 kD heat shock protein (hsp 90) and a 59 kD immunophilin protein and various other inhibitory proteins. The hsp 90 molecules act as a "molecular chaperone," preventing the unoccupied GR from localizing to the nuclear compartment. Once the glucocorticoid binds to GR, hsp 90 dissociates, exposing two nuclear localization signals and allowing the nuclear localization of the activated GR-steroid complex and its binding to DNA (Figure 2).

Effects on Gene Transcription

Corticosteroids produce their effect on responsive cells by activating GR to directly or indirectly regulate the transcription of certain target genes (11–13). The number of genes per cell *directly* regulated by steroids is estimated to be between 10 and 100 in any particular cell, but many genes are indirectly regulated through interaction with other transcription factors, as discussed below. Upon activation, GR forms a dimer that binds to DNA at consensus sites termed glucocorticoid response elements (GREs) in the 5′-upstream promoter region of steroid-responsive genes. This interaction changes the rate of transcription, resulting in either induction or repression of the gene. The consensus sequence for GRE binding is the palindromic 15-base pair sequence GGTACAnnnTGTTCT (where *n* is any nucleotide), although for repression of transcription the putative negative GRE (nGRE) has a more variable sequence (ATYACnnTnTGATCn). Crystallographic

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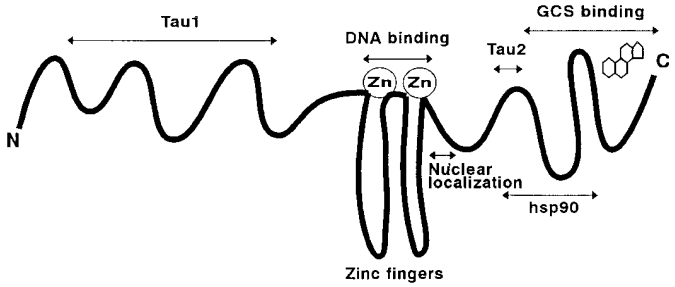

Figure 1. Structure of glucocorticoid receptor. Glucocorticosteroids (GCS) bind to the C-terminal end of the molecule.

studies indicate that the zinc finger binding to DNA occurs within the major groove of DNA, with each finger interacting with one-half of the palindrome. In contrast to these simple GREs, there are composite GREs that do not share these GRE sequences but depend on the presence of other transcription factors binding to DNA (14). Interaction with other transcription factors may also be important in determining differential steroid responsiveness in various cell types. Other transcription factors binding in the vicinity of GRE may have a powerful influence on steroid inducibility, and the relative abundance of different transcription factors may contribute to the steroid responsiveness of a particular cell type. Glucocorticoid receptors may also inhibit protein synthesis by reducing the stability of mRNA via enhanced transcription of specific ribonucleases that break down mRNA containing constitutive AU-rich sequences in the untranslated 3′-region, thus shortening the turnover time of mRNA. There is increasing recognition that corticosteroids may also affect the translation of proteins.

Interaction with Transcription Factors

Glucocorticoid receptors may interact directly with other transcription factors, which bind to each other via so-called leucine zipper interactions (15, 16). This could be an important determinant of steroid responsiveness and is a key mechanism whereby corticosteroids exert their anti-inflammatory actions (3). This interaction was first demonstrated for the collagenase gene, which is induced by the transcription factor activator protein-1 (AP-1), which is a heterodimer of Fos and Jun oncoproteins. AP-1 binds to a specific DNA binding site (TRE or TPA response element, TGACTCA). Steroids are potent inhibitors of collagenase gene transcription induced by tumor necrosis factor-α (TNF-α) and phorbol esters, which activate AP-1. AP-1 forms a protein–protein complex with activated glucocorticoid receptors, and this prevents glucocorticoid receptors from interacting with DNA and thereby reduces steroid responsiveness (17–19).

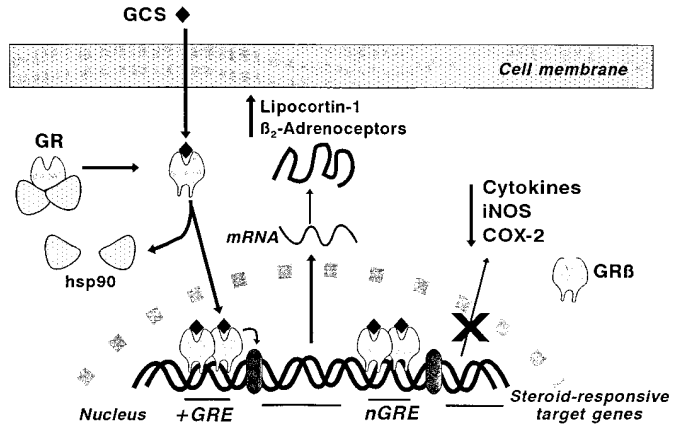

Figure 2. Classic model of glucocorticoid action. The glucocorticoid enters the cell and binds to a cytoplasmic glucocorticoid receptor (GR) that is complexed with two molecules of a 90-kD heat shock protein (hsp 90). GR translocates to the nucleus where, as a dimer, it binds to a glucocorticoid recognition sequence (GRE) on the 5′-upstream promoter sequence of steroid-responsive genes. GREs may increase transcription and nGREs may decrease transcription, resulting in increased or decreased messenger RNA (mRNA) and protein synthesis.

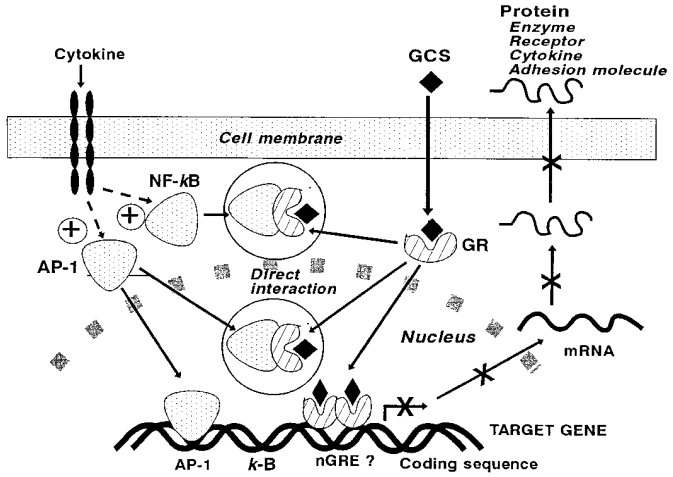

Figure 3. Direct interaction between the transcription factors activator protein-1 (AP-1) and nuclear factor-kappa B (NF-κB) and the glucocorticoid receptor (GR) may result in mutual repression. In this way steroids may counteract the chronic inflammatory effects of cytokines that activate these transcription factors.

In human lung, TNF-α and phorbol esters increase AP-1 binding to DNA; this is inhibited by corticosteroids (20–22). Glucocorticoid receptors may interact with other transcription factors that are activated by inflammatory signals, including nuclear factor-kappa B (NF-κB) in a similar manner (20, 21, 23–25) (Figure 3). There is increasing evidence that NF-κB may play a pivotal role in the orchestration of chronic inflammatory diseases, including asthma (26, 27). Many of the stimuli that lead to an increase in airway inflammation activate NF-κB, and this transcription factor induces many of the inflammatory genes that are abnormally expressed in asthma, including genes for proinflammatory cytokines that amplify inflammation, chemokines involved in recruitment of eosinophils, inflammatory enzymes that synthesize mediators, adhesion molecules involved in the recruitment of eosinophils, and inflammatory receptors (Figure 4). By inhibiting NF-κB, corticosteroids would therefore inhibit many aspects of the inflammatory process in asthma.

There is also evidence that β_2-agonists, via cyclic AMP formation and activation of protein kinase A, result in the activation of the transcription factor CREB that binds to a cyclic AMP responsive element (CRE) on genes. A direct interaction between CREB and GR has been demonstrated (28). β-Agonists increase CRE binding in human lung and epithelial cells *in vitro* and at the same time reduce GRE binding, suggesting that there may be a protein–protein interaction between CREB and GR within the nucleus (29, 30). These interactions between activated GR and transcription factors occur within the nucleus, but recent observations suggest that these

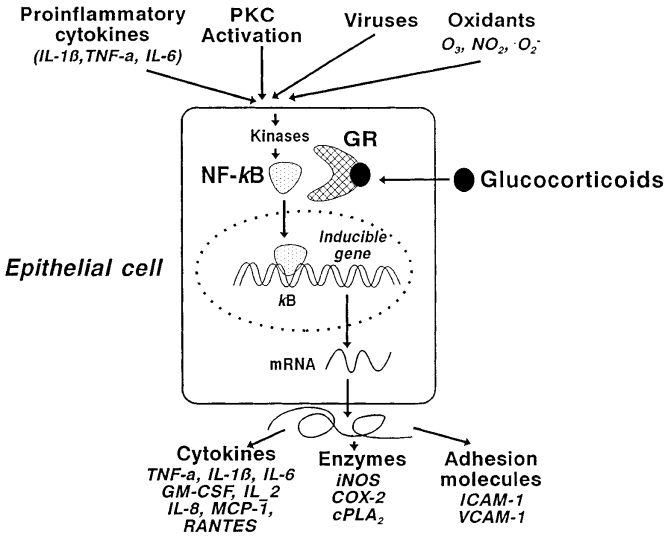

Figure 4. Some anti-inflammatory effects are likely to be mediated by inhibition of NF-κB, which is activated by many stimuli that lead to exacerbations of asthma and leads to the expression of multiple genes that are abnormally expressed in asthmatic airways.

TABLE 1

EFFECT OF CORTICOSTEROIDS ON GENE TRANSCRIPTION

Increased transcription
Lipocortin-1
β_2-Adrenoceptor
Secretory leukocyte inhibitory protein
Clara cell protein-10 (CC10, uteroglobin)
IκB-α
IL-1 receptor antagonist
Neutral endopeptidase
Decreased transcription
Cytokines
(IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-11, IL-12, IL-13, TNFα, GM-CSF, RANTES, MIP-1, eotaxin, SCF)
Inducible nitric oxide synthase (iNOS)
Inducible cyclo-oxygenase (COX-2)
Inducible phospholipase A_2 ($cPLA_2$)
Endothelin-1
NK_1-receptors
Adhesion molecules (ICAM-1, VCAM-1)

protein–protein interactions may also occur in the cytoplasm (31).

Evidence suggests that several transcription factors, including GRs, interact with large co-activator molecules, such as CREB-binding protein (CBP) and the related p300, which bind to the basal transcription factor apparatus (32). Since binding sites on this molecule may be limited, this may result in competition, and several transcription factors, including CREB itself and AP-1, may compete with GR for binding, thus yielding an indirect rather than a direct protein-protein interaction.

Target Genes in Control of Asthmatic Inflammation

Corticosteroids may control airway inflammation in asthma by inhibiting many aspects of the inflammatory process through increasing the transcription of anti-inflammatory genes and decreasing the transcription of inflammatory genes (3, 4, 33) (Table 1).

Anti-inflammatory proteins. Corticosteroids may suppress inflammation by increasing the synthesis of anti-inflammatory proteins. Steroids increase the synthesis of lipocortin-1, a 37-kD protein that has an inhibitory effect on phospholipase A_2 (PLA_2), and therefore may inhibit the production of lipid mediators. Steroids induce the formation of lipocortin-1 in several cells and recombinant lipocortin-1 has acute anti-inflammatory properties (34). However, corticosteroids do not induce lipocortin-1 expression in all cells, and this may be only one of many genes regulated by corticosteroids. Inhaled corticosteroid treatment does not appear to increase the release of lipocortin-1 into bronchoalveolar lavage (BAL) fluid in asthmatic patients (35). Corticosteroids increase the synthesis of secretory leukocyte protease inhibitor (SLPI) in human airway epithelial cells by increasing gene transcription (36). Secretory leukocyte protease inhibitor is the predominant antiprotease in conducting airways and may be important in reducing airway inflammation by counteracting inflammatory enzymes such as tryptase.

Nuclear factor-kappa B may play a pivotal role in asthmatic inflammation and is normally controlled by an inhibitory protein, IκB, which binds to NF-κB within the cytoplasm. Corticosteroids have been found to increase the expression of one form of IκB, IκB-α in certain cell types (37, 38), although this may not apply to all cell types (39, 40). Increased transcription of IκB may thus lead to inhibition of NF-κB and control of inflammation. Gene transfer of IκB-α inhibits the expression of adhesion molecules regulated by NF-κB in endothelial cells (41).

Interleukin (IL)-10 is an anti-inflammatory cytokine secreted predominantly by macrophages in the lung, which inhibits the transcription of many pro-inflammatory cytokines and chemokines (42) and appears to be mediated via an inhibitory effect on NF-κB (43). Interleukin-10 secretion by alveolar macrophages may be impaired in asthmatic patients, resulting in increased macrophage cytokine secretion (44, 45). Glucocorticoid treatment in asthmatic patients increases IL-10 secretion by these cells, although this appears to be an indirect effect, since treatment of alveolar macrophages *in vitro* with corticosteroids tends to decrease IL-10 secretion (45).

Interleukin-1 receptor antagonist (IL-1ra) is another anti-inflammatory cytokine that specifically inhibits the actions of IL-1; it is synthesized by several cells, including airway epithelial cells. Corticosteroids increase the expression of IL-1ra in these cells *in vitro* (46) and *in vivo* (47). Another mechanism whereby corticosteroids may block IL-1 effects is through increased synthesis of a second type of IL-1 receptor (IL-1rII) that binds IL-1 without signaling and therefore acts as a decoy receptor (48).

The enzyme neutral endopeptidase (NEP) degrades bronchoconstrictor and inflammatory peptides, such as bradykinin and tachykinins. There is evidence that expression of this enzyme is increased in cultured human epithelial cells *in vitro* (49) and that patients treated with inhaled corticosteroids have a higher level of NEP expression in airway epithelial cells (50).

β_2-Adrenoceptors. Steroids increase the expression of β_2-adrenoceptors by increasing the rate of transcription; the human β_2-receptor gene has three potential GREs (51). Steroids double the rate of β_2-receptor gene transcription in human lung *in vitro*, resulting in increased expression of β_2-receptors (52). Using autoradiographic mapping and *in situ* hybridization in animals to localize the increase in β_2-receptor expression, there appears to be an increase in all cell types, including airway epithelial cells and airway smooth muscle after chronic glucocorticoid treatment (53). This may be relevant in asthma

because it may prevent downregulation in response to prolonged treatment with β_2-agonists. In rats, corticosteroids prevent the downregulation and reduced transcription of β_2-receptors in response to chronic β-agonist exposure (53). However, inhaled corticosteroids do not appear to prevent the tolerance that develops to the protective effects of inhaled β_2-agonists in asthmatic patients (54), although intravenous steroids provide rapid reversal of the bronchodilator subsensitivity (55).

Cytokines. Although it is not yet possible to be certain of the most critical aspects of steroid action in asthma, it is likely that their inhibitory effects on cytokine synthesis are of particular relevance (56). Steroids inhibit the transcription of several cytokines that are relevant in asthma, including IL-1β, TNF-α, granulocyte/macrophage colony-stimulating factor (GMCSF), IL-2, IL-3, IL-4, IL-5, IL-6, IL-11, and the chemokines IL-8, RANTES, MCP-1, MCP-3, MIP-1, and eotaxin. These effects were at one time thought to be mediated directly via interaction of glucocorticoid receptors with a nGRE in the upstream promoter sequence of the cytokine gene, resulting in reduced gene transcription. Surprisingly, there is no apparent nGRE consensus sequence in the upstream promoter region of these cytokines, suggesting that corticosteroids inhibit transcription indirectly. Thus, the 5′-promoter sequence of the human IL-2 gene has no GRE consensus sequences, yet corticosteroids are potent inhibitors of IL-2 gene transcription in T lymphocytes. Transcription of the IL-2 gene is predominantly regulated by a cell-specific transcription factor, nuclear factor of activated T cells (NF-AT), which is activated in the cytoplasm on T-cell receptor stimulation via calcineurin. A nuclear factor is also necessary for increased activation, and this factor appears to be AP-1, which binds directly to NF-AT to form a transcriptional complex (57). Corticosteroids therefore inhibit IL-2 gene transcription indirectly by binding to AP-1, thus preventing increased transcription due to NF-AT (58). Other examples of cytokine genes negatively regulated by corticosteroids that do not have a GRE in their promoter region include IL-8, which is regulated predominantly via NF-κB (59), and RANTES, which is regulated by NF-κB and AP-1 (60). There may be marked differences in the response of different cells and different cytokines to the inhibitory action of corticosteroids, and this may be dependent on the relative abundance of transcription factors. Thus, in alveolar macrophages and peripheral blood monocytes, GMCSF secretion is more potently inhibited by corticosteroids than IL-1 or IL-6 secretion (61).

Some cytokines may have anti-inflammatory effects in asthma, however, and there is evidence that corticosteroids may increase the expression of these cytokines, such as IL-10 and IL-1ra, as discussed above. IL-12 may play a key role in regulating the balance between T helper 1 (Th1) and Th2 cells, increasing the proliferation of Th1 cells and the secretion of IFN-γ (62). Inhaled corticosteroids are reported to increase the expression of IL-12 in airways (63).

Inflammatory enzymes. Nitric oxide synthase (NOS) may be induced by pro-inflammatory cytokines, resulting in increased nitric oxide (NO) production. NO may increase airway blood flow and plasma exudation and may amplify the proliferation of Th2 lymphocytes, which orchestrate eosinophilic inflammation in the airways (64–66) and act as a chemotactic agent for eosinophils (67). Inducible NOS (iNOS) is potently inhibited by corticosteroids. In cultured human pulmonary epithelial cells, proinflammatory cytokines result in increased expression of iNOS and increased NO formation (68, 69). This is due to increased transcription of the iNOS gene and is inhibited by corticosteroids. There is no nGRE in the promoter sequence of the iNOS gene, but NF-κB appears to be the most important transcription factor in regulating iNOS gene transcription (70). Since TNF-α, IL-1β, and oxidants activate NF-κB in airway epithelial cells, this accounts for their activation of iNOS expression (71). Corticosteroids may therefore prevent induction of iNOS by inactivating NF-κB, thereby inhibiting transcription.

Corticosteroids inhibit the synthesis of several inflammatory mediators implicated in asthma through an inhibitory effect on enzyme induction. Corticosteroids inhibit the induction of the gene coding for inducible cyclo-oxygenase (COX-2) in monocytes and epithelial cells, and this also appears to be via NF-κB activation (72–75). Corticosteroids also inhibit the gene transcription of a form of PLA_2 induced by cytokines (75). Whether steroids also modulate expression of 5′-lipoxygenase has not yet been established, but studies of cysteinyl-leukotriene formation in asthmatic patients *in vivo* indicate that doses of oral or inhaled corticosteroids that are effective clinically do not significantly reduce the excretion of leukotriene E_4 (LTE_4), the major stable metabolite of leukotriene D_4 (LTD_4) (76, 77).

Steroids also inhibit the synthesis of endothelin-1 (ET-1) in lung and airway epithelial cells, and this effect may also be via inhibition of transcription factors that regulate its expression (78). Patients on inhaled corticosteroids have lower levels of ET-1 in BAL fluid than asthmatic patients treated only with bronchodilators (79).

Inflammatory receptors. Corticosteroids decrease the transcription of gene coding for certain receptors. Thus, the NK_1-receptor that mediates the inflammatory effects of substance P in the airways may show increased gene expression in asthma (80). This may be inhibited by steroids through an interaction with AP-1 since the NK_1 receptor gene promoter region has no GRE but has an AP-1 response element (81).

Corticosteroids are potent inducers of IL-1rII, resulting in release of a soluble form of the receptor, thus reducing the functional activity of IL-1, as discussed above (82).

Cell survival. Steroids markedly reduce the survival of certain inflammatory cells, such as eosinophils. Eosinophil survival is dependent on the presence of certain cytokines, such as IL-5 and GMCSF. Exposure to steroids blocks the effects of these cytokines and leads to programmed cell death or apoptosis (83). Steroids may increase the transcription of specific endonucleases, which may be relevant to the action of steroids on eosinophil and mast cell survival in the airways of asthmatic patients.

Adhesion molecules. Adhesion molecules play a key role in the trafficking of inflammatory cells to sites of inflammation. The expression of many adhesion molecules on endothelial cells is induced by cytokines. Steroids may lead indirectly to a reduced expression via their inhibitory effects on cytokines, such as IL-1β and TNF-α. Steroids may also have a direct inhibitory effect on the expression of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and E-selectin at the level of gene transcription (84). Intercellular adhesion molecule-1 expression in bronchial epithelial cell lines and monocytes is inhibited by corticosteroids (85).

EFFECTS ON CELL FUNCTION

Steroids may have direct inhibitory actions on several inflammatory cells implicated in pulmonary and airway diseases (Figure 5).

Macrophages

Steroids inhibit the release of inflammatory mediators and cytokines from alveolar macrophages *in vitro* (61, 86), although their effect after inhalation *in vivo* is modest (87). Steroids

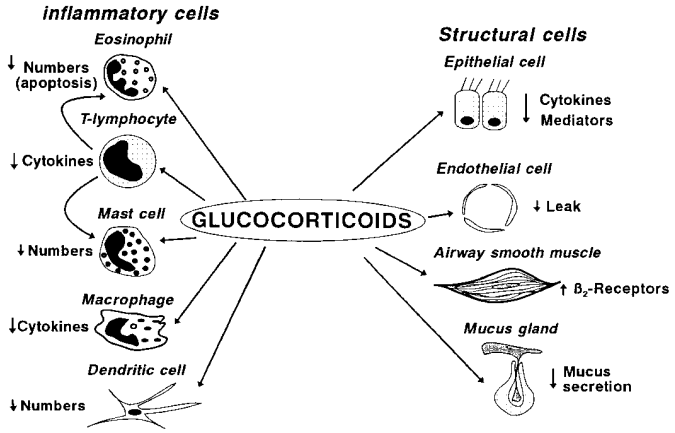

Figure 5. Cellular effect of corticosteroids.

may be more effective in inhibiting cytokine release from alveolar macrophages than in inhibition of lipid mediators and reactive oxygen species *in vitro* (88, 89). Inhaled corticosteroids reduce the secretion of chemokines and proinflammatory cytokines from alveolar macrophages from patients with asthma, whereas the secretion of IL-10 is increased (45). Oral prednisone inhibits the increased gene expression of IL-1β in alveolar macrophages obtained by BAL from patients with asthma (90).

Eosinophils

Steroids have a direct inhibitory effect on mediator release from eosinophils, although they are only weakly effective in inhibiting secretion of reactive oxygen species and eosinophil basic proteins (91, 92). Steroids inhibit the permissive action of cytokines such as GMCSF and IL-5 on eosinophil survival (93, 94), and this contributes to the reduction in airway eosinophils seen with steroid therapy. One of the best-described actions of steroids in asthma is a reduction in circulating eosinophils, which may reflect an action on eosinophil production in the bone marrow (95). In patients with asthma there is an increase in the proportion of low-density eosinophils in the circulation that may reflect an effect of cytokines (96). Inhaled corticosteroids inhibit the increase in circulating eosinophil count at night in patients with nocturnal asthma and also reduce plasma concentrations of eosinophil cationic protein (97). After inhaled corticosteroids (budesonide 800 μg b.i.d.), there is a marked reduction in the number of low-density eosinophils, presumably reflecting inhibition of cytokine production in the airways (98).

T Lymphocytes

An important target cell in asthma may be the T lymphocyte, since steroids are very effective in inhibition of activation of these cells and in blocking the release of cytokines, which are likely to play an important role in the recruitment and survival of inflammatory cells involved in asthmatic inflammation. In an experimental model of asthma that involves sensitization and repeated exposure to allergen in an IgE-producing strain of rat, there is an influx of eosinophils and lymphocytes into the lung with a concomitant increased airway responsiveness to inhaled methacholine (99). Pretreatment with steroids completely inhibits the increased eosinophil and lymphocyte numbers and the increase in airway responsiveness, whereas pretreatment with cyclosporin A, which similarly inhibits cellular influx, fails to block the increased airway responsiveness (100). This suggests that the effect of steroids on airway hyperresponsiveness may be through other cells in addition to T lymphocytes. In T-cell clones derived from BAL, corticosteroids inhibited the secretion of IL-4 and IL-5 to a greater extent than IFN-γ, which may indicate that the balance is tipped in favor of Th1 cells (101).

Mast Cells

While steroids do not appear to have a direct inhibitory effect on mediator release from lung mast cells (102, 103), chronic steroid treatment is associated with a marked reduction in mucosal mast cell number (104, 105). This may be linked to a reduction in IL-3 and stem cell factor (SCF) production, which is necessary for mast cell expression in tissues. Mast cells also secrete various cytokines (TNF-α, IL-4, IL-5, IL-6, IL-8), but whether this is inhibited by steroids is not yet clear.

Dendritic Cells

Dendritic cells in the epithelium of the respiratory tract appear to play a critical role in antigen presentation in the lung because they have the capacity to take up allergen, process it into peptides, and present it via major histocompatibility complex molecules on the cell surface for presentation to uncommitted T lymphocytes (106). In experimental animals the number of dendritic cells is markedly reduced by systemic and inhaled corticosteroids, thus dampening the immune response in the airways (107). Topical steroids markedly reduce the numbers of dendritic cells in the nasal mucosa (108), and it is likely that a similar effect would be seen in airways.

Neutrophils

Neutrophils, which are not prominent in the biopsies of patients with asthma, are not very sensitive to the effects of steroids. Indeed, systemic steroids increase peripheral neutrophil counts, which may reflect an increased survival time due to an inhibitory action of neutrophil apoptosis (in complete contrast to the increased apoptosis seen in eosinophils) (109, 110).

Endothelial Cells

Glucocorticoid receptor gene expression in the airways is most prominent in endothelial cells of the bronchial circulation and airway epithelial cells. Steroids do not appear to directly inhibit the expression of adhesion molecules, although they may inhibit cell adhesion indirectly by suppression of cytokines involved in the regulation of adhesion molecule expression (111). Steroids may have an inhibitory action on airway microvascular leak induced by inflammatory mediators (112, 113). This appears to be a direct effect on postcapillary venular epithelial cells. The mechanism for this antipermeability effect has not been fully elucidated, but there is evidence that synthesis of a 100-kD protein distinct from lipocortin-1, termed vasocortin, may be involved (114). Although there have been no direct measurements of the effects of steroids on airway microvascular leakage in asthmatic airways, regular treatment with inhaled corticosteroids decreases the elevated plasma proteins found in BAL fluid of patients with stable asthma (115).

Epithelial Cells

Epithelial cells may be an important source of inflammatory mediators in asthmatic airways and may drive and amplify the inflammatory response in the airways (116, 117). Airway epithelium may be one of the most important targets for inhaled corticosteroids in asthma (33, 118). Steroids inhibit the increased transcription of the IL-8 gene induced by TNF in cultured human airway epithelial cells *in vitro* (119, 120) and the

transcription of the RANTES gene in an epithelial cell line (121, 122). Eotaxin is a highly selective and potent eosinophil chemoattractant that is expressed in airway epithelial cells (123) and may be an important target for inhaled corticosteroids. Inhaled corticosteroids inhibit the increased expression of GMCSF, MIP-1, and RANTES in the epithelium of patients with asthma (124–126).

There is increased expression of iNOS in the airway epithelium of patients with asthma (127), and this may account for the increase in NO in the exhaled air of patients with asthma compared with normal subjects (128, 129). Patients with asthma who use inhaled corticosteroids regularly, however, do not show such an increase in exhaled NO (128), suggesting that corticosteroids have suppressed epithelial iNOS expression. Furthermore, double-blind randomized studies show that oral and inhaled corticosteroids normalize the elevated exhaled NO in patients with asthma (130, 131).

Corticosteroids decrease the transcription of other inflammatory proteins in airway epithelial cells, including COX-2, $cPLA_2$, and endothelin-1 (72, 78). Airway epithelial cells may be the key cellular target of inhaled corticosteroids; by inhibiting the transcription of several inflammatory genes, inhaled corticosteroids may reduce inflammation in the airway wall (Figure 6).

Mucus Secretion

Steroids inhibit mucus secretion in airways, perhaps through direct action on submucosal gland cells (132). The inhibitory effect of steroids may involve lipocortin-1 synthesis (133). Recent studies suggest that steroids may also inhibit the expression of mucin genes, such as MUC2 and MUC5A (134). In addition, there are indirect inhibitory effects due to the reduction in inflammatory mediators that stimulate increased mucus secretion.

EFFECTS ON ASTHMATIC INFLAMMATION

Bronchial Biopsies and Lavage

Corticosteroids are remarkably effective in controlling the inflammation in asthmatic airways, and it is likely that they have multiple cellular effects. Several biopsy studies in patients with asthma have now confirmed that inhaled corticosteroids reduce the number and activation of inflammatory cells in the airway (104, 105, 125, 135, 136). Similar results have been reported from BAL of patients with asthma after inhaled budesonide, with a reduction in both eosinophil number and eosinophil cationic protein concentrations, a marker of eosinophil degranulation (137, 138). These effects may be due to inhibition of cytokine synthesis in inflammatory and structural cells. There is also a reduction in activated CD4+ T cells (CD4+/CD25+) in BAL fluid after inhaled corticosteroids (139). The disrupted epithelium is restored and the ciliated cell/goblet cell ratio is normalized after 3 mo of therapy with inhaled corticosteroids (104). There is also some evidence that a reduction in the thickness of the basement membrane may occur (125), although in patients with asthma taking inhaled corticosteroids for over 10 yr, the characteristic thickening of the basement membrane was still present (140).

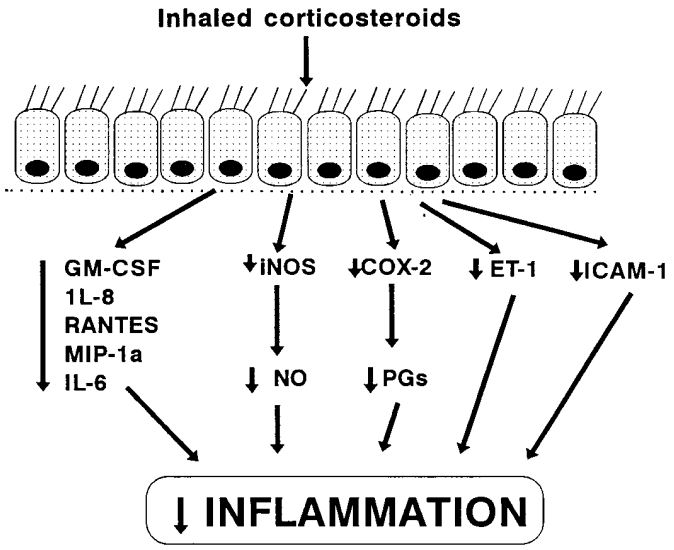

Figure 6. Inhaled corticosteroids may inhibit the transcription of several "inflammatory" genes in airway epithelial cells and thus reduce inflammation in the airway wall.

Induced Sputum

The anti-inflammatory effect of inhaled corticosteroids has been confirmed in less invasive studies using induced sputum. In untreated subjects with asthma there is an increase in eosinophils and eosinophil cationic protein (ECP); these inflammatory markers are reduced by oral and inhaled corticosteroid therapy (141, 142), the use of which is also associated with evidence of apoptosis of eosinophils (143). Conversely, reductions in the dose of steroid results in an increase in sputum eosinophils and an increase in asthma symptoms (144).

Exhaled NO

Exhaled NO correlates with sputum eosinophil counts in patients with asthma (145) and may also be a marker of airway inflammation (146). Patients with asthma who are treated with inhaled corticosteroid have significantly lower levels of exhaled NO than subjects with untreated asthma (128). Controlled studies in patients with asthma demonstrate that oral and inhaled corticosteroids reduce the elevated exhaled NO in a dose-related manner (147–149). Furthermore, reduction in the dose of inhaled corticosteroids in patients with well-controlled asthma results in an increase in exhaled NO which precedes the increase in symptoms and the deterioration in lung function (150). Thus, measurement of exhaled NO may be useful in early detection of loss of anti-inflammatory control in the clinical setting.

Airway Hyperresponsiveness

By reducing airway inflammation, inhaled corticosteroids consistently reduce airway hyperresponsiveness (AHR) in adults and children with asthma (151). Chronic treatment with inhaled corticosteroids reduces responsiveness to histamine, cholinergic agonists, allergen (early and late responses), exercise, fog, cold air, bradykinin, adenosine, and irritants such as sulfur dioxide and metabisulfite. The reduction in AHR takes place over several weeks and may not reach maximum until after several months of therapy. The magnitude of reduction varies among patients but is in the order of one to two 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 steroid therapy. Inhaled corticosteroids not only make the airways less sensitive to spasmogens, but they also limit the maximal airway narrowing in response to spasmogens (152).

CLINICAL EFFICACY OF INHALED CORTICOSTEROIDS

Inhaled corticosteroids are very effective in controlling symptoms in asthmatic patients of all ages and disease severity (1, 153). The clinical efficacy of inhaled corticosteroids in the treatment of asthma has been further established through the research produced during the last few years. New information pertains mainly to:

- Dose–response relationships;
- Clinical comparisons of different inhaled corticosteroids;
- Clinical comparisons with other anti-asthma drugs in adults and schoolchildren;
- Clinical effect in preschool children; and
- Benefits of early intervention with inhaled corticosteroids.

Dose–Response Relationships

The clinical effect of inhaled corticosteroids is best evaluated in dose–response trials. A number of clinical studies have assessed the effects of different doses of specific corticosteroids. These studies have provided clinically important information that can also be of use when interpreting results from trials which have compared two or more different corticosteroids or inhalers. Therefore, a brief review of the published dose–response trials of the various inhaled corticosteroids will be presented.

Beclomethasone Dipropionate

An early 5-mo clinical study of inhaled beclomethasone dipropionate (BDP) looked at 15 patients with asthma who were dependent on inhaled corticosteroids. Despite increasing the dose of inhaled BDP delivered via a pressurized metered-dose inhaler (pMDI) from 400 μg/d to 1,600 μg/d, no additional benefit in FEV_1 was derived from treatment (154). These results contrast with those of a larger 56-wk study, which found that a reduction of oral steroid dose was easier to achieve when an initial dose of 800 μg/d BDP pMDI was used rather than an initial dose of 400 μg/d (155).

Another open, graded-dose trial of BDP included adult patients with oral steroid-dependent asthma who increased their dose of BDP stepwise every 2 wk from 200 μg up to 1,600 μg/day (156). A dose–response effect was seen in terms of symptoms, β_2-agonist inhaler use, and frequency of exacerbations during the 26-wk study. However, this study was not randomized, so it is possible that the progressive improvements noted may have reflected the effect of *duration* of inhaled corticosteroid treatment rather than dose. No significant difference between the effects of adjacent doses was seen. At a later stage in the study, the patients were able to progressively reduce their dose of oral steroid, revealing an apparent dose–response for the oral steroid–sparing effect of the inhaled BDP (157), but again with little difference between individual dose steps.

A more recent randomized, double-blind comparison of the oral steroid–sparing effect of high and low doses of BDP (1,500 μg/d and 300 μg/d, respectively, delivered via pMDI with plastic spacer) in a group of patients with severe asthma showed no dose–response effect (158). Both groups of patients achieved a mean reduction of 5 mg/d in oral prednisolone dose over the 6-mo study period. Finally, control of asthma was better in patients receiving high doses of BDP (1,000–2,000 μg per day) than in patients who received 400 μg/d (159).

Budesonide

An acute dose–response relationship in airway function was seen when single doses of budesonide (BUD) (100 μg, 400 μg, and 1,600 μg) were given by pMDI to 12 patients with chronic stable asthma (160). Another study of 34 patients showed a linear relationship between dose and peak expiratory flow (PEF) when BUD was given by pMDI in the dose range of 400 μg/d to 1,600 μg/d for 2 wk (161). This study was not randomized, however, so the results could reflect the effect of total treatment time with corticosteroid rather than dose. As in most other studies, there was no significant difference between the effects of individual adjacent doses. A 15-wk study of 45 patients with steroid-dependent asthma (162) and a 4-wk crossover study of 24 patients with steroid-dependent asthma (163) both found that 1,600 μg/d BUD given via pMDI produced greater improvement in lung function than 400 μg/d BUD. In a double-blind, crossover study of 18 patients with moderate chronic asthma, dose-dependent increases in PEF were seen when BUD was given at 100 μg, 400 μg, and 1,600 μg/d by pMDI (each dose given for 2 wk) (164). No significant differences were seen between individual dose steps.

Recent double-blind, placebo-controlled, dose-finding studies of 473 adults (165) and 404 children (166) both found a dose–response relationship for lung function with BUD delivered through a multiple-dose dry powder inhaler (Turbuhaler) (Figure 7). The dose–response effect was statistically significant but relatively small, and the difference between placebo and low-dose BUD (200 μg/d) was greater than the difference between low-dose and high-dose BUD (1,600 μg/d). The differences between individual dose steps were not significant in these studies; in particular, there was no difference between the effects of 800 μg/d and 1,600 μg/d.

A double-blind, crossover study of 19 schoolchildren with moderate to severe asthma compared the effects of 100 μg, 200 μg, and 400 μg/d BUD given by pMDI with large-volume plastic spacer (167). Morning PEF values and FEV_1 for all three doses were significantly better than for placebo. There was no dose–response effect in morning PEF values mea-

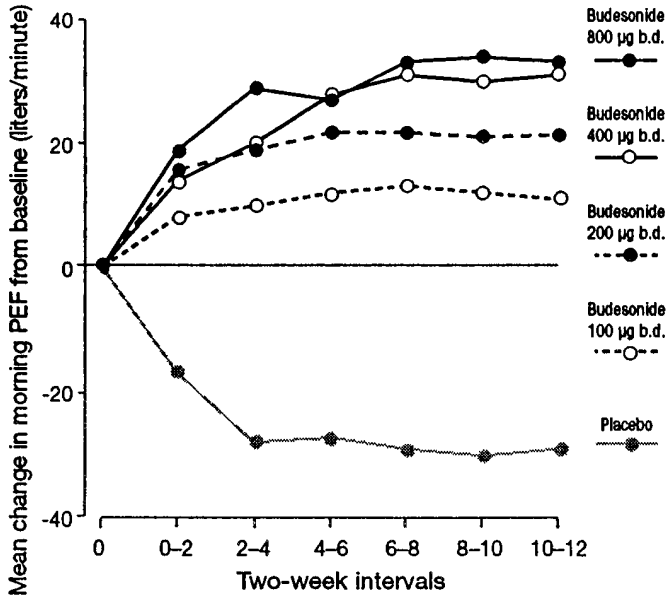

Figure 7. Mean change from baseline in morning peak expiratory flow (PEF) in patients treated with placebo or various doses of BUD (via Turbuhaler). A significant dose–response effect is seen, but it should be noted that the difference between placebo and low-dose BUD is greater than the difference between low-dose and high-dose BUD and that there is no statistically significant difference between the various doses of budesonide (165).

sured at home, but a dose–response effect with significant differences between the effects of individual doses was seen in the FEV_1 values measured at the clinic. The fall in FEV_1 or $FEF_{25–75\%}$ after exercise proved to be a sensitive marker of dose–response with significant differences detected between adjacent doses.

The results of this particular study illustrate an important phenomenon that often goes unrecognized: the dose–response curve differs for the various measurable effects of inhaled corticosteroids. This is reflected by another recent study which reported that low doses of inhaled corticosteroid produced a marked effect on symptoms and lung function, whereas somewhat higher doses were required to normalize NO concentration in exhaled air (168). In an early study, Toogood and colleagues (156) also found that the shape of the dose–response curve depended on the parameter measured, with symptom control and β_2-agonist use revealing steeper curves than those of PEF and lung functions. The dose of inhaled corticosteroids necessary to prevent asthma exacerbations may differ from that needed to control chronic asthma.

Fluticasone Propionate

A dose-dependent increase in PEF was seen in 672 adult patients with asthma treated for 4 wk with 100–800 μg/d fluticasone propionate (FP) delivered by pMDI. Mean morning PEF was 364 liters/min at a dose of 100 μg/d and 378 liters/min at 800 μg/d (169). No significant difference was seen between any of the individual doses used in the study.

Similar results were found in three randomized, double-blind, parallel group studies, each including over 300 adults with mild to moderate asthma (170–172). Significant differences were seen between the effects of placebo and those of 50 μg/d, 200 μg/d, and 1,000 μg/d FP pMDI (170), between placebo and 100 μg/d, 200 μg/d, and 500 μg/d (Diskhaler) (171), and between placebo and 200 μg/d, 500 μg/d, and 1,000 μg/d (pMDI). Once again, however, no significant differences were seen between the effects of the different doses of FP (although there was a nonsignificant trend toward greater efficacy of the higher doses in two of the three studies).

Another study compared the effect of two high doses of FP pMDI (1,500 μg/d and 2,000 μg/d) with that of placebo in a group of 96 adult oral steroid-dependent patients (173). Both FP doses were significantly better than placebo in eliminating oral steroid dependence and in leading to improvements in FEV_1. A significant difference between the two doses was seen in effect on FEV_1 but not on oral steroid dose.

The effect of 100 μg/d and 200 μg/d FP Diskhaler was compared with that of placebo among 169 children with asthma (174). Both doses of FP led to significant improvements in PEF and asthma symptom scores over 6 and 12 wk, but no significant difference was seen between the effects of the two doses of FP in any other measured parameter. Similar findings were reported in a study comparing daily doses of 100, 200, and 500 μg FP Diskhaler in 331 adults with moderate asthma ($FEV_1 > 50\%$ and $< 80\%$ predicted normal) in a randomized, placebo-controlled trial. All doses significantly improved asthma symptom scores and lung function and decreased the need for rescue β_2-agonists. However, no differences were detected among the three FP treatments in any of the other outcome measures (171).

Summary of Dose–Response Studies

All dose–response studies reported so far share some common features. They all show marked and statistically significant differences between the effects of all doses of inhaled corticosteroid and placebo, and most of them also show significant dose–response relationships between dose and effect. However, virtually all have failed to show statistically significant differences between the clinical effects of adjacent doses on the dose–response curve. 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 β_2-agonist, and lung functions; 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. An awareness of this is important for the interpretation of clinical comparisons between different inhaled corticosteroids or inhalers.

More studies are needed to assess whether other outcome measures such as AHR or a steroid-sparing effect may be more sensitive than traditional outcome measures such as symptoms or lung function tests. One study measuring changes in response to provocation by methacholine showed a dose–response effect of two doses of BUD (200 μg/d and 800 μg/d) (175). The fall in FEV_1 after exercise testing may also act as a surrogate measure for underlying airway inflammation; a dose–response relationship for inhaled BUD therapy has been demonstrated using this technique (167). Unlike most dose–response studies of inhaled corticosteroids, this study showed significant differences in response *between each dose step* when this outcome parameter was measured. As for other outcome parameters, the lowest dose was very effective, producing about 50% of the maximum achievable response.

Clinical Comparisons of Different Inhaled Corticosteroids

Many factors other than dose and drug may influence the clinical and systemic effects of inhaled corticosteroids. These factors should always be considered and presented in the resulting publication to allow accurate interpretation and comparison of results. Some of the more important factors are briefly discussed.

- To avoid bias and to demonstrate that the patients under study do indeed require treatment with inhaled corticosteroids, trials should be of a randomized, double-blind, and preferably placebo-controlled design. However, the use of different inhaler devices and the necessity of maintaining clinical control of asthma may make such trials very difficult to perform, especially in patients with severe asthma.
- Precise details of the devices and inhalation techniques used to administer the corticosteroids are essential. Different inhaler devices perform differently, a major complicating factor when comparing different inhaled corticosteroids. Various inhalers and inhalation techniques may affect oropharyngeal drug deposition by a factor of 10, and both intrabronchial drug deposition and clinical effect by a factor of two or more (176–178). This makes it obvious that precise details of the inhaler devices used, and of any maneuvers associated with their use, must be clearly stated in any research study. Without such information, it may be impossible to distinguish differences between drugs from differences between inhalers or inhalation techniques. Results may be confounded by differences in ease of use among different inhalers, especially if an inhaler familiar to the patient is compared with one which is unfamiliar. Precise descriptions of the teaching and monitoring of inhaler use should also be provided.
- With plastic (polycarbonate) spacer devices, the time interval between actuation of the pMDI and inhalation should

be standardized and specified. The cleaning and washing recommendations given to the trial participants should also be stated, as this affects the electrostatic charge of the spacer device, which in turn influences its delivery characteristics.
- Patient compliance with different forms of inhaled therapy may vary, so some measure of patient compliance should be included and documented.

Each of these factors may influence the measured clinical and systemic effects of an inhaled corticosteroid to at least the same extent as doubling or halving the specified dose and thus are of critical importance. The value of comparative studies of inhaled corticosteroids that ignore these factors is doubtful. Furthermore, the difficulties encountered when attempting to establish whether significant clinical differences exist between individual doses on the dose–response curve for a specific inhaled corticosteroid are likely to be multiplied when comparisons between different inhaled corticosteroids are performed. These difficulties may be particularly prominent when standard outcome parameters, such as symptoms, FEV_1, or morning PEF, are used.

Comparisons of the effects of different inhaled corticosteroids, or of the same inhaled corticosteroid administered with different dosing frequencies, or via different inhaler devices are subject to many inaccuracies if careful consideration is not given to the study design and subsequently to the resulting publication. The optimal design of a comparative trial of corticosteroids has not yet been identified, but true differences between corticosteroids are most likely to be detected in well-designed trials that control for the factors mentioned above. While our present knowledge does not allow us to accurately specify the ideal study design, examples of inappropriate and unsuitable study designs abound.

One reason for the apparently flat dose–response curve for inhaled corticosteroids is probably that most studies have included a very heterogeneous study population with marked differences in *individual* dose–response curves. Alternatively, the studies may have measured insensitive outcome parameters. This problem may be reduced by studying different doses in more homogeneous populations using crossover designs (167) or by using designs that make multiple individual dose adjustments to assess the minimal effective dose. Further studies are needed to confirm this.

Many trial designs have been used to compare different inhaled corticosteroids, and again there is no consensus view on the best design. The various trial designs published to date are listed below in descending order of what is currently believed to be their likely value.

- *Dose–response comparison*: A comparison of two drugs, each of which is randomized to be given in at least two doses that are deemed comparable, thus providing a within-trial comparison of dose–response. At present, only one such trial of the clinical efficacy of inhaled corticosteroid therapy in asthma has been reported (179).
- *Dose down-titration comparison*: Studies in which well controlled patients on established therapy undergo down-titration of dose in order to establish a true need for treatment. Those in whom asthma becomes uncontrolled can then be considered for entry to the trial, which may involve subsequent dose adjustments to maintain or re-establish control, or further dose reductions to define the minimal effective dose of each drug. This design yields a potency comparison and was used in a recent comparison of BUD and FP in children (180).
- *Dose-halving comparison*: Studies in which well-controlled patients are first followed on their established therapy. When the trial drugs are started, the dose is halved, and the progress of the groups of patients receiving different drugs is compared. This design allows for the detection of differences between different corticosteroids but does not provide an exact comparison of potency. It was used in a comparison of BUD and FP (181).
- *Dose–response versus one-dose comparison*: A comparison of two drugs, in which the principal trial drug is given in two or more doses, while a larger group of patients is given an established form of therapy at a single-dose level that has previously been shown (in separate dose–response studies) likely to be effective. The established drug serves as a comparator for the new therapy. Only when significant differences are found between the different doses of the principal trial drug can an estimate of the potency ratio between the two drugs be made. This design was used, for example, in a comparison of FP and BDP (169).

Studies based on other designs may also contribute to the assessment of the effects of different forms of inhaled corticosteroid therapy but are of more limited value in the quantitative comparison of the effects of different corticosteroids. Such studies take two main forms:

- *Equal dose comparison*: A comparison of two drugs in single and equal or near-equal nominal doses (μg for μg). Such studies may be short term or long term. They may show clinical similarities or differences between the effects of different corticosteroids (or inhaler devices) at the same nominal dose but cannot be used to calculate numerical potency ratios.
- *Two-to-one comparison*: Comparisons between a single dose of one drug and approximately half or double the dose of another drug. Such studies are of little or no value in establishing true potency differences between different drugs or inhalers (particularly if no differences are found), since virtually all dose–response studies performed so far have failed to show significant differences between doubling doses of the same drug on even the most commonly used outcome parameters.

The foregoing classification of studies will be used in the next sections which discuss the key comparative studies reported to date.

BUD and BDP

Dose–response comparison. In a double-blind, four-period, crossover study, BDP pMDI 200 μg and 500 μg twice daily was compared with BUD pMDI 200 μg and 400 μg twice daily. The effects of both doses of both drugs on PEF, symptom scores, and β_2-agonist use were comparable and significant when compared with the effect of placebo. No dose–response effect was seen for either drug (179). Although the study was well designed, no firm conclusion about equivalence of dose can be drawn from it because of the absence of a dose-response with either drug.

Dose down-titration comparisons. Two studies have indicated a greater efficacy for BUD Turbuhaler than for BDP pMDI (182, 183). These studies were open in design and included extensive dose adjustments of the two drugs. After 3 mo of treatment, the two groups of patients in the first study had equivalent control of their asthma at a mean dose of BUD of 900 μg/d and a mean dose of BDP of 1,350 μg/d (182). The second study (183) suggested that BUD Turbuhaler 600 μg/d is equivalent in efficacy to BDP 1,000 μg/d.

Equal dose comparisons. In a double-blind, crossover-designed, oral steroid-sparing study of 40 adults, BDP pMDI (100 μg q.i.d.) had a greater effect than an equal dose of BUD pMDI (184).

In a double-blind, crossover study of 28 patients receiving high doses of either BDP (750 μg twice daily) or BUD (800 μg twice daily), no differences in asthma control were observed (185). Another double-blind, crossover trial involving 21 children showed that equal doses of BDP and BUD (100 μg twice daily) had similar positive effects on lung function (186). The power of these two studies to detect differences between the two drugs was very low, however, because of the study designs and the small groups of patients.

Finally, results from an open crossover study suggested a greater efficacy for 400 μg/d BUD Turbuhaler than for 400 μg/d BDP Rotahaler (187). More pronounced increases in FEV_1, FVC, and FEF_{50} were seen in the BUD group than in the BDP group, and only the BUD group showed a significant improvement in AHR after provocation with histamine.

Two-to-one comparison. A comparison between BDP pMDI (1,500 μg/d) and BUD Turbuhaler (800 μg/d) found no significant difference in any outcome parameters between the two treatments (188). In contrast, an open multicenter study found that BUD Turbuhaler 400 μg/d was significantly more effective than BDP pMDI 800 μg/d in 227 patients with moderate asthma (189).

No firm conclusions can be drawn from these studies. BUD Turbuhaler may be more potent than BDP pMDI and Rotahaler, but further studies are needed to confirm this.

BDP and FP

Dose–response versus one-dose comparison. The most comprehensive comparison between BDP and FP to date compared multiple doses of FP (100–800 μg/d by pMDI) with a single dose of BDP (400 μg/d by pMDI) in 672 patients (169). A flat dose–response curve of lung function was seen, with no statistically significant differences in clinical efficacy between any dose of FP compared with the single dose of BDP, nor between the various doses of FP. The authors' conclusion was that 400 μg BDP pMDI was equivalent to 200 g FP pMDI.

Equal dose comparison. One 3-mo study comparing nearly equal doses of BDP (1,600 μg/d) and FP (2,000 μg/d), both delivered by pMDI, showed that the two were similar in improving the efficacy of asthma control when prescribed to 134 patients who had previously received a lower dose of inhaled corticosteroid (190). Another double-blind, parallel group study in 274 adults found that treatment with 1,500 μg/d FP pMDI resulted in significantly higher morning and evening PEF values and fewer exacerbations than the same dose of BDP pMDI (191).

Two-to-one comparisons. Three studies have compared BDP with half the dose of FP; no difference in clinical effect was found between the two treatments in any of them. One compared BDP (2,000 μg/d) and FP (1,000 μg/d) in 154 adults with severe asthma (192). Another compared BDP (400 μg/d) and FP (200 μg/d), both given by pMDI with plastic spacer to 398 children with asthma (193). The third compared BDP (400 μg/d) and FP (200 μg/d), both given by pMDI to 261 adult patients with mild to moderate asthma (194).

As seen with the comparisons between BDP and BUD, it is not possible to draw any firm conclusion about the comparative potency of BDP and FP on the basis of these studies. Fluticasone propionate may be clinically more potent than BDP. Further studies are needed, however, to accurately assess their potency ratio.

BUD and FP

Dose down-titration comparison. A recent double-blind study compared the efficacy of BUD Turbuhaler and FP Diskhaler in 217 children with moderate asthma (180). On entry, all the children were receiving BUD by pMDI with large-volume plastic spacer; the dose was gradually reduced to define the minimal effective dose. After this, the children entered a run-in period, followed by randomization to half this dose of BUD Turbuhaler or FP Diskhaler for 5 wk. If there was no deterioration over that period, the dose was further reduced by 50% at 5-wk intervals until deterioration in asthma control was seen, as defined by criteria based on diary card variables and exercise testing. Compliance with therapy was monitored, and inhalation technique was known to be optimal for both devices. The mean minimal effective doses for the two treatments were nearly identical, and neither dose was significantly different from the other in clinical effect.

Dose-halving comparison. A randomized open study in 171 adults compared BUD Turbuhaler and FP Diskhaler, both in doses of 200 μg/d and 400 μg/d, in patients who had previously been treated for mild to moderate asthma with conventional inhaled corticosteroids (mainly BDP) at twice the dose of BUD or FP used in the study (181). No difference was seen between the effects of equal doses of the two drugs in this study, and reducing the dose of BDP by half proved possible since patients were switched to either BUD or FP without loss of asthma control. The study results were not analyzed to detect differences between the effects of the two doses of each drug.

Dose-response versus one-dose comparison. A double-blind, multicenter study in 671 patients with severe asthma compared FP pMDI (1,000 μg/d and 2,000 μg/d) with BUD pMDI (1,600 μg/d) (195). Both doses of FP led to significantly greater increases in lung function than the single dose of BUD. The increases in mean morning PEF from baseline for FP 2,000 μg/d was 24 L/min, for FP 1,000 μg/d was 21 L/min, and for BUD 1,600 μg/d was 13 L/min. No dose–response effect was seen between the two doses of FP.

Equal dose comparison. An 8-wk randomized, parallel, double-blind, double-dummy study in 229 children with already well-controlled asthma compared the effects of BUD Turbuhaler (400 μg/d) and FP Diskhaler (400 μg/d) (196). Both forms of therapy led to small improvements in mean morning and evening PEF; during the middle part of the study the increase for the FP treatment group was significantly greater than for the BUD group. However, the difference was transient and had disappeared by 8 wk. There were no differences between the two drugs in the other measured efficacy markers, including day and nighttime asthma scores and rescue bronchodilator use. In contrast, a multicenter, randomized, open, parallel group study involving 230 adult patients with mild to moderate asthma comparing BUD Turbuhaler (400 μg/d once daily; 200 μg twice daily) with that of FP Diskhaler (200 μg twice daily) found no difference in clinical effect between any of the treatments (197).

Two-to-one comparisons. A number of open, randomized, parallel group studies utilizing unequal doses of the two drugs have been performed in adult patients with asthma. One compared FP (200 μg/d) with BUD (400 μg/d), both via pMDI, in 122 patients for 8 wk (198). Another compared FP pMDI (500 μg/d) with BUD Turbuhaler (1,200 μg) in 456 patients for 8 wk (199). Five more compared the dry powder preparations of BUD and FP. One of these compared FP Diskhaler (400 μg/d) with BUD Turbuhaler (800 μg/d) in 243 patients during 8 wk (200). Another compared FP Diskhaler (200 μg/d) with BUD Turbuhaler (400 μg/d) in 164 patients, also over 8 wk (201). A third (double-blind) study compared FP Diskhaler (800 μg/d) with BUD Turbuhaler (1,600 μg/d) in 486 patients during 12 wk (202). A fourth open study compared FP Diskus/Accuhaler (500 μg/d) with BUD Turbuhaler (1,200 μg/d) in 259 pa-

tients for 4 wk (203). A similar open study compared FP Diskus (200 μg/d) with BUD Turbuhaler (400 μg/d) in 321 children during 4 wk (204). The authors of these studies all concluded approximate therapeutic equivalence between the compared doses of the two drugs. A recent meta-analysis of seven of the studies with this design was said to show that the FP:BUD potency ratio is at least 2:1 (205).

As seen with the comparisons of other drugs, it is impossible to draw unequivocal conclusions about the comparative efficacy of FP and BUD based on the studies published to date. The studies suggest that FP pMDI is more potent than BUD pMDI, whereas FP pMDI and FP Diskhaler appear to be approximately equipotent with BUD Turbuhaler (by microgram nominal dose).

FP and Triamcinolone Acetonide

Treatment with 500 μg/d FP Diskhaler was found to be significantly more effective than 800 μg/d triamcinolone acetonide (TAA) with regard to PEF measurements, albuterol use, and exacerbation rate in 304 patients with moderate asthma in a 6-mo study (206). Both drugs were more effective than placebo. In light of the problems discussed earlier associated with identifying clinical differences between inhaled corticosteroids, these findings suggest quite marked differences in clinical potency (at least 4-fold) between the two drugs.

FP, TAA, and Flunisolide

A recent study compared dose–response relations between BDP, flunisolide (FLU), and TAA by evaluating their blocking effect on acute antigen-induced bronchoconstriction (207). Results reflected a dose–related increase in effect. It is possible, however, that prolonged treatment contributed to the increased effect (rather than dose alone) since the order of doses was not randomized. No significant differences were detected between adjacent doses on the dose–response curve for any of the outcome parameters measured. On the basis of the trial design, the validity of the conclusion of this study, that BDP, FLU, and TAA have similar potencies, must be questioned.

Conclusions

Although a substantial number of comparative studies have been performed, it is difficult to draw firm conclusions about the comparative efficacy of different inhaled corticosteroids. This may be partially explained by differences between the designs of studies, the flat dose–response relationship for inhaled corticosteroids, the differences between inhalers, and the lack of control over important confounding factors in many studies. Additional well-designed comparisons, perhaps examining different outcome parameters, are required before any definite conclusions can be made.

Clinical Efficacy in Adults

Inhaled corticosteroids are also very effective in the treatment of asthma in adults (208). Their efficacy has been shown by a reduction of symptoms and exacerbations, improvement of lung function, and a decreased need for bronchodilator rescue therapy (209, 210). Reduction of airway inflammation, manifested both by airway histology findings and improved AHR, has also been documented (104, 135, 139, 211).

Systemic corticosteroids are effective in the management of severe asthma. However, their long-term use is associated with significant and undesirable side effects. Early studies with inhaled corticosteroids demonstrated their effectiveness in reducing or eliminating the need for systemic steroids while maintaining symptom control and lung function. Despite use of high-dose inhaled corticosteroids, a number of patients are unable to dispense with oral corticosteroid therapy. Noonan and collaborators (173) identified 96 patients in a multicenter trial who required oral prednisone despite significant doses of inhaled corticosteroids. These patients with severe, persistent asthma were randomized to treatment with either 1,500 μg/d or 3,000 μg/d FP via pMDI or placebo. Only 3% of the placebo-treated patients were able to eliminate their oral prednisone. In contrast, 69%–88% of the FP-treated groups were able to safely and effectively stop prednisone, and moreover, these patients demonstrated improved FEV_1 values. Those treated with inhaled FP also showed greater symptomatic control of asthma. These results suggest that inhaled corticosteroids may have greater effectiveness in the control of asthma than oral prednisone when chronic disease is evaluated, although the mechanisms for this difference in effect is not apparent.

There has been some discussion as to whether single or divided doses of inhaled corticosteroids are most effective. Weiner and colleagues (212) compared single versus twice-daily dosing and Malo and associates (213) compared four times versus twice-daily dosing in patients requiring less than 1,200 μg BUD daily. Although different in design and frequency of daily dosing, both trials were able to demonstrate that more frequent dosing yielded more effective asthma control, as manifested by lower β_2-agonist use and decreased peak flow variability, symptoms, and rate of exacerbations. The differences in results between the two dosing approaches of each study were not striking, but they do indicate that overall effectiveness is likely greater with more frequent dosing. The mechanisms behind this effect are not established. Issues such as compliance, convenience, and acceptability, factors influenced in part by dosing frequency, need to be considered when selecting the dosing regimen for individual patients.

Clinical Efficacy in Children

Controlled trials have established that inhaled corticosteroids are effective in all children regardless of asthma severity. Continuous treatment controls both day and nighttime symptoms, reduces the frequency of acute exacerbations and the number of hospital admissions, and improves lung function and AHR (214–228) both in patients treated at hospital clinics and in patients seen in general practice.

Normally, quite marked and rapid clinical improvements and changes in lung function are seen at very low daily doses (around 100 μg), even in children with moderate and severe asthma (167, 214, 215) (Figure 8). These improvements in lung function and symptoms precede and reach a plateau before a reduction in AHR (229). Further improvement in these parameters with increasing doses is rather small; often it may take an additional 4-fold increase in dose to produce supplementary significant effect on symptoms or peak flow measurements. A daily dose of 400 μg BUD pMDI with plastic spacer produced about 80% of the maximum achievable protection against exercise-induced asthma. This indicates that the vast majority of schoolchildren can achieve optimal symptom control on quite low daily doses of inhaled corticosteroids, around 100–200 μg (167, 214–216). Somewhat higher doses and/or longer treatment are required to control AHR as assessed by protection against exercise-induced asthma or histamine challenge (167, 217–219, 229–232).

Clinical Effect in Preschool Children and Infants

Though the number of controlled studies in preschool children and infants is not as high as in schoolchildren, an increasing number of placebo-controlled clinical trials in this age

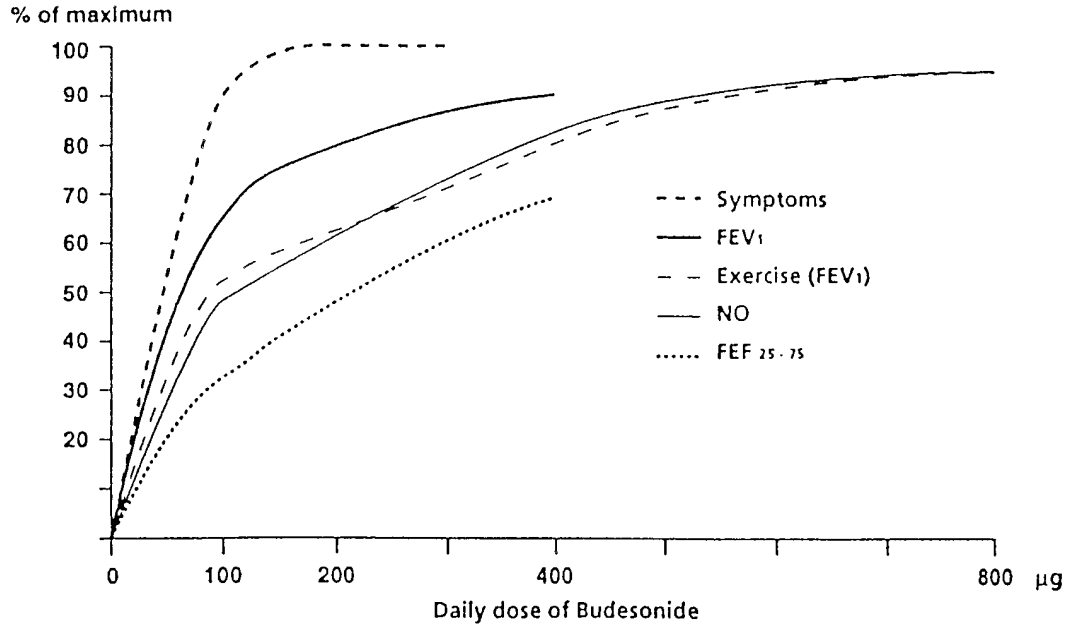

Figure 8. Steroid dose–response relationships for various outcome parameters (167, 168). The shape of the dose–response curve varies for different outcomes. The dose–response curve for normalization of chronic inflammatory changes in the airways or for maintaining normal growth of lung function is not known.

group demonstrate marked clinical effects of inhaled corticosteroids, including improvement in lung function, reduction of AHR, oral steroid requirement, and need for rescue bronchodilators (233–238). Results from these studies indicate that benefits similar to those achieved in schoolchildren may also be achieved in preschool children. Virus-induced wheeze, which is common in these age groups, is also modified (239), and two controlled trials have found that nebulized BDP reduced the frequency (but not the severity) of respiratory symptoms and improved lung function in infants with wheezing postbronchiolitis (240, 241). Finally, three uncontrolled studies and one double-blind, placebo-controlled trial have reported clinical improvement among infants with severe asthma who had not responded to other treatment (238, 242–244). Two dose-finding studies have been performed with nebulized BUD (245, 246). A mean minimal effective daily dose of around 1,000 µg was found in one study (245); however, marked individual variations were seen and the conclusion of both studies was that the dose of nebulized BUD must be individualized. A problem with young children and infants—in addition to difficulties with effective drug delivery to the intrapulmonary airways—is that in the daily clinical situation it is impossible to distinguish between children with recurrent wheeze who have asthma and children with no asthma suffering from recurrent virus-induced wheeze. The optimal use of inhaled corticosteroids may differ between these two groups.

Just as with older children, treatment with inhaled corticosteroids has also been shown to be cost-effective in children aged 1–3 yr (247). No formal comparisons with other treatments have been performed in young children. However, the children recruited for the controlled trials had all tried unsuccessfully to obtain asthma control with other anti-asthma medications, including theophylline, inhaled and oral bronchodilators, cromolyn sodium, and alternate-day oral steroids. Still, inhaled corticosteroids improved their condition, indicating that this treatment is also more effective than any other anti-asthma treatment in young children. Further studies are needed to confirm this.

Comparisons with Other Drugs

In comparing inhaled corticosteroids with other therapies for asthma, efficacy outcome measures represent a fundamental problem. Since inhaled corticosteroids differ from other agents in their mechanism of action, results of trials comparing steroids with other agents may be heavily influenced by the outcome parameter chosen for measurement. Though inhaled corticosteroids affect more outcome measures than any other class of anti-asthma drugs, the risk of reaching a misleading conclusion is great when the main emphasis is placed on a single outcome parameter, such as PEF. When an inhaled corticosteroid is compared with a bronchodilator, for example, and no difference in PEF is found between the two treatments, it is incorrect to conclude that the two treatments are equally effective. The results might likely have been quite different if another outcome measure, such as exacerbations or control of AHR, had been evaluated. Finally, recognizing that asthma is heterogeneous (i.e., patients with long history of symptoms may respond less well to inhaled corticosteroids than those with a shorter history), comparisons may also depend on the subgroup of patients with asthma chosen for study.

Adults

Bronchodilators. Several studies have compared the effects of inhaled corticosteroids with bronchodilators. One series of studies, conducted by the Dutch Chronic Nonspecific Lung Disease Study Group, compared the addition of inhaled corticosteroid, placebo, and the anticholinergic bronchodilator, ipratropium bromide, in a mixed group of patients with chronic obstructive pulmonary disease (COPD) and asthma (248–250). Addition of inhaled corticosteroid, but not placebo or ipratropium bromide, was associated with improvements in airflow as reflected by FEV_1 and improvement in AHR as assessed by

peak flow variation. Interestingly, these benefits were achieved with increased cost, even allowing for improved health status (251). Assessing cost/benefit, therefore, very much depends on assessing the value of reduced symptoms.

In another study, treatment with BUD was associated with a significant improvement in AHR, morning and evening PEF and peak flow variations, asthma symptom scores, and rescue medication usage compared with terbutaline (209). The improvement in AHR observed with BUD was persistent throughout the 2 yr of study. Bambuterol and BUD have also been compared in a study of 4 wks' duration (252). Both improved airflow, AHR, and nocturnal symptoms, although inhaled BUD was more effective than oral bambuterol.

Cockcroft and colleagues (253) compared the effectiveness of β_2-agonists and inhaled BUD on AHR with chronic dosing. The study confirmed previous observations that chronic usage of β_2-agonists can induce tolerance to the protective effect against methacholine challenge and can increase reactivity to inhaled allergen. In contrast, BUD was associated with improved AHR. When the two therapies were combined, the inhaled corticosteroid was not able to block the increase in AHR induced by the β_2-agonist.

These studies clearly show that inhaled corticosteroids are more beneficial in reducing nocturnal symptoms and reactivity of the airways than long-acting α_2-agonists. Short-acting β_2-agonists may have adverse effects on airway response to β_2-agonist and on reactivity to antigen, effects that corticosteroids may not be able to block.

As discussed above, inhaled corticosteroids reduce airway inflammation as measured by biopsies, induced sputum, and exhaled NO. In contrast, salmeterol was found to have little effect on eosinophils or mast cell tryptase in BAL fluid (254). Similarly, terbutaline has also been shown to be ineffective in improving airway inflammation (104, 255). Another study showed corticosteroids were superior to terbutaline in improving airway epithelial cell metaplasia (104). It appears, then, that inhaled corticosteroids are superior to β_2-agonists in modulating airway inflammation.

Cromones. Data are also available comparing inhaled corticosteroids with cromolyn sodium. In an open, parallel group study, FP was superior to cromolyn sodium in improving morning and evening peak flows and symptoms (216). Treatment with nedocromil sodium did not have any significant effect on inflammatory markers in bronchial biopsies of patients with asthma (256).

In summary, corticosteroids are superior to β_2-agonists, anticholinergics, and cromones, when compared head-to-head and examined for effects on AHR, FEV_1, morning and evening peak flow variation, rate of exacerbations, and airway inflammation. However, additive effects may be obtained in some patients when other therapy is combined with inhaled corticosteroids.

Children

Generally, the beneficial effects of inhaled corticosteroids in children are more pronounced than for any other anti-asthma drug (216, 221, 224–228, 257–259). In two studies, children with mild asthma seen in general practice achieved markedly better symptom control and significantly higher morning and evening PEF rates and lung function during treatment with 50 μg FP twice daily as compared with children treated with cromolyn sodium 20 μg four times daily (216, 258) (Figure 9). In addition, FP treatment was associated with markedly fewer exacerbations. In three studies, 200 and 400 μg/d BDP was significantly more effective than continuous theophylline treatment in optimal doses and inhaled bronchodilators (224, 226, 227). Verbene and coworkers (257) compared 200 μg BDP twice daily with 50 μg salmeterol twice daily for 1 yr in children with mild and moderate asthma. Marked differences were seen in favor of BDP in reduction of AHR, number of acute exacerbations, and improvements in lung function, both before and after inhalation of a bronchodilator. A trend toward a decrease in lung function and a worsening in AHR over the year was seen in the patients treated with salmeterol, while significant improvements were seen in these parameters among the children receiving BDP.

BUD was better than nedocromil sodium and cromolyn sodium in controlling asthma and reducing exacerbations in two studies (221, 259). In another long-term study, BUD was better than combinations of all other anti-asthma drugs in controlling symptoms and improving lung function, and in reducing peak flow variability, hospitalizations, and the use of other anti-asthma drugs (228). Furthermore, BUD significantly increased the growth rate of lung function to normal levels, while an annual decline was seen in percent predicted lung functions of the children not receiving inhaled corticosteroid. Similar findings were reported in another long-term trial in which BUD was compared with inhaled short-acting β_2-agonists (260) and in a trial comparing BDP with salmeterol (257).

In recent years, cost-benefit evaluations have become important tools for use when making decisions about therapy. The cost-effectiveness of inhaled corticosteroids in the treatment of asthma in children has been documented both in western and developing countries (225, 228, 261).

High-dose Inhaled Corticosteroids or Combination of Drugs?

When asthma control is not optimal, the clinician is faced with an important decision: whether to increase the current dose of inhaled corticosteroid or add another therapeutic, such as long-acting, inhaled β_2-agonist. This issue was addressed in a study of 429 patients with asthma in general practice (262). All were symptomatic despite the daily use of 400 μg BDP. The patients were randomized to receive either an increased daily dose (1,000 μg) of BDP or remain at their current dose of BDP and simply add to their therapy the long-acting β_2-agonist, salmeterol, at 50 μg twice daily. Although morning peak flow values increased significantly in both treatment groups,

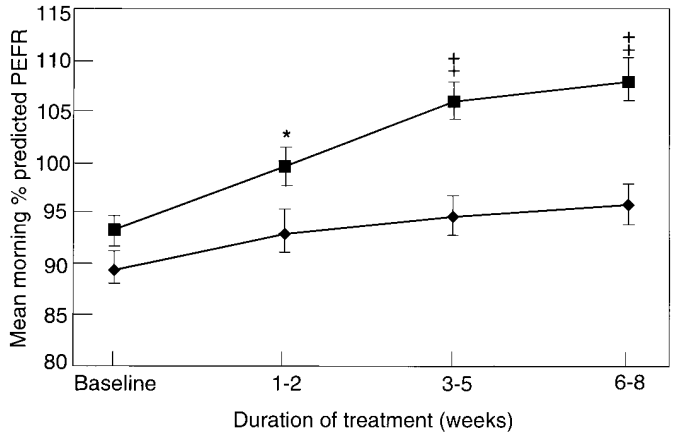

Figure 9. Mean morning (SE) peak expiratory flow rate (PEFR) expressed as percent of predicted in children with mild asthma treated with *solid squares* = fluticasone propionate, 50 μg bid (n = 110); *solid diamonds* = cromolyn sodium, 20 mg q.i.d. (n = 115); *$p < 0.05$; ‡$p < 0.0001$ (216).

improvements were greater in the group that had continued with the low dose of BDP and merely added salmeterol. Side effects and rate of asthma exacerbations were equivalent in the two groups. These results have been substantiated in a subsequent study in patients with more severe asthma (263). These investigators identified 738 patients who had symptomatic asthma despite daily treatment with 1,000 μg BDP. The patients were randomized into three different treatment groups: (*1*) salmeterol, 50 μg twice daily, and 1,000 μg/d BDP; (*2*) salmeterol, 100 μg twice daily, and 1,000 μg/d BDP; and (*3*) 2,000 μg/d BDP. Both groups receiving salmeterol showed greater improvement in morning and evening PEF values and experienced fewer symptomatic days. However, there was no change in AHR among the salmeterol-treated patients. Similar benefit was observed by Russell and colleagues (264) when they compared the addition of salmeterol and placebo to inhaled corticosteroids. Slightly different results were obtained by Sears and associates (265), who observed that increasing inhaled corticosteroid dose was more effective than adding more bronchodilator in patients with moderate asthma.

Similar data have recently been shown with another long-acting, inhaled β_2-agonist, formoterol. In a parallel group study involving 852 patients with moderate asthma, addition of formoterol (12 μg twice daily) improved asthma control in patients treated with either 200 μg or 800 μg daily BUD (266). Furthermore, addition of formoterol also reduced the frequency of severe and mild exacerbations of asthma over a 1-yr period. In agreement with this, 101 patients with mild and moderate asthma, taking at least 400 μg inhaled corticosteroid per day, could maintain good asthma control on a 17% lower dose of inhaled corticosteroid when treated concomitantly with salmeterol (50 μg twice daily) (267).

In 62 patients with moderate asthma not adequately controlled on 800 μg BUD daily, addition of a low dose of theophylline (mean plasma concentrations of approximately 8 mg/L) gave better control of asthma and improvement in lung function than doubling the dose of inhaled corticosteroids (268).

Results from one study have suggested that adding nedocromil sodium to high-dose inhaled corticosteroids may improve asthma control by improving symptoms and morning peak flow (269). Acute administration of cromolyn sodium has also been found to reduce the fall in lung function after challenge with 4.5% saline in patients treated for 3 mo with BUD (270), but the clinical relevance of this finding for continuous treatment remains to be shown.

Anti-leukotrienes, such as the leukotriene antagonists zafirlukast and montelukast, and the 5′-lipoxygenase inhibitor zileuton may also be beneficial when added to inhaled corticosteroids and may give better control than increasing the dose of inhaled corticosteroids, although this has not yet been demonstrated in clinical studies. This is reinforced by the fact that anti-leukotrienes do not appear to inhibit the increased production of leukotrienes in patients with asthma (76, 77).

The data from these studies are in agreement with the findings of dose–response studies: dose-dependent effects of inhaled corticosteroids on airway function are difficult to detect. Addition of a drug that acts in a different manner may be a better option than increasing the dose of inhaled corticosteroids. However, it is likely that there are subgroups of patients with asthma who respond better to an increased dose of inhaled corticosteroids, whereas others do better with the addition of a bronchodilator or alternative anti-inflammatory treatment. Inhaled corticosteroids are markedly more effective than any other anti-asthma drug in improving most asthma outcomes, but these agents may work through different mechanisms. The various published studies differ with regard to study design and patient population but, taken together, the results suggest that in some patients optimal control of asthma may be more effectively achieved by adding another drug rather than by increasing the dose of inhaled corticosteroid. More trials are needed to determine which drug(s) to add, to which patients, and when extra therapy should be added. These trials should measure several outcome measures during both short- and long-term therapy.

Benefits of Early Intervention with Inhaled Corticosteroids

Although inhaled corticosteroids were initially introduced to reduce the need for systemic corticosteroids, and thereby side effects, the use of these products in the treatment of asthma has expanded significantly. Now inhaled corticosteroids are considered first-line therapy in patients with persistent or chronic asthma. Thus, many guidelines for the treatment of asthma recommend the introduction of anti-inflammatory therapy for patients requiring regular use of an inhaled β_2-agonist.

Early intervention with anti-inflammatory medication, especially with inhaled corticosteroids, is a new concept in asthma therapy, being neither studied nor discussed widely until the 1990s. Bronchial biopsy specimens (271, 272), sputum, or fluid obtained by BAL have shown that significant inflammation is present in early asthma, even in patients who have had symptoms for only a short time and in those with mild disease. The relationship of inflammation to the disturbances of lung function, specifically AHR, is not straightforward. AHR without signs of inflammation has been reported (273). Nevertheless, the recognition that asthma, even in its mildest forms, is fundamentally an inflammatory disorder has led to the use of inhaled corticosteroids at increasingly earlier stages in disease management (274).

Clinically, asthma may be a mild, episodic nuisance or a severe, persistent disease. If asthma manifests with a severe attack, anti-inflammatory treatment with systemic steroids is started immediately. If the diagnosis of lung function disturbance is not obvious, the subsequent treatment may vary from repeated courses of antibiotics to prolonged use of β_2-agonists. It is common for patients to have symptoms compatible with asthma for months or even years before the correct diagnosis is made (275). During that time, the disease may have already progressed in some patients into the persistent stage, and some lung function may be permanently lost. This seems to occur over time in poorly controlled asthma (276, 277). The question arises: can early intervention with inhaled corticosteroids stop the disease and prevent deterioration of lung function? A number of studies have provided results relevant to the question.

Adults. Juniper and coworkers (278) studied adult steroid-naive patients with persistent asthma (duration of disease not specified) described as having "symptoms that were non-troublesome when treated with β_2-agonists alone." These patients showed an almost 4-fold mean improvement in AHR when a daily dose of 400 μg BUD was introduced for 1 yr. Additionally, a dramatic improvement in symptoms was seen. These results revealed severe undertreatment of patients who would normally be judged as having clinically mild, well-controlled asthma. The beneficial results of inhaled BUD were maintained for 3 mo after therapy was stopped (279).

These findings were corroborated by O'Byrne and coworkers (280), who compared the efficacy of as-needed inhaled bronchodilators plus a daily dose of 400 μg BUD Turbuhaler with inhaled bronchodilators alone, as first-line treatment of asthma in primary care practice. Despite the fact that the patients were judged by their physicians as having mild asthma

and thereby not requiring inhaled corticosteroids, marked differences in clinical effect in favor of BUD were found between the two groups. Similar to the results obtained by Juniper and colleagues, this study also revealed marked undertreatment of patients diagnosed with mild asthma. These results strongly support early intervention with inhaled corticosteroids for patients with regular symptoms of asthma.

A directly relevant study of early intervention compared two treatment strategies: treatment with inhaled corticosteroids as first-line therapy and treatment with β_2-agonist alone (209). Patients with asthmatic symptoms for less than a year and with no previous history of anti-inflammatory therapy were randomized to daily treatment with either 1,200 μg BUD or 750 μg terbutaline as the first and only regular medication. Two years' treatment with inhaled BUD resulted in almost complete clinical recovery and normalization of lung function. Furthermore, BUD treatment was superior to β_2-agonist treatment. Bronchial biopsies taken from a subgroup of patients showed a significantly greater reduction in the numbers of inflammatory cells in the BUD-treated patients than in the terbutaline-treated patients (104). The study was continued for a third year to investigate the effects of dose reduction or discontinuation of steroid treatment. A delayed introduction of inhaled corticosteroids was also studied. Peak expiratory flow was well maintained throughout the third year in patients in whom the daily BUD dose was reduced from 1,200 μg (via pMDI with large volume plastic spacer) to 400 μg (via Turbuhaler). Most of the patients who switched from BUD to placebo showed a gradual and slight decline in lung function that became significant toward the end of the third year, but five patients did not deteriorate at all (281). The patients who received terbutaline for 2 yr prior to initiation of treatment with BUD did not reach the same level of lung function or improvement in AHR within the third year as those who were treated with BUD as first-line therapy (Figure 10). This suggests that some functional reversibility was lost by delaying the start of steroid treatment. This is consistent with the known failure of β_2-agonist drugs to positively affect the underlying airway inflammation of asthma.

A group of adult patients with persistent asthma or COPD, of whom approximately half had already been exposed to inhaled corticosteroids, and who were on maintenance β_2-agonist therapy, were randomized to 2.5 yrs' additional intervention with either inhaled anticholinergic, inhaled corticosteroid (BDP), or placebo (250). The addition of inhaled corticosteroids to maintenance treatment with β_2-agonist, but not the inhaled anticholinergic agent, improved symptoms and AHR. At the end of the treatment period, those patients treated with bronchodilator and anticholinergic therapy were then given 800 μg BDP for 6 mo (282). Airway hyperreactivity was reduced to a lesser extent at the end of this 6-mo period when compared with those patients who had started inhaled corticosteroid treatment at the beginning of the original study. The authors suggested that the use of inhaled corticosteroids should not be postponed in patients with asthma with documented airway obstruction. This investigation cannot be considered a true early intervention study, since the patients had disease of at least moderate severity and a long history of symptoms (duration unspecified).

The protective effect of inhaled corticosteroids on the possible decline in lung function associated with nonspecific chronic obstructive lung disease has also been addressed in another study in which 56 patients were enrolled, of whom approximately half had asthma and half had COPD (283). During the first 2 yr of study, the patients were treated with bronchodilator therapy alone. While the patients demonstrated

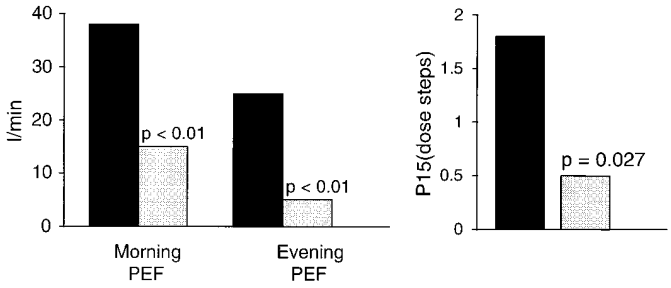

Figure 10. Increase in morning and evening peak expiratory flow rates (PEF) and reduction in bronchial hyperresponsiveness (concentration of methacholine inducing a 15% fall in FEV_1) in patients with asthma symptoms for less than 1 yr (281). One group started treatment with inhaled budesonide early after asthma diagnosis (*black bars*). The other group had this treatment delayed by 2 yr (*gray bars*). The improvements in those who started inhaled budesonide early were significantly better than the improvements seen in the group in which this treatment was delayed for 2 yr.

and maintained a bronchodilator response to inhaled β_2-agonist, lung function (FEV_1) showed a decline greater than that normally seen over time. At the end of the first 2 yr, 800 μg/d BDP was initiated. Significant improvements were observed in pre-bronchodilator lung function, and equivalent improvement in FEV_1 values measured post-bronchodilator. Additionally, the annual decline in lung function noted during the initial 2 yr (when treated with bronchodilator alone) was reduced during subsequent treatment with inhaled corticosteroids. This study has some limitations that make it difficult to apply the results to asthmatics in general. First, it included both asthma and COPD patients. Secondly, the improvements in lung function were in general small, and finally, the decline in lung function noted during the bronchodilator run-in period were greater than that normally found in asthma, suggesting that this particular group of patients with asthma was unique.

Selroos and coworkers (284) evaluated the possible correlation between treatment response and symptom duration prior to starting inhaled corticosteroids for the first time. A group of steroid-naive adult patients with asthma (mean age 50 ± 15 yr) were started on an average daily dose of 800 μg BUD Turbuhaler. At the end of the 2-yr treatment phase, the investigators found that those patients who had experienced symptoms of asthma for less than 2-yr prior to initiation of inhaled corticosteroid had higher mean FEV_1 and PEF values than those who had experienced symptoms for a longer period of time prior to initiation of inhaled corticosteroid therapy. Furthermore, while continuous use of inhaled corticosteroids controlled symptoms and prevented deterioration in lung function, maximal improvement in lung function was seen after the first year of therapy in most of these patients. Finally, the investigators found a significant negative correlation between the improvement in lung function that followed inhaled corticosteroid therapy and duration of asthma. Although there are limitations to this study, the results suggest that early initiation of anti-inflammatory therapy may lead to an improved disease outcome, manifested in this study by greater improvements in lung function. The results of this and other studies provide some evidence that early treatment of asthma with inhaled corticosteroids yields good clinical results and may even prevent patients from developing chronic airways obstruction.

Children. Studies of children also indicate that many have more substantial symptoms than appreciated by their doctors, even among those patients judged to have the mildest of asthma. Hence, undertreatment is common. When children who were

considered mild asthmatics were given a low dose of inhaled corticosteroid (100 μg/d BUD or FP), marked improvements were seen in symptom control, morning and evening peak expiratory flow rates, and lung function (216, 258).

A long-term study provided interesting information about the beneficial clinical effects and importance of early intervention with inhaled corticosteroids in children (228). Budesonide treatment was compared with combination treatment of other anti-asthma drugs (β_2-agonist, theophylline, and cromolyn sodium) in 278 children over a period of 3 to 6 yr. Substantial improvements were seen in lung function, peak flow variability, symptoms, and rate of hospitalization in the BUD-treated group. Furthermore, this group exhibited significantly increased lung function growth rates with age compared with the children not receiving inhaled corticosteroids. The effect on lung function was significantly greater when BUD was started within 2 yr of asthma diagnosis. Children who started treatment early showed a more rapid response and obtained significantly better lung function than the children in whom BUD was not started until some years after the onset of asthma symptoms (228). Moreover, the accumulated dose of BUD taken during the 4.5 yr of continuous treatment was significantly lower in the children who started treatment early than in the group of children in whom BUD treatment was initiated after more than 5 yr of continuous symptoms. The annual decline in FEV_1 in the control group was 1.3% lower than the predicted value. This, taken together with the higher lung function results and lower cumulative doses of BUD required among the children who started inhaled corticosteroid early, provides evidence that early treatment with inhaled corticosteroids may prevent airway remodeling and the development of irreversible, persistent structural changes in the airways of children. It also suggests that early intervention with inhaled corticosteroids may reduce the risk of undertreatment.

In agreement with these findings, Verbene and colleagues (257) found that 1-yr's treatment with 400 μg/d BDP yielded significantly better effect on lung function, rate of exacerbations, morning and evening PEF, and symptom control than 50 μg salmeterol given twice daily. Furthermore, both pre- and post-bronchodilator lung function grew significantly better during treatment with BDP. Indeed, there was a trend during the treatment year toward a decrease in lung function and worsening of AHR ($p = 0.05$) in the children in the salmeterol group.

In summary, several studies have found that patients assessed with mild asthma are often undertreated, and that early use of inhaled corticosteroid produces a better clinical result than delayed introduction.

Treatment Duration

Despite long periods of treatment with inhaled corticosteroids, the inflammatory changes of the airways are not totally reversed, even in patients with relatively mild asthma (272, 285). The question arises, then, how long should treatment with inhaled corticosteroids be continued once clinical remission is achieved? At present, only a limited number of adult and pediatric studies have addressed this question.

Adults. Studies looking at the withdrawal of inhaled corticosteroid therapy after short-term treatment, i.e., for periods of 4 wk or less, suggest that control of AHR deteriorates within weeks of inhaled corticosteroid reduction or withdrawal (286, 287). However, patients in these studies had experienced long-standing, persistent asthma before treatment initiation.

Juniper and colleagues showed that asthma control obtained by steroid-naive patients during 1 yr's continuous treatment with inhaled corticosteroid (278) was maintained for an average of 3 mo after steroid therapy was reduced (279). Duration of symptoms prior to treatment was not specified. Similarly, the majority of patients in the study by Haahtela and associates (281), who were switched to placebo after 2 yr of BUD therapy, showed a gradual and slight decline in lung function. This decline became significant toward the end of the third year, although five patients did not deteriorate at all (281).

van Schayck and coworkers (288) treated a group of patients with a long history of persistent asthma with bronchodilators alone for 2 yr, followed by treatment with BDP for two additional years. When treatment was withdrawn, some patients with poor lung function showed an accelerated rate of decline in FEV_1 while the rate of decline observed in those patients with good lung function was normal. The investigators concluded that patients in the latter group could appropriately stop inhaled corticosteroid treatment after 2 yr.

Osterman and coworkers (289) studied adults with asthma whose diagnosis had been established for less than 1 yr. The patients inhaled 400 μg/d BUD Turbuhaler for 1 yr, after which marked improvement in lung function and AHR was seen when compared with placebo treatment. The patients were then followed for another 6 mo without steroid treatment. During this time, the BUD-treated patients maintained about 50% of their previously achieved improvement in AHR. Although the patients in this study were newly diagnosed with asthma, most had experienced symptoms for years.

Children. A Dutch study of children with chronic obstruction and rather severe, persistent asthma aimed to compare long-term (28–36 mo) BUD treatment with β_2-agonist treatment alone (260). The results were conclusive: the steroid-treated group did better in every respect, and full remission was achieved in 60% of the children. After treatment, therapy was tapered off in some of the children over a period of 6 mo and a gradual worsening of the disease was seen. All of the patients regularly used albuterol while tapering the dose of BUD (290).

For the majority of children it appears that treatment with inhaled corticosteroids suppresses the underlying mechanisms of asthma and causes remission of the condition, but does not cure the disease (225, 230). However, as is the case in adults, steroid cessation in children has only been evaluated after less than 2 yr continuous treatment, and never in a group of children in whom the treatment had been initiated shortly after the start of the disease.

Summary. It is now well documented, in both adults and children, that long-term treatment with inhaled corticosteroids suppresses the disease by affecting the underlying airway inflammation. As a result, symptoms disappear and lung function improves. The outcome parameter responding most rapidly to the initiation of inhaled corticosteroid therapy is symptoms; PEF values improve more gradually, while improvements in AHR may continue over many months or even years. In addition to suppressing the disease, it appears that inhaled corticosteroid therapy may also modify the disease outcome if prescribed early enough and long enough (104, 209, 281). When inhaled corticosteroid therapy is stopped, most patients will eventually experience symptoms of asthma again. The speed of this relapse is probably related to patient age, length of symptom history, severity of symptoms, signs evident at the onset of therapy, and the total duration of therapy. Infiltration of inflammatory cells into the lamina propria of the airways has been shown to persist in patients with mild-to-moderate asthma, despite regular treatment with inhaled corticosteroids (291), which indicates the need for regular maintenance anti-

inflammatory treatment. Asthmatic inflammation is a response usually provoked by allergic reactions, infections, and other environmental factors; continued or repeated anti-inflammatory therapy is therefore usually necessary for optimal control of the condition. The data suggest, however, that in the majority of patients the dose can be stepped-down over time without loss of asthma control.

Transient or variable eosinophilic inflammation of the bronchial mucosa may be quite common, especially in atopic subjects, but it does not always cause deterioration of lung function. It may be argued that the diagnosis is always late if asthma accompanied by increased AHR is detected. Those subjects with disturbed lung function ("real asthmatics") represent only a portion of the total population with recurrent eosinophilic airway inflammation (274, 292). Broadening the definition of asthma to include even those with asthma-like symptoms (i.e., airway inflammation) would certainly improve early detection of symptoms and encourage correct interventions. Whether this approach would have any impact on asthma severity remains to be seen.

The concept of early intervention has drawn attention to the period of the disease when asthmatic symptoms and events debut. There may be a window of opportunity in relationship to the diagnosis and treatment of asthma after which lung function changes caused by the disease occur; the introduction of rigorous, high-dose inhaled corticosteroids after this point may still not lead to a "catch-up" in lung function. This contention is supported by studies in which airway histology has been studied and collagen deposition observed (293, 294). The term "early intervention" has not yet been universally defined. Most of the patients included in the studies described above had experienced symptoms for a long time prior to intervention, and their asthma was persistent, i.e., already well established. The characterization of study populations is essential for correct interpretation of results. Are the patients experiencing new asthma, with symptoms present for less than a year, or is it newly diagnosed asthma with a variable length of symptoms, or is it simply well established asthma already treated with several types of medication? Are the symptoms occasional or persistent? In many chronic immunologic/inflammatory diseases, the concepts of induction, maintenance, and relapse treatments are used. Perhaps these concepts should also be applied to asthma treatment. Further studies are needed in this area.

Inhaled Corticosteroids in COPD

As mentioned earlier, inhaled corticosteroids are very effective in the treatment of asthma. In COPD, however, the effect of corticosteroids, both inhaled and parenteral, is much less obvious. To establish the effectiveness of any intervention, it is essential that critical endpoint parameters are clearly expressed and employed. The effects of steroids have traditionally been expressed quite differently in COPD than asthma. In asthma, response to inhaled corticosteroids is often expressed as absolute or percent improvement in FEV_1, or absolute change in PEF. Additionally, effectiveness has been documented through changes in symptoms and quality-of-life measurements. In contrast, the effects of corticosteroids in COPD have been judged almost exclusively on the basis of change in lung function, expressed in an all-or-nothing fashion, i.e., whether a 15–20% improvement in FEV_1 occurred. Even in moderate-to-severe asthma, with a mean FEV_1 of 68% of predicted, it is unusual to see a greater than 20% response to bronchodilators (295).

COPD is characterized by a different type of inflammation in induced sputum from that seen in asthma, with a preponderance of neutrophils rather than eosinophils (296, 297). Neither oral nor inhaled corticosteroids influence this inflammatory response, in contrast to their clear anti-inflammatory effect in patients with asthma (142).

There are two other criteria employed to judge the effect of interventions in COPD that are different from parameters used in asthma. The first is survival. Thus far, continuous oxygen delivery to hypoxemic patients and smoking cessation have been the only interventions that have been proven to increase life expectancy in COPD. The second parameter is decline in FEV_1. Although an increased decline in FEV_1 occurs in some patients with asthma (277), accelerated decline is a predominant feature of COPD. It is clear that testing the effect of any intervention in COPD on either survival or decline in FEV_1 requires very large patient numbers and a long-term follow-up period.

Systemic corticosteroids have been used in the treatment of airway obstruction since 1950 (298). Today, their role in COPD is still controversial. In COPD exacerbations, intravenous steroids are usually added to bronchodilator therapy (299). However, the number of clinical trials supporting this intervention is small.

Most trials have evaluated the use of oral steroids in stable COPD. Callahan and colleagues (300) performed a meta-analysis of studies with oral steroids in stable COPD. Response rates were defined as an improvement in FEV_1 of at least 20%, and effect size was defined as the proportion of responders to steroids minus the proportion of placebo responders. Effect sizes ranged from 0% to 56%, with a calculated mean effect size of 10% (95% CI, 4–19%). The mean duration of this study was only 2 wk; retrospective studies of oral steroids suggest that a follow-up of at least 6 mo is needed to demonstrate effects on decline in lung function in COPD (301, 302).

Whether inhaled corticosteroids are beneficial in COPD is even more controversial than the data for oral steroids in COPD (299, 303–307). Since 1972, more than 100 studies have attempted to evaluate inhaled corticosteroids in COPD. There have, however, been only 12 randomized, placebo-controlled studies (Table 2). Unfortunately, most of these studies have been short term, varying from 10 d to 12 wk in duration (308–317). None of the studies measuring AHR was able to document a change in PC_{20} histamine (311, 313, 315, 317). All but one of these short-term studies in COPD failed to show significant improvement in FEV_1 with the use of inhaled corticosteroids. The sole exception was the study by Thompson and associates (308). Although patients with a history of atopy were excluded, no skin tests or IgE measurements were performed. In addition, the patient group was larger than in most other studies. The authors performed bronchoscopy before and 6 wk after treatment in order to determine the effect of therapy on airway inflammation. The airways were also inspected for visual evidence of inflammation, and a bronchitis index was assigned. This index improved significantly among the patients receiving inhaled corticosteroids. Analyses of BAL fluids revealed the improvement of epithelial permeability and cellularity in the inhaled corticosteroid treatment group.

Only three long-term, randomized, placebo-controlled studies in COPD have evaluated the effectiveness of inhaled corticosteroids. A Dutch multicenter trial studied a mixed group of subjects with airway obstruction (250). In a subgroup with COPD (defined as chronic cough and/or sputum production, no asthma attacks, all current or ex-smokers, $FEV_1 <$ 95% CI, and bronchodilator response $\geq$ 15%), a small, nonsignificant improvement of 4.4% in FEV_1 was seen, and a small, statistically nonsignificant improvement in PC_{20} histamine was seen (250).

TABLE 2

RANDOMIZED, PLACEBO-CONTROLLED STUDIES OF INHALED CORTICOSTEROIDS IN COPD

Reference No.	312	311	320	315	316	308	313	252	212	250[§]	319	318
Duration, wk	2	12	2	8	6	6	12	3	6	130	104	104
Dose, μg, and inhaled corticosteroid	1,500 BDP	800 BDP	1,500 BDP	1,600 BUD	1,600 BUD	1,000 BDP	1,200 BUD	1,600 BUD	800 BUD	800 BDP	1,500 BDP	1,600 BDP
n	83	18	127	24	35	100	14	10	30	22	194	58
Mean age, yr	61	50	63	57	52	49	60	57	?	46	63	56
Current smokers, %	51	18	38	100	46	100	100	60	100	73	?	45
Atopic, %	?	0	43	0	?	?	21	0	?	18	?	0
FEV_1, % predicted	44	97	44	53	96	72	80	59	(1.4 L)	70	(1.3 L)	63
ΔFEV_1, % initial	13	?	11	7	?	8	11	10	10	5	3	10
FEV_1, % improvement	?	−9.0	?	+3.8	+2.7	+7.3*	−2.0	−0.3	?	+4.4	+0.8*	30 ml/yr[‖]
FEV_1, % responders[†]	?[‡]	?	15	0	?	?	?	0	23	17	?	?
PC_{20}, mg/ml	?	0.6	0.8	1	?	?	2.8	0.5	?	1	?	1.3

Definition of abbreviations: BDP = beclomethasone dipropionate; BUD = budesonide.

* Significant improvement in FEV_1 with inhaled coricosteroids compared to placebo ($p < 0.05$).

† Percentage of subjects with a change in FEV_1 of ⩾ 20% in inhaled corticosteroids arm minus the percentage responders in placebo arm.

‡ Response percentage in beclomethasone arm 30%; unclear response percentage in placebo group.

§ Subgroup: chronic cough and/or sputum production; current or ex-smokers; $FEV_1 < 95\%$ CI; response to bronchodilator < 15%; no asthma attacks.

‖ Median slope in placebo arm −60 ml/yr compared to −30 ml/yr in budesonide arm.

Renkema and colleagues (318) evaluated 58 patients with COPD (and no allergies). The subjects were randomized to 2 yr of treatment with either placebo, 1,600 μg/d BUD, or 1,600 μg/d BUD and 5 mg/d prednisolone (318). Significantly more patients in the placebo group (300) dropped out of the study due to pulmonary problems than did patients in the BUD prednisolone group (277) or in the BUD group ($p < 0.04$). Change in FEV_1 was assessed by calculating least-squares regression lines over the 2-yr treatment period. The average declines in FEV_1 varied greatly and were skewed so that median slopes per group were: (−60 ml/yr in the placebo group, −40 ml/yr in the BUD + prednisolone group, and −30 ml/yr in the BUD group. These differences, though perhaps clinically relevant, were not statistically significant. No improvement in AHR was detected.

Finally, a French multicenter study, which involved 194 patients, evaluated the effect of 1,500 μg/d BDP (319). The treated individuals recorded a mean increase in FEV_1 of 1.44% compared to 0.62% in the placebo group. This small difference of 0.8%, surprisingly, was significant ($p = 0.05$) and probably reflects the large number of patients evaluated.

A number of studies have compared inhaled and oral steroids in the treatment of COPD (310, 312, 317, 320–322). Most of these are short-term studies that found oral prednisolone to have greater effect than inhaled corticosteroids, although the differences were not significant.

Available data do not seem to support the use of inhaled corticosteroids in patients with COPD. Nevertheless, many clinicians administer inhaled corticosteroids to their patients with COPD, probably because of an impression that steroids provide benefit in some patients. It would be useful if there were prognostic factors that could indicate a more favorable response to steroids among COPD patients. In asthma and asthmatic bronchitis, the improvement in FEV_1 associated with inhaled corticosteroid treatment may be estimated by smoking status, AHR, allergy, and bronchodilator response (323). Similarly, the improvement in AHR with inhaled corticosteroid treatment may be predicted by total serum IgE (better predictive value than skin test, specific IgE to house dust mite, or blood eosinophils) (324). Reliable data in COPD, however, are scarce. Bronchodilator response has been suggested by some authors to predict improvement with inhaled corticosteroids (309, 321, 325) as well as sputum or blood eosinophilia (321, 325, 326).

Many physicians administer a short course of oral steroids to predict benefits from inhaled corticosteroids. However, it is important to realize that random variations in levels of lung function also occur in patients with COPD (327), so that the prediction of any future benefit from long-term inhaled corticosteroid use by a change in FEV_1 occurring during a short course of oral steroids is quite imprecise (312, 314, 318, 321). It is therefore not surprising that there exists no consensus about the use of short-course trials of oral steroids in COPD, nor about the suggested dose or duration of therapy (299, 307). There is currently insufficient scientific evidence to support the use of inhaled corticosteroids in patients with COPD. This may also be due to the relatively small groups of patients studied over short periods of time in the majority of studies. Several large-scale, multicenter studies investigating the use of inhaled corticosteroids in COPD are currently under way (328, 329) and results are eagerly awaited.

Rhinitis and Asthma

Rhinitis and asthma frequently coexist (330), and rhinitis is recognized as a risk factor for subsequent asthma (331). Treatment of seasonal allergic rhinitis with nasal corticosteroids has been shown to improve asthma symptoms and reduce bronchial hyperresponsiveness (332).

Although antihistamines are effective at controlling itching/sneezing and nasal discharge, they have minimal bronchodilating properties and are not effective in bronchial asthma. Conversely, β_2-agonists are extremely potent bronchodilators but are not efficacious in the nose. Topical corticosteroids, however, are effective anti-inflammatory and prophylactic agents in both the upper and lower airways (333, 334). Recent data suggest leukotriene antagonists may be effective in both the upper and lower airways as well (335, 336).

Most information on the pathophysiology of rhinitis has been derived from studies of allergic rhinitis. Immunoglobin E-dependent mechanisms operate in both the upper and lower airways, although the effect of different mediators (histamine, leukotrienes) may differ between the upper and lower airways and may explain the differential effects of therapy.

Mast cell numbers are increased within both the nasal and bronchial epithelium in rhinitis and asthma (337, 338). Tissue eosinophilia is a cardinal feature of both rhinitis and asthma (339, 340). In contrast, the bronchial epithelium is disrupted and damaged in asthma, whereas in allergic rhinitis epithelial integrity remains normal despite inflammatory infiltration (339). Recruitment and activation of T lymphocytes occurs in rhinitis, as in asthma (341–343). Rhinitis is similarly associated with activation of Th2-type cells, with preferential production of IL-4 and IL-5 (344, 345).

Topical corticosteroids are effective in reducing mast cell epithelial migration (346), migration of Langerhans cells (108), tissue eosinophilia (347), and T-cell recruitment and activation in rhinitis (348). Corticosteroids appear to act by inhibiting cytokine synthesis, particularly IL-4 (349). In contrast, recent studies suggest that immunotherapy may act by promoting an additional Th1 response with production of IFN-γ (350). Interferon-γ suppresses IL-4-induced B cell IgE synthesis. These responses after immunotherapy may be driven by IL-12 produced by activated macrophages or B cells (351).

Allergen avoidance, where possible, should always be considered in patients with rhinitis. Patients with occasional symptoms may require only symptomatic use of oral antihistamines. If symptoms are confined to the occasional itch/sneeze or watery discharge, there may be a place for the recently introduced topical antihistamines (352). In patients with moderate and/or persistent symptoms, topical corticosteroids represent the mainstay of treatment. There is an increasing analogy between asthma and rhinitis treatment, i.e., drugs for *relief* (antihistamines) and drugs for *prevention* (topical corticosteroids) (353). Antihistamines may be effectively combined with topical corticosteroids, particularly for associated symptoms of conjunctivitis or palatal itch.

Nasal polyps occur in association with late-onset asthma with/without aspirin sensitivity. They may also complicate rhinosinusitis due to other causes (cystic fibrosis, Churg–Strauss syndrome, immunodeficiency syndromes, etc.). Treatment of the underlying condition, where possible, should occur first, followed by treatment with topical corticosteroids (48, 354). Initial treatment may need to be with oral corticosteroids, particularly when large nasal polyps exist and cause obstruction. Long-term treatment with topical corticosteroids has been shown to reduce symptoms of nasal polyposis and reduce polyp recurrence following surgery (48, 355–358).

Topical corticosteroids are effective in inhibiting both early and late nasal responses to allergen challenge (359). In general, they are more effective in the treatment of allergic rhinitis than either antihistamines (360, 361) or cromolyn sodium (362). Nasal use of corticosteroids may also improve seasonal asthma (362) and reduce seasonal increases in AHR (332). The effects of topical steroids are indeed local and not due to systemic absorption (363, 364). Several studies have shown that topical corticosteroids are virtually without systemic effects in patients (333, 334, 365). A single study suggested some reduction in short-term lower leg growth in children taking twice daily topical BUD (366), although this finding is not thought to be relevant to long-term growth. A subsequent study of once daily topical BUD showed no effect on lower leg growth (367). Nasal corticosteroids may be used long term without detrimental effects on the nasal mucosa (368, 369). Bleeding may occur in 5–10% of patients (370) and only occasionally ($< 5\%$) does bleeding result in the need for discontinuation of topical corticosteroid.

Rhinitis is commonly associated with asthma and frequently goes unrecognized and undertreated. The mainstay of treatment is topical corticosteroid and antihistamines (371). Moreover, treatment of rhinitis with topical corticosteroids may also improve asthma and reduce AHR.

Pregnancy

Data on the use of inhaled corticosteroids during pregnancy must be interpreted in the context of the effect of asthma on pregnancy in general, and particularly the effect of severe asthma. New data (372–377) suggest that women with severe asthma may have a greater risk of experiencing pre-eclampsia and delivering low birth weight, preterm, or growth-retarded infants than control subjects or patients with mild asthma. However, the mechanisms of this increased risk remain undefined and could include medications (especially oral steroids), poor asthma control, or common pathogenetic factors leading to hyperreactivity of smooth muscle (bronchial and uterine) and vasculature. It is important to note that, in contrast to prior reports of perinatal mortality associated with severe asthma (378–381), none of the most recent studies has reported an increase in perinatal mortality in the infants of asthmatic versus control mothers. In addition, although a higher incidence of congenital malformations was seen in theophylline-treated patients in one study (377), no statistically significant increases in congenital malformations were reported in any of the studies.

A surveillance study of Michigan Medicaid recipients was conducted in the United States between 1985 and 1992, and involved 229,101 completed pregnancies; 395 newborns were exposed to BDP during the first trimester (382). A total of 16 (4.1%) major birth defects were observed, which is the number expected in a normal population of this size. Thus, it was concluded that an association between BDP and congenital defects does not exist.

Dombrowski and colleagues (383) reported the results of a very small retrospective cohort study describing 15 pregnant women treated with inhaled TAA, 14 treated with inhaled BDP, and 25 treated with theophylline. There were no significant differences in mean birth weight among groups. A smaller proportion of patients treated with inhaled TAA (33%) and theophylline (28%) required hospital admission for asthma exacerbations compared with those treated with BDP (79%, $p < 0.05$). Birth weights did not differ among the three groups. These results need to be confirmed by clinical trials to further evaluate the safety and efficacy of inhaled BDP during pregnancy.

Schatz and coworkers (373) evaluated outcomes of pregnancy in relation to medication exposure in 824 asthmatic and 678 nonasthmatic pregnant women enrolled in the Kaiser-Permanente Prospective Study of Asthma during Pregnancy. Of these, 297 subjects were exposed to some form of corticosteroid therapy. No relationship was found between first trimester ($n = 204$), or any exposure to corticosteroids ($n = 297$), and increased risk of congenital malformations. Inhaled corticosteroids were used by 149 subjects (137 of whom used BDP) in this study. After accounting for other medication exposure, age, parity, smoking history, race, and acute asthmatic episodes, use of inhaled corticosteroids was independently associated with an increased risk of preterm birth (odds ratio 2.40; 95% CI 1.19–4.84, $p = 0.037$). Although the use of inhaled corticosteroid was also associated with increased incidences of pre-eclampsia and low-birth-weight infants in univariate analyses, independent associations with these outcomes were not demonstrated in multivariate analyses.

Thus, there is no evidence to suggest that inhaled corticosteroids increase the risk of congenital malformations. Although the use of inhaled corticosteroids was independently associated with increased preterm births in one study (373),

a medication effect cannot be differentiated from an effect of inadequately controlled asthma or an effect of common pathogenetic factors in patients with asthma requiring inhaled corticosteroid and those with preterm deliveries. As recommended by the Working Group on Asthma and Pregnancy of the National Asthma Education Program (295), benefit-risk considerations favor the use of inhaled corticosteroids for the management of moderate or severe asthma during pregnancy. One may choose to use BDP because there are more published data on the use of this specific inhaled corticosteroid during pregnancy; however, there is no reason to suspect that any of the newer inhaled corticosteroids would be less safe during pregnancy.

Health Economics

In assessing the economic impact of various diseases on society, it is essential to consider costs—both the direct (medications, health providers, etc.) as well as the indirect (i.e., school days missed, work missed, etc.) (384). Although the mortality of asthma is not high, it is a very common chronic disease. Table 3 illustrates that the total costs of asthma to society can be quite significant, as can the per-patient expenses. Furthermore, it is also apparent the per-patient costs vary considerably from country to country. For example, costs per patient per year in Australia were $326 (1990, U.S. dollars) in 1991 (385), whereas in Sweden the corresponding figure was $1,315 (based on data from 1975 prior to the introduction of inhaled corticosteroids). In assessing the effects of a new therapy on a disease, it is important to consider not only its effectiveness in modifying the physiological parameters of disease, but also its influence on health care costs. This puts an additional burden upon new products and on the outcome parameters used to evaluate these products. Of all the asthma-related health care costs, exacerbations, particularly those involving hospitalization, are a major target for achieving considerable savings. The clinical trials of new drugs under development for the treatment of asthma have also begun to focus on this outcome parameter.

In determining whether a new technology or management step is effective, there are various outcomes to consider. For example, if the cost of A is less than B and the outcome is better with A, the implication is obvious: A is an excellent new therapy. However, there are situations in which the correct decision is less obvious. Hence, the assessment of pharmacoeconomics of therapy for any disease, including asthma, can become complex. A number of studies can be re-analyzed to determine the cost effectiveness of an asthma intervention. For example, Adelroth and Thompson (386) evaluated the intervention of inhaled BUD on direct health care costs, particularly the need for oral corticosteroids. Based on these observations, it was estimated that there would be a 55% reduction in direct costs (Table 4). In contrast, Campbell and colleagues (387) conducted a 12-wk study to compare the effectiveness of BUD given in daily doses of 400 and 800 μg. Lung function and symptoms were measured. In this short-term study, it was not possible to determine an increase in cost-effectiveness by using the higher dose of inhaled corticosteroid. Analysis of previous data or well-designed future studies will help to shed light on this emerging dimension of therapy: cost-effectiveness. In a detailed analysis of costs involved in adding an inhaled corticosteroid to inhaled β_2-agonists in children, there was an expected increase in drug costs, but this was compensated for by savings in the use of medical services (251, 388). Furthermore, for similar costs patients had significant advantages in terms of symptom control and increased activity. Inhaled budesonide has also been compared with other nonsteroidal anti-asthma treatments in a long-term (up to 7 yr) study of 278 children (228, 261). In that study, inhaled budesonide treatment was associated with a greater than 50% reduction in annual direct health care costs per child and improved asthma control compared with children receiving other nonsteroidal anti-asthma treatments.

Quality of Life

Quality of life is another important consideration in the assessment of long-term therapy. With this outcome parameter one aims to measure the influence of therapy on a patient's functional status. Instruments have been designed to determine how patients assess an intervention or how they assess the outcome of their functional status (389, 390). There are a number of important issues to address in using quality-of-life measurements. First, are these measurements clinically significant? Do these measurements parallel what is considered a relevant clinical measurement? Second, these instruments need to be user friendly and not excessively time-consuming. Third, the instruments need to be disease-specific in addition to being able to capture general quality of life features. The use of nonspecific measures may give misleading results. Thus, in a prospective study of patients with asthma and COPD, introduction of BDP improved lung function and symptoms, but there was no increase in the Inventory of Specific Health or the Nottingham Health Profile, two widely used quality-of-life questionnaires (391). Finally, these instruments need to be adapted to cross-cultural situations so that implications can be

TABLE 3

COMPARISON OF DIRECT AND INDIRECT COSTS OF ASTHMA FROM SEVEN STUDIES ADJUSTED TO 1990 U.S. DOLLARS

Country, Year of Data, Reference No.	Monetary Conversion	Asthma Prevalence in 1990	Direct Medical Costs	Indirect Costs	Total Costs*	Costs per Patient per Year
Australia, 1991 (581)	1.28A$/1$	8.5%	$250.0 million	$207.0 million	$457.0 million	$326
New South Wales, Australia, 1989 (582)	1.28A$/1$	6.0%	$161.0 million	$48.0 million	$208.8 million	$769
Canada, 1990 (583)	1.16C$/1$	2.5%	$263.8 million	$169.7 million	$433.5 million	$826
Germany, 1992 (584)†	1.53DEM/1$	5.0%	$2.06 billion	$1.29 billion	$3.35 billion	$1,048
Sweden, 1975 (585)	6SKr/1$	3.0%	$90.8 million	$257.5 million	$348.3 million	$1,315
UK, 1988 (586)	.562£/1$	3.0%	$722.5 million	$1.07 billion	$1.79 billion	$1,043
USA, 1990 (587)	1$/1$	4.0%	$3.6 billion	$2.6 billion	$6.4 billion	$640

* Direct medical care costs were adjusted using the all-item price index, and indirect medical care costs were adjusted using the labor compensation index for each country code. The price and labor indices, monetary conversion factor, and population estimates were derived from volumes 1–4 of the Australia Country Report 1989–1991, Canada Country Report 1989–1991, Germany Country Report, 1985–1991, Sweden Country Report 1985–1991, and United Kingdom Country Report 1988–1991. All were published and authored in London by the Economist Intelligence Unit.

† German data are for 1992.

TABLE 4

SUMMARY OF PHARMACOTHERAPY ECONOMIC EVALUATION STUDIES

Study Method (Reference No.)	Sample Size	Treatments Studied	Length of Study	Costs Measured	Health Outcomes Measured	Economy Outcomes
Retrospective; pre/post quasi-experimental design (386)	36 adults	Budesonide	5 yr: 2 + 3 yr	Direct	Reduction in need for oral steroid after introduction of inhaled budesonide	Estimated 55% reduction in direct costs
Retrospective; econometric model (589)	*	All inhaled corticosteroids	11 yr	Direct	Reduction in hospital bed days and discharges for asthma	Estimated benefit:cost ratio of between 1.5:1 and 2.8:1
Randomized controlled trial (387)	556 adults	Two groups: budesonide 400 μg compared to budesonide 800 μg	12 wk	Direct	Lung function (FEV_1) and symptoms	Not cost-effective to increase dose from 400 μg to 800 μg in mild to moderate patients
Randomized controlled trial (247)	40 children	Two groups: budesonide compared to placebo	26 wk	Direct and indirect	Lung function (FEV_1), symptoms, symptom-free days	Dominant therapy, saved about $9.43 per symptom-free day gained
Randomized controlled trial (388)	116 children	Two groups: budesonide and albuterol, albuterol alone	3 yr†	Direct and indirect	Lung function (FEV_1), symptom-free days, school absences	Cost-effective; $83 per 10% improvement in FEV_1, $4.75 per symptom-free day gained
Randomized controlled trial (251)	274 adults	Three groups: beclomethasone and terbutaline, ipratropium and terbutaline, terbutaline alone	2, 5 yr	Direct and indirect	Lung function (FEV_1, PC_{20}), symptom-free days	Cost-effective; $201 per 10% improvement in FEV_1, $5 per symptom-free day gained
Uncontrolled pre/post trial (222)	86 children	Two groups: beclomethasone, budesonide	4 yr	Direct	Treatment satisfaction, acute severe attacks, breakthrough wheezing, and loss of school days	Estimated an 82% reduction in mean monthly treatment costs
Controlled, prospective trial (228, 261)	278 children	Two groups: budesonide,all other nonsteroidal anti-asthma pharmacotherapy	4–7 yr	Direct	Lung function, hospital admissions, asthma exacerbations, unscheduled clinic visits, medication, hospital bed days	Total health care costs reduced from $2,021 USD/yr to $851 USD/yr in the budesonide-treated group

* Unit of analysis is counties and not persons. The study represents a total of 71% of the Swedish population.
† The study had a planned 3-yr follow-up but only 39 patients reached a follow-up period of 22 mo.

applied to all subjects. At present, studies of quality of life with inhaled corticosteroids are limited in number, but this area is increasing in importance as a tool for assessing therapeutic interventions, particularly in patients with mild disease when changes in lung function may be minimal. In a trial of oral steroid reduction with introduction of inhaled FP, there was improvement in lung function as well as improvement in several quality-of-life variables (173).

PHARMACOKINETICS

The airway selectivity of inhaled corticosteroids is due to a combination of a high topical corticosteroid activity and a low systemic bioavailability. The most relevant comparison among the various inhaled corticosteroids and between the different formulations of a particular inhaled corticosteroid seems to be a measure of the *therapeutic index*, which is the ratio between the clinical (desired) effects and the systemic (undesired) effects of a drug/inhaler combination (Figure 11). This is often, but not always, reflected in the ratio between the amount of topically and systemically available steroid. The higher the therapeutic index, the better the risk/benefit ratio.

The *topical* effects depend on the glucocorticoid activity of the molecule and probably also on the local pharmacokinetics in the target tissue and cells. *Systemic* effects are related to the glucocorticoid activity of the molecule, the total amount of steroid that gets absorbed (becoming *systemically* bioavailable), and the rate of clearance of the steroid from the body. *Systemic bioavailability* is the sum of the amount of the drug that becomes systemically available after absorption from the lung, and after gastrointestinal absorption and first-pass metabolism of the swallowed fraction of the dose (Figure 11). For most of the more recently developed inhaled corticosteroids, the oral bioavailability is low (Table 5), and therefore most of the systemically available steroid comes from the inhaled fraction that enters the systemic circulation after absorption from the lung (177, 333, 392–403).

Recently, accurate methods of measuring blood and tissue concentrations of drugs have provided new information about

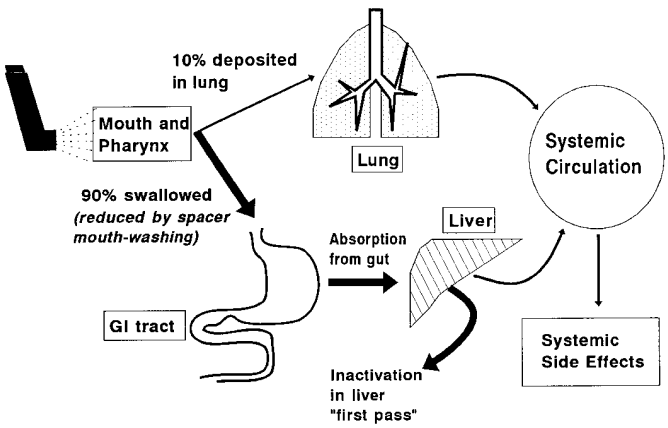

Figure 11. The fate of inhaled steroids. The amount of an inhaled corticosteroid reaching the systemic circulation is the sum of the pulmonary and orally bioavailable fractions. The fraction deposited in the mouth will be swallowed, and the systemic availability will be determined by absorption from the gastrointestinal tract and degree of first-pass metabolism. The fraction deposited in the intrapulmonary airways is likely to be more or less completely absorbed in active form to the systemic circulation, as there is no evidence for any metabolic inactivation of currently available inhaled corticosteroid. The systemic concentration will be reduced by continuous recirculation and inactivation of the drug by the liver.

TABLE 5

RELATIVE RECEPTOR AFFINITY AND BASIC PHARMACOKINETIC PARAMETERS OF INHALED STEROIDS

Inhaled Steroid	Relative Receptor Affinity* (407, 590)	$T_{1/2}$ (*h*)	Vd (*L/kg*)	Clearance (*L/min*)	Oral Availability (%)
BDP	0.5†	ND	ND	ND	ND
Budesonide (406)	9.4	2–3	2.7	0.9–1.3	6–13
Flunisolide (392, 591)	1.9	1.6	1.8	1.0	21
Fluticasone proprionate (398, 592)	22.0	8–14	12.1	0.9–1.3	< 2
Tipredane	27.0	ND	ND	ND	ND
Triamcinolone acetonide (401)	2.0	1.5	1.3	0.7	23

Definition of abbreviations: $T_{1/2}$ = plasma half-life; Vd = volume of distribution; and ND = not determined.

* Relative to dexamethasone given a value of 1.

† Beclomethasone monopropionate, the active metabolite, has a relative receptor affinity of 13.0.

the systemic availability of the various inhaled corticosteroids, their routes and rates of absorption, and their rates of elimination. The clinical importance of some of this information needs further study, whereas the relevance of some has already been established in clinical studies. Several factors are important in determining the clinical and systemic effects and therapeutic index of inhaled corticosteroids.

Deposition

The amount of topically available steroid is determined by the nominal dose, the delivery characteristics of the inhaler, and the patient's inhalation technique. A higher deposition in the intrapulmonary airways will normally result in a better therapeutic index for those inhaled corticosteroids that are systemically bioavailable by the oral route. For inhaled corticosteroids with a zero bioavailability after oral dosing, the characteristics of the inhaler device and the patient's inhalation technique determine only the efficacy of the treatment; the therapeutic index is not affected (404) (Table 6). Fluticasone propionate and mometasone furoate have almost negligible oral availability (398, 405). Other inhaled corticosteroids have oral availability ranging from 6–23% (406).

Receptor Affinity and Local Retention

Corticosteroids differ in their receptor affinity. Among the currently available inhaled corticosteroids, FP appears to have the highest affinity, followed by the active metabolite of BDP, beclomethasone monopropionate (BMP), and BUD (Table 5). Although receptor affinity and therapeutic effect appear to show some correlation, there is no clear-cut relationship, even after correcting for the amounts deposited in the lung. Thus, tipredane has a very high receptor affinity (about 50% higher than FP) but virtually no therapeutic effect (407). This may be due to the many steps preceding the actual steroid–receptor interaction, which may affect the therapeutic outcome. The steroid must be retained in the target tissue in sufficient concentrations for a sufficient time span if it is to exert any therapeutic effect. It should also readily diffuse over cell membranes with little or no metabolic inactivation in order to reach the cytosolic glucocorticoid receptor.

Tissue retention of inhaled corticosteroids has not been studied extensively but the *in vitro* binding of different steroids appears to correlate closely with lipophilicity. It is highest for FP and BDP and lowest for hydrocortisone (408). *In vivo*, after topical superperfusion of rat trachea, BUD and FP were retained to a similar extent, and both were retained

TABLE 6

SYSTEMIC AVAILABILITY AND LUNG DEPOSITION OF SOME GCS IN DIFFERENT FORMULATIONS*

Substance	Formulation	Systemic Availability	Lung Deposition
Budesonide	pMDI	26%(177)	15%(177)
	pMDI + Nebuhaler (primed)	—	38%(594)
	pMDI + Nebuhaler (unprimed)	—	27%(594)
	pMDI + Nebuchamber (primed)	—	34%(594)
	pMDI + Nebuchamber (unprimed)	—	33%(594)
	Turbuhaler	38%(177)	32%(177)
	Turbuhaler (58 liter/min)	—	28%(595)
	Turbuhaler (36 liter/min)	—	15%(595)
	Nebulized suspension Pari Inhalierboy	—	—
	Nebulized suspension Pari LC Jet Plus	17%(593)†	14%(593)†
	Nebulized suspension Maxin MA-2	15%(593)†	14%(593)†
		17%(593)†	16%(593)†
Fluticasone propionate	pMDI (10% lecithin)	26%(596)	—
	pMDI (1% lecithin)	31%(596)	—
	Diskhaler	12%(596)	—
	Diskhaler	16%(398)	15%(398)
Beclomethasone dipropionate	pMDI (CFC)	—	4%(597)
	pMDI (HFA)	—	56%(597)
	pMDI with Autohaler™ (HFA)	—	59%(597)
Triamcinolone acetonide	pMDI	22%(401)	—
Flunisolide	pMDI (with mouthwash)	32%(591)‡	—
	pMDI (no mouthwash)	39%(591)‡	—
	Nebulized solution (Respimat®)		40%(598)
	pMDI		15%(598)
	pMDI with Inhacort® spacer		28%(598)

* Values are given with reference to the metered dose.

† Calculated with reference to the nominal dose.

‡ Calculated with reference to the delivered dose.

longer than BDP (409). During washing, the subsequent release was slower for BUD than for any of the other steroids tested, including FP. Recently, this retention was reported to be associated with an intracellular formation of long-chain fatty acid conjugates of BUD (410) (Figure 12). Intact BUD was regained in a rate-limited fashion, and this appeared to prolong the pharmacologic effect of the drug. Neither FP nor hydrocortisone formed corresponding conjugates, and their duration of action was lower in the tested systems (411, 412). It remains to be studied whether this retention mechanism contributes to the duration of therapeutic action and/or airway selectivity of BUD.

Lipophilicity differs markedly between the various inhaled corticosteroids. Theoretically, lipophilicity should be high to allow a slow dissolution within the lung and free diffusion over cell membranes. However, a high water solubility (low lipophilicity) increases the rate of dissolution and intracellular receptor site concentration. In addition, a high water solubility normally reduces tissue retention and increases elimination. This, in turn, diminishes the risk for systemic effects. Hence, it is difficult to predict what effect a change in lipophilicity will have on the pharmacologic potency and therapeutic index. Budesonide, flunisolide, BMP and TAA all have similar intermediate water solubility (about 10 mg/ml), whereas BDP and FP are more lipophilic (water solubility $\sim$ 0.1 mg/ml).

Distribution

Tissue distribution, expressed as the volume of distribution and assessed pharmacokinetically as Vss or Vd, shows a marked difference among different steroids and correlates strongly with lipophilicity (413) (Figure 13). Fluticasone propionate appears to be the most widely distributed of the currently available steroids, with a volume of distribution 3–5 times higher than most of the other inhaled corticosteroids. There are currently no good data on the volume of distribution of BDP. An important consequence of the different volumes of distribution for the different steroids is that plasma concentration and systemic effects do not correlate *between* steroids as has sometimes been implied in the literature. For example, BUD at a dose of 3,200 μg/d produces peak plasma concentrations of about 7 nmol/L and has about the same effect on serum cortisol levels as 10 mg of prednisolone (415, 416). Prednisolone in such doses results in peak plasma concentrations of about 500 nmol/L (416). Moreover, a high dose of FP results in greater suppression of plasma cortisol than the same dose of BUD even if FP plasma concentrations initially are about six times lower than the BUD plasma concentrations (398, 409, 416).

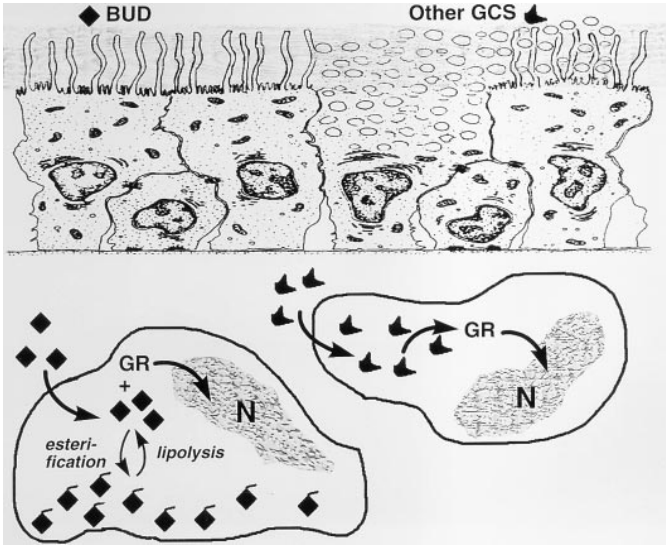

Figure 12. Local pharmacokinetics of inhaled corticosteroids deposited in the airways. First the drug has to become dissolved in the watery layer on the surface of the epithelium. Then it is absorbed into the cell where it exerts its action. Budesonide seems to be retained longer than other steroids because it forms conjugates with long-chain fatty acids within cells (410). These fatty acids—typically oleic acid—bind reversibly to the budesonide molecule; such conjugation does not appear to occur with BDP, FP, or hydrocortisone. Budesonide fatty acid conjugates appear to act as an intracellular store of inactive budesonide. Only free budesonide binds at the glucocorticoid receptor (GR), but as the airways concentration of free budesonide decreases, lipase enzymes in mucosal airway cells release more of the free compound from its conjugated fatty acids, thus raising the level of budesonide available for receptor binding.

Elimination

Inhaled corticosteroids are primarily eliminated by oxidative liver metabolism via the isoenzyme CYP3A. For most inhaled corticosteroids, the rate of clearance is close to hepatic blood flow rate and therefore quite similar for the various products (Table 5). The dependence on CYP3A means that inhibitors of this isoenzyme may increase the systemic effects of the inhaled corticosteroid. Caution may therefore be warranted for the simultaneous intake of inhaled corticosteroids and ketoconazole, troleandomycin, or ethinylestradiole, all of which have been reported to interact with the metabolism of steroids (406).

Elimination half-life, which is a function of both clearance and distribution, differs among the various steroids. Elimination half-life affects the amount of drug present in the body at steady state as well as the rate and extent of accumulation. Accumulation is a function of the frequency of dosing relative to the half-life of the drug. Drugs that have a terminal half-life of the same magnitude as the dosing interval or longer will accumulate. At present, only FP has been shown to accumulate to an important extent (398, 417). A long elimination half-life also reduces the peak versus trough plasma concentration ra-

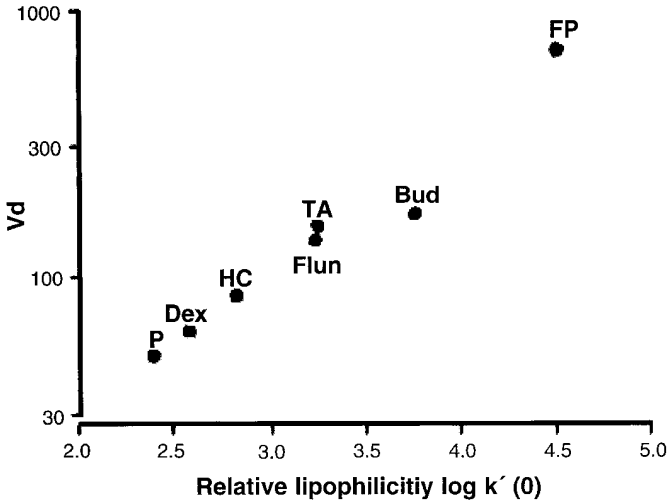

Figure 13. Relationship between lipophilicity and volume of distribution (Vd) in humans. P = prednisolone; Dex = dexamethasone; HC = hydrocortisone; Flun = flunisolide; TA = triamcinolone acetonide; Bud = budesonide; and FP = fluticasone propionate (413).

tio. The clinical importance of differences in half-life is not known. Studies comparing daily versus alternate day dosing of prednisone have suggested that the effect on the HPA axis is more dependent on persistent plasma levels than on high peak plasma concentrations (418). Further studies are needed to assess whether this is also true for inhaled corticosteroids.

An appreciation of the various pharmacokinetic differences between inhaled corticosteroids may increase the possibility of further improvements and hasten the development of the "ideal" steroid formulation. Major pharmacokinetic prerequisites for an improved therapeutic profile include efficient delivery to the intrapulmonary airways. Molecular properties of importance seem to include a high intrinsic activity and retention within the lung coupled with a rapid systemic elimination and low tissue retention elsewhere in the body. The differences in pharmacokinetic parameters between the various inhaled corticosteroids should be correlated with parameters of systemic bioavailability, such as suppression of cortisol production (419, 420).

SYSTEMIC ACTIVITY AND SAFETY

Adverse effects of inhaled corticosteroids should preferably be studied in controlled, long-term clinical trials, using clinically relevant doses in groups of patients with a disease severity and age similar to the groups in which the drugs would normally be prescribed. Such studies require large numbers of patients and are difficult to conduct. As a substitute, the systemic activity of the various inhaled corticosteroids is often studied in short-term, standardized, crossover studies on healthy volunteers or patients with mild disease who will tolerate treatment with placebo for a certain period. The clinical relevance of findings from such studies to patients with more severe asthma is not known. A recent study suggested that significant differences may exist between findings in patients and healthy volunteers (417), the systemic effects being markedly higher in healthy volunteers than patients. Therefore, the results of such studies utilizing sensitive measures of systemic activity of inhaled corticosteroids should preferably be confirmed by similar studies in patients with moderate-to-severe asthma whenever possible. However, even when this is done, the long-term clinical implications of the findings of short-term studies conducted under conditions quite different from the day-to-day clinical treatment remain unknown. It is normally assumed that treatment with a drug–inhaler combination that has been found to have twice as high systemic activity as another drug–inhaler combination in a short-term trial will also be associated with twice as high risk of unwanted systemic side effects during long-term treatment. There is some indirect evidence that this is the case, but further studies are needed to clarify the long-term clinical relevance of the findings in standardized short-term studies comparing the systemic activity of different drugs.

The systemic activity of an inhaled corticosteroid depends on several factors, including:

- Dose delivered to the patient;
- Potency;
- Pharmacokinetic fate (e.g., extent of first-pass hepatic metabolism);
- Site of deposition (gastrointestinal tract and lung); and
- Individual differences in steroid response between different patients.

Many of these parameters are markedly influenced by the choice of inhaler. Therefore, differences among the delivery characteristics of different inhaler devices, the need for full instruction and regular control of optimal inhaler use, and the assessment of compliance are just as relevant to the assessment of systemic effects as to that of the desired effects of inhaled corticosteroids. If these factors are not controlled, the study will not provide any information about the systemic potency of the various drugs or drug–inhaler combinations being compared.

Before discussing the various reports of systemic effects of inhaled corticosteroids and the best study design for comparisons of various drugs, it is important to consider some general aspects of the dose–response relationships of systemic effects of inhaled corticosteroids (Figure 14). For a given drug or inhaler, there will always be a dose below which no systemic effects can be detected no matter which investigative method is used. There will also be a dose range within which systemic effects are measurable in one or more systems (this dose varies from system to system). Within a certain dose range there will be a linear (or log-linear) relationship between the magnitude of the systemic effect and the dose of drug. At a certain dose, the dose–response curve flattens out. Increasing the dose beyond that point is associated with only small changes in the outcome measurement. Our knowledge about the dose level at which measurable systemic effects can be detected in healthy volunteers or patients with mild disease is quite good. It is normally assumed that doses that are not associated with any measurable systemic effects in sensitive laboratory test systems will be clinically safe. In contrast, our knowledge about the dose level at which the dose–response curve starts to flatten out is more sparse.

As in studies of efficacy, the optimal design of a trial comparing or measuring the systemic activity of various inhaled corticosteroids is not yet known, but true differences between corticosteroids are most likely to be detected in well-designed, controlled trials. The best experimental study design depends upon the questions the study aims to clarify. Some of the more important questions are (Figure 15):

- *What is the lowest dose level at which a systemic effect can be detected?*

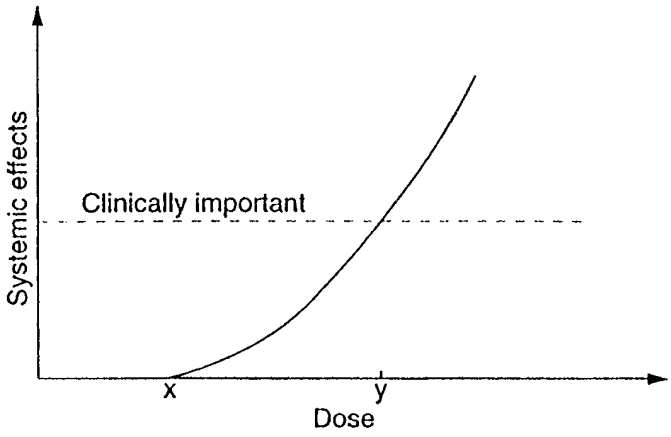

Figure 14. Dose–response curves for the systemic effects of an inhaled steroid. At low doses no detectable effects are seen. This is followed by a dose range (from dose x) in which measurable systemic effects can be detected with sensitive methods. These effects are without clinical importance. At dose y the measurable effects are so marked that they become clinically important because the reduction in endogenous cortisol production can no longer compensate the effects of the systemically bioavailable exogenous steroid.

Important for assessing the sensitivity of comparative trials and defining safe doses.

- *Which dose is required to produce a certain systemic effect (i.e., 50% change)?*
  Important for an accurate potency comparison.
- *What is the slope of the dose–response curve?*
  Important for an accurate potency comparison and for assessment of the risk of overdosing (therapeutic index); the steeper the slope, the higher the risk.
- *When does the dose–response curve start to flatten out (become less steep)?* Important for assessing the sensitivity of comparative trials.
- *Are there differences between single and steady state (repeated) dosing?*
  Important for choice of study design and clinical relevance of single-dose studies.

These questions can only be answered in placebo-controlled, dose–response studies. However, useful information about some of the points can also be obtained in trials of different design. We discuss some recent studies on the systemic activity and adverse effects of inhaled corticosteroids and compare these parameters among different inhaled corticosteroids. For systemic effects of inhaled corticosteroids, the main focus has been on the hypothalamic-pituitary-adrenal (HPA) axis, bone metabolism and growth in children. Many recent studies have compared the systemic activity of the various inhaled corticosteroids.

Effects on HPA Axis

The occurrence/magnitude of adrenal suppression is the most extensively studied systemic effect of inhaled corticosteroids. However, even if moderate and high doses of exogenous corticosteroids will affect the HPA axis, this rarely appears to be clinically important, as no cases of adrenal crisis have been reported in adults using only inhaled corticosteroids while only two such cases have been reported in children (421, 422).

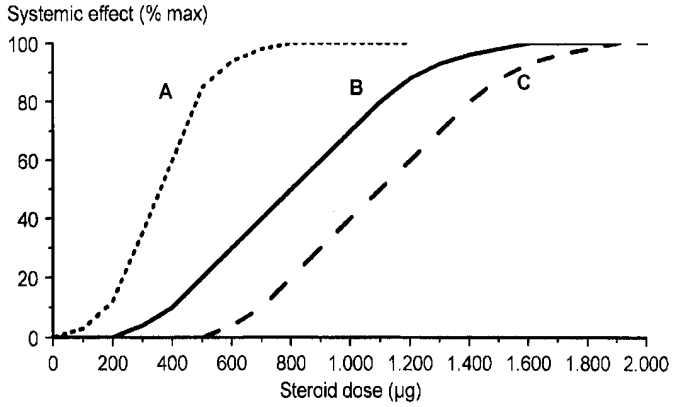

Figure 15. Different dose–response curves of systemic effects of different inhaled corticosteroids or inhalers. For a given drug or inhaler there will always be a dose below which no systemic effects can be detected no matter which method is used. Then there will be a dose range within which systemic effects are measurable in one or more systems (this dose varies from system to system). Within a certain dose range there will be a linear (or log-linear) relationship between the magnitude of the systemic effect and dose of drug. At a certain dose the dose–response curve becomes more flat. Increasing the dose beyond that point is only associated with a small change in the measurement. Only a full dose–response curve can answer all the important questions about systemic effects (*see text*). Partial dose–response curves may lead to false conclusions about equipotent doses.

The most sensitive investigations of HPA axis function fall into three groups: (*1*) Multiple blood sampling for plasma cortisol at frequent intervals over a period of up to 24 h, which allows the kinetic representation of cortisol secretion as the area under the cortisol versus time curve (AUC); (*2*) urinary cortisol measurement overnight or for a period of 24 h; and (*3*) stimulation tests using low-dose tetracosactrin or adrenocorticotropic hormone (ACTH). Only studies using these outcome parameters will be discussed.

Children

Urinary cortisol excretion measured at home. No significant effects on urinary cortisol excretion have been reported with doses up to 400 µg/d BUD pMDI with spacer (167, 423) and 200 µg/d BUD Turbuhaler (424). In contrast, 200 µg/d and 400 µg/d FP Diskhaler, and 400 µg/d BUD Turbuhaler seemed to reduce urinary cortisol excretion (424). A significant effect on urinary cortisol excretion by 300–400 µg/d BDP has been found in some studies (425–428), whereas others did not find any effect at these same doses (429–431). Cortisol excretion was still within the normal range in all the studies that found a significant effect.

Frequent plasma cortisol measurements. Among studies in which plasma cortisol was measured at frequent intervals during nighttime or over a 24-h period, 400–1,000 µg/d BDP pMDI was associated with a significant reduction in the normal physiologic secretion of cortisol (426, 432, 433). Similar findings have been reported for BUD pMDI with large volume plastic spacer when plasma cortisol was measured at frequent intervals during nighttime (426). Overnight urinary cortisol excretion was also affected, whereas no effects were seen on ACTH or growth hormone values (426). In contrast, preschool children treated with daily doses of 200–300 µg BUD for 3–5 yr showed normal adrenal function as assessed by frequent plasma cortisol measurements over 24 h (244). Finally, the influence of a daily dose of 200 µg FP and 800 µg BUD on plasma cortisol profile over a 24-h period and increase in plasma cortisol after ACTH stimulation have been studied (434). No significant effects were found on these parameters by either of the two drugs at these doses. Both had significantly less effect than 2.5–7.5 mg prednisolone per day.

HPA response. Studies assessing long-term treatment with BDP or BUD in doses of up to 400 µg/d have not found suppression of the HPA axis response to stimulation (217, 435). One study evaluating high-dose therapy with these drugs found a reduced response in some children (436). None of the children had any clinical symptoms of adrenal insufficiency.

Summary. Though differences exist between the various inhaled corticosteroids and inhalation devices, treatment with low doses (< 400 µg/d) of inhaled corticosteroids is normally not associated with any significant suppression of the HPA axis in children. With higher doses, small changes can be detected with sensitive methods. The clinical relevance of these findings needs further study.

Adults

Since no cases of adrenal crisis have been reported in adults using only inhaled corticosteroids, studies of effects of exogenous steroids on the HPA axis function in adults have mainly been performed to compare the systemic activity of different inhaled corticosteroids. These studies are described later.

Effects on Bone

In adults, up to 10% of bone is replaced each year, but the rate differs in cortical bone (about 5%), in trabecular bone (up to 20%), and at different individual sites. If bone mass is to re-

main constant, resorption and formation must be in balance. Systemic steroids can induce osteoporosis by increasing bone resorption and decreasing bone formation (437, 438). Although no controlled, prospective, longitudinal studies have been performed, cross-sectional studies in children and adults suggest that steroid-induced osteoporosis is clinically important since a large proportion of patients receiving long-term oral steroids experience rib or vertebral fractures (439–441).

In children, the rate of bone modeling, or turnover, is much higher than in adults. Furthermore, in adults the skeletal mass is decreasing, while in children it is increasing throughout childhood and adolescence until peak bone mass/density is reached in early adulthood. The increase in bone mass is not a constant process but varies with age and season of the year. Skeletal modeling/turnover rate and calcium retention is highest during spring and summer and during infancy and adolescence. Normally, most of the skeletal mass will be accumulated by late adolescence. As final height in relation to predicted adult height is the most important outcome when growth is studied in children, so too is maximal peak bone mass/density probably the most clinically relevant outcome measure to assess when the influence of steroids on bones in children is studied. In addition to nutrition (including calcium intake), heredity (both parents), endocrine factors (sexual development), and physical activity appear to have profound effects on peak bone mass formation. Therefore, these confounding factors as well as age and sex should be considered when designing studies comparing the effects of steroids on bone metabolism.

The effect of exogenous steroids on bone can be evaluated by measurement of biochemical markers of bone metabolism (bone formation and degradation), bone mineral density (BMD), or frequency of fractures. Fracture is the only important endpoint to assess regarding the effect of steroids on bones.

Bone Markers

Levels of all the markers of bone formation and resorption are normally measurable since normal bone is in a constant state of turnover, maintaining a balance between resorption and formation. In simple terms, an elevation of all markers could occur when there is increased bone turnover without net loss or gain in bone mass, while a reduction of all markers, which is normally seen with low doses of oral steroids or high doses of inhaled corticosteroids, could signify a reduction in bone turnover with a constant bone mass. Therefore, it is probably most clinically relevant to consider the net effect of bone formation and bone resorption (442). An elevation of markers of bone resorption alone supposedly suggests net bone loss, whereas an elevation of markers of bone formation alone suggests net bone formation. However, no isolated marker can be considered reliable as a guide to the extent of bone formation or resorption; furthermore, the significance of some markers is not clear.

Markers of Bone Formation

Alkaline phosphatase. It is important to measure *bone-specific* serum alkaline phosphatase. Serum levels are higher during bone synthesis, that is, at times of high osteoblast activity. It shows no diurnal variation in plasma concentration and is a rather insensitive measure of *acute* changes in bone formation.

Procollagen type 1 carboxyterminal propeptide and procollagen type 1 N-terminal propeptide. Procollagen type 1 carboxyterminal propeptide (P1CP) is released from the carboxyterminal end and procollagen type 1 N-terminal propeptide (P1NP) from the N-terminal end of procollagen during synthesis of collagen. Serum levels of both correlate with collagen 1 synthesis. Collagen 1 is found in both bone and soft tissue. The disadvantage of these markers is that the contribution from soft tissue is not known. Furthermore, the concentration in serum is genetically determined in each individual so it is of little use as a reference value. A small diurnal variation is seen, with maximum levels measured at night when bone turnover is increased.

Osteocalcin. Osteocalcin is a calcium-binding, vitamin K-dependent gamma-carboxyglutamic acid-containing noncollagenous protein (also called bone Gla protein or BGP) synthesized by osteoblasts. It comprises 1–2% of bone protein. Osteoblastic synthesis of osteocalcin is increased by $1,25(OH)D_2$ and D_3, and the circulating levels reflect osteoblast activity. Osteocalcin levels show a small diurnal variation, with maximum levels occurring during the night due to increased bone turnover. Approximately 20–30% of the osteocalcin escapes into the circulation. *Intact osteocalcin* reflects bone formation and osteoblast activity, whereas *osteocalcin fragments* reflect osteoclast activity and degradation of bone. Therefore, it is important to have specific immunoassays that detect as much as possible of the intact osteocalcin molecule and little or no fragments. Correct handling of the serum samples is also important because proteolytic enzymes in the serum will degrade the osteocalcin molecule into fragments. There are a number of different immunoassays for measuring osteocalcin, some using polyclonal antibodies and others monoclonal antibodies.

Markers of Bone Resorption and Degradation

Hydroxyproline. Hydroxyproline is the specific amino acid of collagen that is released during collagen degradation. It is a nonspecific bone marker present in all collagens and in some other proteins. Approximately 10% is released into the urine, but only 50% of what is found in the urine originates from bone. Urinary levels are increased after ingestion of gelatin, but fasting for 12 h eliminates this problem.

Glycolysated hydroxylysine. This marker exists in two forms, GH and GHH. It is released from all types of collagens. GH is found in higher concentration than GHH in bone and in lower concentration than GHH in skin.

Tartrate-resistant acid phosphatase. Tartrate-resistant acid phosphatase (TRAP) exists as several isoenzymes and is synthesized from blood cells, prostate, and bone. Bone-specific TRAP is abundant in osteoclasts and levels of TRAP are thought to reflect osteoclast activity.

Pyridinoline/desoxypyridinoline. Pyridinoline/desoxypyridinoline are used much more frequently than the two previous markers. They are collagen crosslinks released by the osteoclast during bone resorption. Pyridinoline is present both in bone and cartilage, whereas desoxypyridinoline is more bone-specific. There is a diurnal, age, sex, and day-to-day variation that has to be kept in mind when assessing these markers.

Cross-linked carboxyterminal telopeptide of type 1 collagen. Cross-linked carboxyterminal telopeptide of type 1 collagen (1CTP) is released into the circulation as fragments during collagen degradation. These fragments are intact and resist further degradation. During bone resorption 1CTP increases, and the serum level correlates with the bone resorption rate. There is a small diurnal variation, with levels increasing during the night due to increased bone turnover.

Urinary calcium excretion in relation to creatinine. After a 12 h fast, urinary calcium excretion is a measure of the calcium coming mainly from bone. It is thought to reflect the difference between the rates of mineralization and resorption.

Children. Reduced osteocalcin levels have been reported in children with asthma, independent of whether the children re-

ceived steroids (443). Serum levels of calcium, phosphate, magnesium, total and bone-specific alkaline phosphatase, osteocalcin, parathyroid hormone, 1,25 dihydroxy-vitamin D, or urinary hydroxyproline excretion have been found to be unaffected by daily doses of up to 800 μg BUD or BDP and up to 400 μg FP (425, 428, 443–447).

Tartrate-resistant acid phosphatase was significantly reduced in children treated with 300–800 μg/d BDP (443), indicating a reduced degradation of bone. Serum levels of P1CP and 1CTP and hydroxyproline excretion in the urine were not affected by treatment with 400 μg/d BUD (447–449), but 800 μg/d has significantly reduced P1CP and 1CTP (447–449), suggesting a reduction in both formation and degradation of collagen 1 at this dose. By contrast, low doses (2.5–5 mg) of oral prednisolone cause significant reductions in serum levels of osteocalcin, P1CP, and 1CTP and in hydroxyproline excretion in the urine of children (445, 446).

In short, no adverse effects on markers of bone formation and degradation have been reported at standard pediatric doses of inhaled corticosteroids. High doses can cause significant changes, which suggests a reduced bone turnover rate (reduced formation and reduced degradation). The importance of these significant changes during steroid treatment (which is often short term) has yet to be elucidated. It is probably most clinically relevant to consider the net effect of bone formation and bone resorption (442). If, for instance, formation and resorption decrease to the same extent, the changes may not be important since the net effect may be zero. It has still not been shown that such changes in short-term studies have any clinical relevance (450). In one study, bone density was no different among patients with asthma using high doses of inhaled corticosteroids (BUD or BDP, $>$ 800 μg/d) for more than 18 mo than that among patients using little or no inhaled corticosteroid therapy, although serum osteocalcin levels were lower and urine phosphate levels higher in the high-dose group (451).

Adults. A study in healthy volunteers receiving inhaled BDP at doses ranging from 400–2,000 μg/d found a dose-dependent effect on osteocalcin (452). Another study also found significant changes in osteocalcin levels in healthy volunteers receiving high doses of BDP (2,000 μg/d) (453). In contrast to these findings, BUD or BDP given via pMDI in doses of 800 μg/d for 2.5 yr did not affect serum levels of 1CTP or P1CP in patients with asthma (249). In the same study, a rise in 1CTP was noted in patients receiving only bronchodilator therapy. This could be the result of a direct effect of β_2-agonist therapy on bone metabolism, but it is also possible that this group of patients may have been less active physically as a result of poorer disease control; increased immobilization is known to result in increased bone resorption. Other studies on markers of bone turnover will be discussed in the section comparing inhaled corticosteroids.

Bone Density

At present, dual X-ray absorptiometry (DEXA) is the most commonly used and best-validated technique for measuring bone mineral density (BMD). Though a low BMD in adults has been shown to be associated with an increased risk of fracture as compared with patients with high BMD (454, 455), the association is statistical and not very useful clinically. Considerable overlap in BMD levels exists between subjects who have a fracture and those who do not. Generally, BMD is thought to predict fracture with approximately the same power as blood pressure predicts a stroke. One population standard deviation decrease in bone density has been associated with a 1.4- to 3.5-fold increase in risk of fracture in prospective and retrospective studies (455).

Recently, ultrasound of the calcaneus bone, reflecting the quality of trabecular bone, has been used to measure osteoporosis. Preliminary data look interesting, but further validation is needed to assess its value in detecting steroid-induced osteoporosis.

It appears that children and adolescents with asthma never treated with exogenous corticosteroids may have decreased bone density and reduced osteocalcin levels in the blood when compared with normal nonasthmatic children (443). The reason for this is not known. When the clinical condition of a child improves as a result of therapy, the physical activity and dietary habits of the child may change. These factors have been shown to affect bone density (456–458). Conclusions from studies on the effects of inhaled corticosteroids in healthy children or children not requiring the therapy may not be relevant for children with asthma requiring the treatment (244).

Children. Bone densitometry has been only sparsely applied to assess the bone mineral density in children receiving inhaled corticosteroids. In a cross-sectional study, 4.5 yr of treatment with inhaled BUD at a mean dose of 500 μg/d was not associated with reduced bone density in 148 children with asthma when compared with 111 children with asthma who had never received exogenous steroids (Figure 16). Furthermore, bone density did not correlate with years of BUD treatment nor current or accumulated doses of BUD (459). Similar findings were reported in 26 children treated for 2 yr with 300–800 μg/d BDP (443), in 26 children aged 5 to 18 yr receiving inhaled corticosteroids for at least 1 yr (460), and in 15 children receiving 200–450 μg/d inhaled corticosteroids for 0.5–5 yr (461). Furthermore, lumbar vertebral BMD measured at L_2–L_4 was similar in 60 children treated with either BDP or cromolyn sodium (462). In agreement with these cross-sectional studies, normal increases in vertebral bone density were found in two longitudinal studies: one assessing the development of bone mineral density over a period of 6 mo in 14 children receiving inhaled BDP (463) and one over 7–16 mo of treatment of 21 children with inhaled BDP (464). Thus, at present there are no indications that long-term treatment with inhaled corticosteroids is associated with reduced BMD or increased risk of osteoporosis or fracture in children.

Adults. Assessment of the effects of inhaled corticosteroids on bone has often been complicated by the fact that many patients have previously received short- or long-term therapy with oral steroids, which are likely to have had effects on bone turnover and may have resulted in residual structural abnormalities. Moreover, severe asthma may in itself affect BMD through an effect on the lifestyle of the patient (less exercise, different dietary habits). Therefore, a causal link between any abnormalities found and the inhaled therapy is often impossible to prove. Most studies compare BMD of asthmatic patients treated with inhaled corticosteroids with BMD of healthy adults. This may lead to false conclusions about cause–effect relationships since it is not known how BMD values would appear in nonsteroid-treated asthmatic patients with similar disease severity.

A recent review of nine published surveys of BMD in patients receiving inhaled corticosteroid therapy (465) revealed conflicting results. In studies that showed a reduction in BMD, confounding factors such as effects of past or current oral steroid therapy, or coexisting nonsteroidal factors such as the postmenopausal state, could not be excluded. However, even when patients who have never received exogenous steroids are studied, the BMD results are conflicting.

Hanania and coworkers (466) found reduced bone mineral

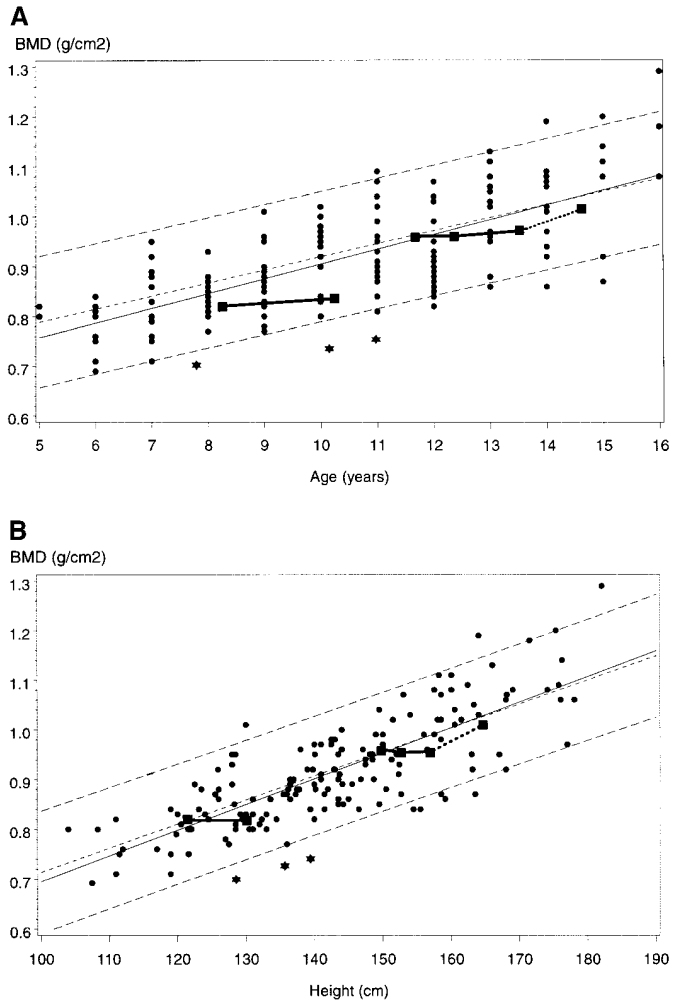

Figure 16. Individual bone mineral density (BMD) as a function of age (*A*) and height (*B*) in 157 asthmatic children treated continuously for 3–6 yr with the inhaled corticosteroid budesonide at a mean daily dose of 504 μg (459). For comparison the 95% prediction interval and mean regression lines from measurements in 111 children with asthma who had never received continuous treatment with exogenous steroids are given . ★ = three children who were on a diet with insufficient amounts of calcium. ■—■ = longitudinal measurements in two children treated with prednisolone. - - - - = longitudinal measurement after prednisolone was stopped in one child.

density among patients inhaling between 800–2,000 μg/d of corticosteroids (mean dose 1,300 μg) for an average of 24 mo (466). Marystone and associates (467) described a similar effect, but only in women. In contrast to these studies, Herrala and colleagues (468), using a similar technique, did not identify any change in BMD among a slightly older group of patients who were treated with 1,000 μg inhaled corticosteroids for 1 yr. Finally, Egan and collaborators (469) compared the changes in BMD during continuous treatment with 1,000 μg/d FP (n = 15) and 2,000 μg/d BDP (n = 9) for 2 yr in a prospective, randomized study. The change from baseline BMD was significantly greater in the BDP-treated group, whereas the group treated with FP showed no changes.

The complexity of the whole issue is best illustrated by the findings of Toogood and colleagues (470) in a recent cross-sectional survey. A minor inverse relationship between BMD and the current daily dose of inhaled corticosteroid was found. However, the relationship was offset by a major increase in BMD with increasing cumulative lifetime dose of inhaled corticosteroid. Furthermore, vertebral fracture rate was inversely related to cumulative inhaled corticosteroid dose but directly related to oral steroid dose. It was suggested that the observed increase in BMD and decrease in vertebral fractures associated with high cumulative doses of inhaled corticosteroids may reflect bone repair following withdrawal from oral steroid therapy. Finally, it was found that postmenopausal women receiving inhaled corticosteroids and an estrogen supplement had normal BMD. Further controlled, prospective studies in different age groups are required to obtain more information about the effects of inhaled corticosteroids, if any, on BMD.

Growth

It is difficult to conduct controlled growth studies in children, and it is inappropriate to extrapolate growth data from one age group to another because the principal determining factors of growth differ at different ages during childhood. In infancy, nutritional factors are the main influence, in later childhood growth hormone (and other hormones) plays a predominant role, and at puberty the sex hormones are additional major factors.

Growth can be assessed by a variety of techniques, each measuring different facets of growth, including:

- Short-term growth (days or wk);
- Medium-term growth (months);
- Long-term growth (yr), including an assessment of final height in relation to predicted height; and
- Biochemical markers of growth.

Children often grow in spurts interspersed with periods during which no growth occurs; this natural variation makes the interpretation of short-term studies in individual children difficult. Studies have demonstrated poor correlations between short-term height velocity and annual height velocity, and between steroid-induced changes in short-term lower leg growth rate and statural growth during the subsequent year (471, 472). One-month lower leg growth velocity explains virtually nothing of the variation in annual statural height velocity (471, 472). In addition, the correlation between two consecutive annual height velocity values for normal prepubertal children is also very poor. A low gain in 1 yr is not necessarily followed by a low gain the next year and vice versa (471). The correlations between 1-, 2-, 3-, and 4-yr values only partially correlate with one another (471). Furthermore, childhood height velocity computed over a period of 3 and 4 yr accounts for only 34% and 38%, respectively, of the variation in final height.

In many parts of the world, growth is less rapid during the winter; this is also the season during which many children require more intensive treatment for asthma. False conclusions about the cause–effect relationship between increased inhaled therapy and seemingly impaired growth may be drawn from studies that do not control for these confounding factors. Another problem in children is that chronic asthma and other atopic diseases are commonly associated with a prepubertal deceleration of growth velocity, which may resemble growth retardation. However, this deceleration is usually accompanied by retarded bone age on X-ray, and later "catch-up" growth ordinarily occurs in these patients. Thus, expected final height is normally attained.

Poor control of asthma may also retard growth. Before the start of inhaled corticosteroid therapy, both height and weight growth curves were normal among children whose asthma

was well controlled, slightly impaired among children whose asthma was moderately well controlled, and significantly impaired among children whose asthma was poorly controlled (473). This correlation persisted when inhaled corticosteroid therapy was introduced, a finding that emphasizes the difficulty of separating the effects of corticosteroids on growth from those of asthma.

A steroid-induced reduction in growth rate is normally accompanied by a similar retardation in bone age development so that the height age of the child remains proportional to the bone age. This makes the commonly used term "growth stunting" inappropriate, since the child often has the full potential for later "catch-up" growth and subsequent attainment of normal or expected final height. The term "growth retardation" describes more accurately this reduction in growth rate (Figure 17).

In practice, conclusions about the effects of inhaled therapy on growth must often be drawn by inference from studies of more than one kind rather than from single definitive studies. Furthermore, it must be remembered that the most clinically important outcome measure of human growth is final height in relation to expected final height, allowing for sex and midparental height differences. This is far more relevant than transient changes in growth velocity during a short-term trial.

Knemometry. Knemometry measures changes in lower leg growth rate within weeks. This allows standardized assessments of the systemic effect of exogenous steroids, which can be useful when comparing various inhaler–steroid combinations (Figure 18). However, findings from knemometry studies cannot be used to predict long-term growth (474). Several knemometry studies have evaluated the influence of 400 μg/d BUD delivered from a large-volume plastic spacer on short-term growth in schoolchildren (475–477). In these studies, no adverse effect on short-term growth was found. Short-term lower leg growth rate was significantly reduced in three studies where 800 μg/d BUD pMDI with large-volume plastic spacer or 400 μg/d BUD Turbuhaler were given (424, 475, 476). However, this effect was less than the effect observed during daily treatment with 2.5 mg prednisolone (478). An important aspect of these studies is that all children participating had mild asthma not requiring inhaled corticosteroids.

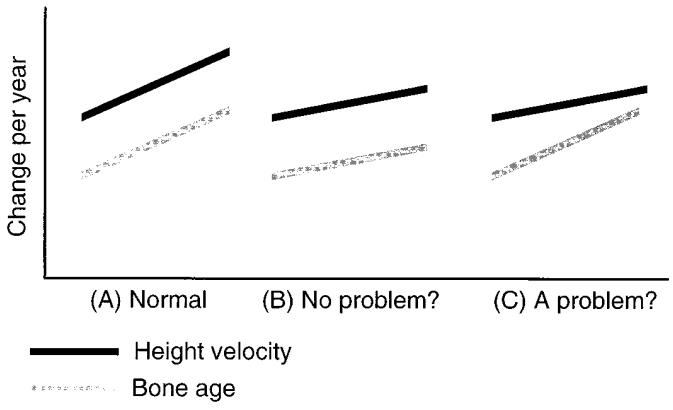

Figure 17. Growth rate and increase in bone age in children not receiving any exogenous steroids (A) and in children receiving low (B) and high (C) doses of exogenous steroids. The reduction in growth rate in group B is accompanied by a similar retardation in the increase in bone age. As a consequence, the long-term growth potential is not adversely affected since the height age of the child still corresponds to the bone age. Final height is unlikely to be affected. At a higher systemic effect (C), growth rate is decreased to a greater extent than bone age and final height is likely to be adversely affected.

In preschool children aged 13 to 36 mo, 200 μg/d BUD pMDI with large-volume plastic spacer did not affect short-term lower leg growth rate (479), whereas 800 μg/d was associated with a significant rate reduction. In agreement with this finding, preschool children treated with 200–300 μg/d BUD pMDI with large-volume plastic spacer grew normally during 3–5 yr continuous inhaled BUD treatment (244).

BDP delivered from a Diskhaler has been assessed in two knemometry studies with different designs (480, 481). In both studies, treatment with a daily dose of 400 μg was associated with significant suppression of short-term lower leg growth rate. In one of these studies, the growth-suppressive effect of BDP was significantly higher than that observed during treatment with 200 μg/d FP in the same children (480), and it was of the same magnitude as the effect of 2.5 mg prednisolone in another study of similar design (478).

BUD Turbuhaler and FP Diskhaler have been compared in a recent placebo-controlled, dose–response study (424). It was found that, microgram for microgram, the two drug–device combinations had similar effects. No adverse effects in short-term lower leg growth rate were seen with 200 μg/d, whereas a slight reduction was associated with 400 μg/d; this reduction was statistically significant for BUD compared with placebo but not compared with FP.

Statural growth. Two studies did not find any statural growth impairment in a total of 127 children on continuous BUD treatment for 1–2 yr (217, 220). Ninan and Russell (473) measured height velocity in 58 prepubertal children with chronic asthma before they were treated with inhaled corticosteroids and followed their growth for a mean of 4.9 yr after such treatment was started. The height velocity standard deviation scores (SDS) were maximal when asthma was well controlled, both before and after starting inhaled corticosteroids. The effectiveness of asthma control correlated significantly with the height SDS, both before and after inhaled corticosteroids were started. Inhaled corticosteroids did not adversely affect growth.

In a longitudinal study of 1-yr's duration, 10 of 20 children receiving BDP and 4 of 19 children treated with BUD seemed to exhibit a reduced growth rate; 4 of 19 is the number expected, based on the normal variation in growth rate of children with asthma. Three of four children treated with prednisolone grew slowly (482). McKenzie and Wales (483) followed 43 children receiving continuous daily treatment with 200 μg FP for 1 yr and found that growth was unaffected by treatment when compared with the expected growth of children of that age.

Few studies have examined growth in children with asthma taking doses of inhaled corticosteroids in excess of 800 μg/d. Of 50 children with a mean age of 11 yr who were receiving 750–1,500 μg/d BDP for an average of 19 mo, six children showed a decrease in height percentile (484). In four of these, the growth deceleration might be accounted for by a physiologic delay just prior to the onset of puberty. A Japanese study (485), which did not include a control group, concluded that growth was not adversely affected in children receiving BDP at a daily dose less than 15 μg/kg. In contrast, some growth retardation was seen in children receiving higher doses. The latter group seemed to have more severe asthma, which can itself adversely affect growth.

There is little information about the long-term effects of inhaled corticosteroids on growth in preschool children. However, recent studies allow some analyses of this age group (237, 244, 484, 486). No adverse effect on height velocity or bone age was found with inhaled BUD pMDI with large-volume plastic spacer at a dose of 200 μg/d (486), and neither

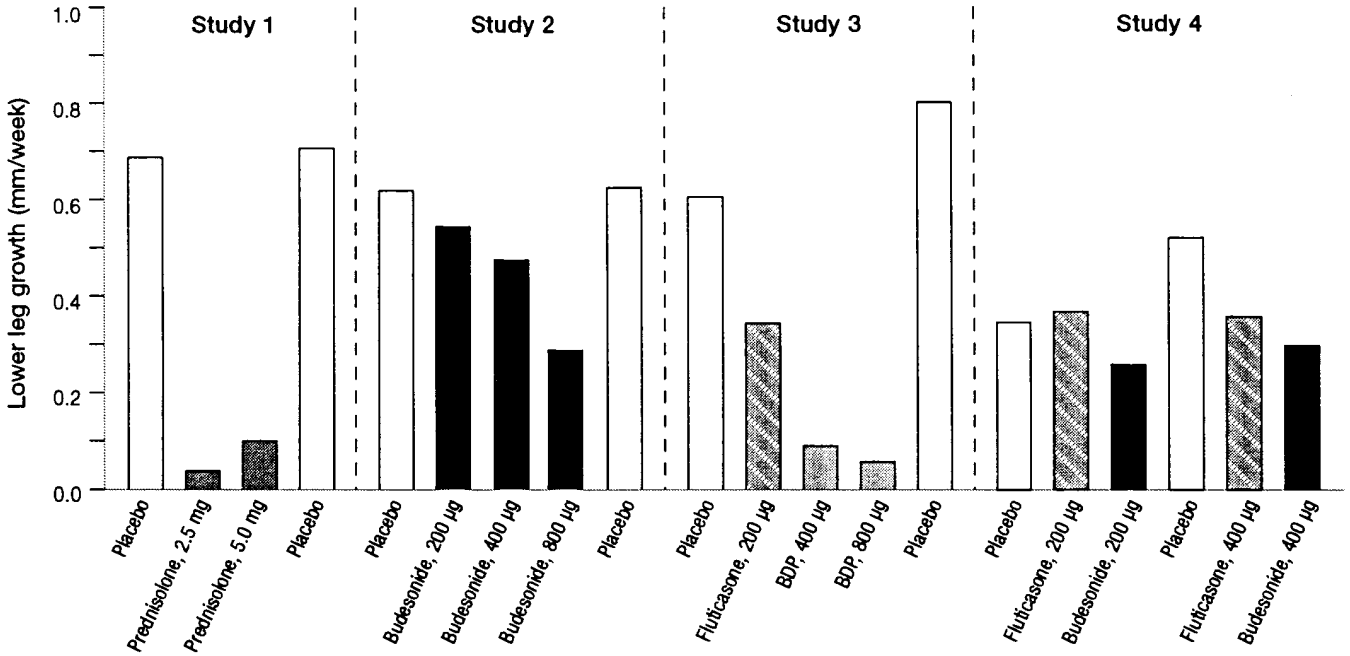

Figure 18. The effects of oral and inhaled corticosteroids on short-term lower leg growth (mm/wk) in children as assessed by knemometry in four different studies. Study 1: Oral prednisolone, 2.5 and 5 mg/d were compared with placebo (478). Study 2: Budesonide (200, 400, and 800 µg/d) inhaled via pMDI + Nebuhaler spacer was compared with placebo (475). Study 3: Fluticasone propionate (200 µg/d) inhaled via Diskhaler was compared with placebo and beclomethasone dipropionate (BDP) (400 and 800 µg/d) (480) inhaled via Diskhaler. In these studies, the placebo values were obtained both before and after the active treatment period in the same patients. Study 4: One group of children received 200 µg/d budesonide Turbuhaler and fluticasone propionate Diskhaler (and dry powder placebo) in a randomized, crossover fashion while another group received 400 µg/d of the same (424). Each 2-wk treatment period was separated by 2-wks' wash-out. The growth rates in the various studies should not be compared.

BUD nor BDP exerted adverse effects in either of these parameters when given at doses ranging between 200–1,100 µg/m^2/d for a year (237, 484). Finally, no effects on height velocity or bone age were found with 200–300 µg/d BUD when given to preschool children for between 3–5 yr (244).

Six controlled, prospective studies including control groups have been published: two with BUD (228, 487), two with BDP (224, 430), and two with FP (258, 488). Growth and lung function were measured in 216 children with asthma during long-term treatment with inhaled BUD and compared these findings with those obtained from children not treated with corticosteroids (228). Children were followed at 6-mo intervals for 1–2 yr without inhaled BUD and then for 3–6 yr on inhaled BUD. A total of 62 children with asthma who were treated with theophylline, β_2-agonists, and cromolyn sodium, but not with inhaled or oral steroids, were also followed for 3–7 yr (control subjects). During BUD therapy, the mean daily dose decreased from 710 µg to 430 µg. A positive correlation between height SDS and percent predicted FEV_1 was found during run-in, indicating that asthma severity influenced growth. Compared with run-in and with the control group treatment, inhaled BUD did not cause any change in growth rate during the 3–6 yr of treatment. Over the whole period, the annual increase in height was 5.62 cm (control group) and 5.48 cm (BUD group). Furthermore, the mean annual change in height SDS was similar between the two groups and not significantly affected by BUD treatment. Because the dose of BUD varied for each individual child during the treatment period, the influence of BUD dose upon growth could not be accurately assessed. However, when high doses were used ($>$ 400 µg/d), both growth rate and lung function were lower than during run-in and lower than during treatment with 400 µg/d, indicating that either high doses or poor asthma control (or both) may adversely affect growth.

The prospective investigation of Merkus and colleagues (487) corroborated these findings. These investigators studied 40 children with asthma who were randomized to treatment with 600 µg/d BUD or placebo for 2 yr. Growth in these two groups was compared with the growth of 80 matched healthy control subjects. The mean difference in growth rates between patients treated with placebo and their matched control subjects was −0.70 cm/yr, and between children treated with BUD and their matched control subjects was −0.44 cm/yr. The observed mean (± SEM) case-control difference between treatment groups was +0.27 (± 0.58) in favor of BUD treatment. The authors concluded that children with asthma (especially boys) experience a prepubertal growth delay, and that a daily dose of 600 µg BUD does not adversely affect growth over a 2-yr period.

Tinkelman and associates (224) compared 400 µg/d BDP pMDI *without* spacer with twice daily sustained-release theophylline in a controlled, randomized, prospective study of 195 children with asthma between the ages of 6 and 16 yr. The observed mean growth rate for those children who had their first and last measurement more than 100 d apart (linear regression on height measurements) was 4.2 cm/yr for the BDP-treated children and 5.5 cm/yr for the theophylline-treated children ($p < 0.005$). The growth retarding effect was mainly observed in boys, and there was no significant difference between the two groups when the girls were studied separately. In this study, the steroid dose was not adjusted during the treatment year nor tailored to the severity of the disease; it is probable that these children with mild asthma did not require the dose of BDP used in the study.

A similar study design was used by Doull and colleagues (430), who assessed the effect of 400 μg/d BDP Diskhaler on virus-induced wheezing episodes in 7–9-yr-olds who, between these episodes (around three per year), had no asthma symptoms requiring continuous inhaled corticosteroid treatment (430). Out of 4,800 children, 200 were eligible and of these, 104 entered a randomized, double-blind, parallel group comparison between BDP and placebo. A total of 94 children completed the 31-wk study, where statural height was measured at least once a month. After the double-blind period, there was a 17-wk wash-out period during which the children were seen twice. Growth rate during BDP treatment was significantly lower than during placebo treatment; the placebo children grew an average of 1 cm more during the study than did the BDP-treated children. No catch-up growth was seen during the wash-out period. Once again, the inhaled corticosteroid dose was not adjusted nor tailored to the severity of the disease, and most of the children included in the study would not normally have been given continuous inhaled corticosteroids, even in low doses.

Price and coworkers (258) compared growth rates during treatment with 50 μg FP twice daily and 20 mg cromolyn sodium four times daily in 122 prepubertal children with mild asthma. Due to numerous treatment failures in the cromolyn group, more children were randomized to cromolyn treatment in an attempt to provide similar group sizes after 1 yr of treatment; in this way, the study groups were randomized in an unbalanced fashion. No differences were found in growth rate between the two groups. The FP-treated children experienced better asthma control than the children in the cromolyn sodium group despite the fact that the latter group had somewhat milder disease. Another prospective, double-blind, placebo-controlled, randomized trial of 1-yr's duration found that daily doses of 100 μg and 200 μg FP did not adversely affect statural growth as compared with placebo (488). The number of children in each of the three treatment groups was around 100.

Finally, a meta-analysis including 21 studies representing 810 patients compared attained height with expected height of children with asthma treated with inhaled or oral corticosteroids (489). Results revealed a significant but weak growth impairment in children receiving oral steroids whereas children treated with inhaled corticosteroids attained normal height. Furthermore, there was no statistical evidence of associations between inhaled corticosteroid therapy and growth impairment at higher doses or with longer therapy duration.

Biochemical growth markers. Blood levels of various biochemical markers, such as growth hormone, somatomedin-1 (IGF-1), IGF-binding protein-3 (IGFBP-3), P1CP, and the aminoterminal propeptide of type III procollagen (PIIINP), have been found to correlate to some extent with growth rate. However, the predictive value of drug-induced changes in the levels of these markers is not known. The effect of inhaled corticosteroids on some of these markers has been discussed earlier (*see* BONE MARKERS). Treatment with even low doses of prednisolone (2.5–5 mg/d) is associated with significant reductions in the levels of some of these markers, while daily doses of 400 μg BDP, BUD, or FP have not affected any of the markers (428, 445–449). This gives further support to the view that such doses of inhaled corticosteroid are safe. Furthermore, daily doses of around 400 μg (range 200–1,200 μg) BUD and BDP do not adversely affect the output of urinary growth hormone (425, 426, 431).

Case reports have suggested that growth inhibition in individual children may be seen with inhaled corticosteroid doses that do not normally adversely affect growth (490). Since growth is such a fluctuating process, further studies are needed to evaluate the validity of such observations. Two recent studies suggest that such children are "biochemically similar" to children without any indications of growth suppression (482) and without any disturbance in the growth hormone axis (491).

Summary. Although differences exist between the various inhaled corticosteroids and inhalation devices, treatment with low doses (< 400 μg/d) of inhaled corticosteroids is normally not associated with any significant growth suppression in children with asthma when the dose is tailored to the severity of the disease. When higher doses are given to children with mild disease, significant growth retardation has been reported during 1 yr's treatment with some steroid–inhaler combinations. The clinical importance of these findings for children with more severe asthma needs to be elucidated, since children with severe disease may have less systemic absorption of drug and a higher growth suppressive effect from the disease itself. Finally, the implications of these results for final height in relation to expected final height need further study.

Cataracts and Glaucoma

Ocular cataracts that are posterior and subcapsular are a well-recognized unwanted effect of oral corticosteroids. Two recent studies have evaluated the risk of posterior subcapsular cataracts in children receiving long-term treatment with inhaled corticosteroids. The conclusions were the same: continuous treatment with inhaled corticosteroids is not associated with an increased occurrence of cataract development in children (492, 493).

In agreement with the findings in children, the currently available data indicate that posterior subcapsular cataract is not a risk for patients being treated with inhaled corticosteroids alone, even when high doses (up to a mean dose of 1,500 μg/d) were used for a mean of 9 yr of treatment (494). However, one recent epidemiologic study suggested that there was a small increased risk of subcapsular and nuclear cataracts in Australian patients over 49 yr of age taking high doses of inhaled corticosteroids for prolonged periods of time (495). Only a very low number of the patients with lens opacities had received inhaled corticosteroids without systemic steroids. The analyses did not adjust for possible differences in occurrence of atopic conditions between the groups, which is important since atopic disease may in itself increase the risk of cataracts (496, 497).

Another recent epidemiologic study suggested that Canadian patients aged 66 and older receiving high-dose inhaled corticosteroids (1,500 μg/d) continuously for at least 3 mo stood an increased risk of glaucoma (odds ratio 1.4; CI 1.1–3.0) (498). This observation needs further assessment in controlled, preferably prospective, studies.

Skin Thinning and Easy Bruising

Skin thinning and easy bruising are unwanted effects that occur in a dose-dependent fashion with inhaled corticosteroids and have a higher prevalence in older female patients (499, 500). The effects are due to a reduction in extracellular ground substance in the dermis, possibly because of reduced dermal fibroblast activity. The effects are very rarely seen when total daily doses of inhaled corticosteroid are less than 1,000 μg. Increased occurrence of skin thinning and easy bruising has not been reported in children.

Local Side Effects

Oral candidiasis. Oral candidiasis, or thrush, has been reported in up to 5% of adult patients receiving inhaled corticosteroids, and positive mouth cultures have been found in up to 25%. Its occurrence is higher with the concomitant use of

antibiotics. The incidence of oral candidiasis is greatly reduced when inhaled corticosteroids are delivered by a pMDI with spacer device and when the patient mouth-rinses with water immediately after inhalation. The prevalence of oral candidiasis appears to be lower when inhaled corticosteroids are delivered by the Turbuhaler inhaler (501). Oral candidiasis can be easily managed by nystatin mouthwash and seems to be less frequent in children than in adults.

Dysphonia. Dysphonia, or nonspecific throat symptoms, are unwanted effects that have been reported to occur in up to 58% of patients taking inhaled corticosteroids via pMDI (502). These effects were not diminished by the use of spacer devices. However, the prevalence of this local side effect may, too, be lower when inhaled corticosteroids are delivered by Turbuhaler inhaler (501), probably because the vocal cords are positioned differently during the inhalation when inhaling from this device than during inhalation from a pMDI (503).

Comparisons of Systemic Activity between Different Steroids

The anti-asthma effects of different corticosteroids must be balanced against the systemic activity of the drugs, which may lead to systemic side effects. The possible long-term effects of inhaled corticosteroids are difficult to assess because of the confounding influence of other factors, including courses of oral steroids and other therapy as well as the effects that chronic asthma itself may have on variables such as growth and bone density. No long-term comparisons of the adverse systemic effects of different inhaled corticosteroids are available. In their current absence, attempts must be made to assess the risk of long-term adverse effects on the basis of short-term studies. The problem with such attempts is a lack of understanding of the relationship between any changes that may be found in short-term markers and the development of clinically relevant long-term effects. Furthermore, many comparisons have been performed in healthy volunteers even though the clinical relevance of such, or of studies in patients with mild asthma, to patients with more severe asthma is not known. A recent study suggested that significant differences may exist between findings in patients and healthy volunteers (417). Therefore, the results of studies in healthy volunteers should be confirmed by similar studies in patients with moderate-to-severe asthma whenever possible.

Differences between the delivery characteristics of different inhaler devices, the need for full instruction in inhaler use, and the assessment of compliance are factors just as relevant to the assessment of systemic effect studies as to studies of the beneficial effects of inhaled corticosteroids. Finally, when drug–inhaler combinations are compared, it must be remembered that the comparison of the systemic effects cannot stand alone. The systemic effect should always be related to the clinical effect; otherwise, false conclusions may be made. If a steroid–inhaler combination (*A*) has twice as high systemic effects as another inhaler–drug combination (*B*), it may be concluded that *B* is preferable to *A*. However, if *A* is clinically twice as effective as *B*, there is no obvious advantage of one treatment over the other.

Direct comparisons of the systemic effects of inhaled corticosteroid therapy have concentrated on the effect on the HPA axis function. In addition, a few direct comparisons have been made upon markers of bone metabolism and short-term growth in children.

HPA axis. Studies using sensitive outcome measures of HPA axis function, as discussed previously, are most likely to detect differences in systemic activity between the various drugs, so only comparative studies using these outcomes will be discussed. In addition, studies using a single morning plasma cortisol will be briefly mentioned, though the results from such studies should be given little weight when drawing general conclusions.

BUD versus BDP. Plasma cortisol levels monitored at intervals between 8–12 h after oral and inhaled dosing with placebo, BDP, and BUD pMDI in healthy volunteers found BDP to be twice as potent as BUD in suppressing adrenocortical function (504). In agreement with this, Jennings and colleagues (505) reported a greater systemic potency of BDP pMDI manifested by 24-h urine cortisol values in healthy adults than did BUD. This study design did not allow an assessment of potency ratio.

The 24-h urinary cortisol was significantly higher in children with asthma who were receiving regular inhaled BUD therapy than in those receiving regular BDP (both drugs administered by pMDI, with or without large volume spacer, at doses of 800–1,200 μg/d) (506). Another pediatric study compared the effects of daily doses of 200, 400, and 800 μg of BUD and BDP (both delivered by pMDI) administered for three consecutive periods of 4 wk (507). The ACTH response was not affected by any dose of either drug. There was a significant dose-related suppression of 24-h urine cortisol with BDP, but not with BUD. The number of patients receiving BUD in this study was too small to allow a good comparison between the effects of the two drugs, but in a further study (508) the 24-h urinary cortisol in 33 children treated for 8 wk with 200, 400, or 800 μg of BUD was found to be similar, with no dose-related suppression of cortisol excretion. At variance with these studies, an equal-dose comparison in 12 children with asthma (426) demonstrated similar effects on nocturnal serum cortisol AUC and 24-h urinary cortisol with BDP and BUD (400 μg daily by pMDI with plastic spacer for 2 wk). Although the number of comparisons with sensitive markers is limited, the majority of studies have found that BDP pMDI has a somewhat greater systemic effect than BUD pMDI. No good comparisons of the dry powder devices are available.

FP versus BDP. No full dose–response comparisons of the systemic effects of FP and BDP have been published. In an equal-dose comparison, 1,500 μg/d FP was compared with 1,500 μg/d BDP over a 1-yr period in patients with symptomatic moderate to severe asthma (191). Adrenal function was assessed by measurement of single morning plasma cortisol and urine-free cortisol excretion; in some patients, the short tetracosactrin test was administered. No difference was revealed between the two treatments in any of these tests.

Several other comparisons between the HPA axis effects of BDP and FP have been reported. Some utilized only single measurements of serum cortisol (with or without plasma ACTH) (190, 192, 194). One used mainly single measurements of plasma cortisol, although the short tetracosactrin stimulation test was also performed in an unspecified number of patients and was reported to show no significant abnormality in either group (169). Finally, 200 μg FP had less effect than 400 μg and 800 μg BDP on cortisol excretion in the urine of children with mild asthma (480).

No firm overall conclusion on the numerical relationship between the effects of BDP and FP can be drawn from the studies utilizing sensitive methods. Further dose–response studies are required for this to be possible.

BUD versus FP. In contrast with comparisons between other inhaled corticosteroids, the systemic activity of BUD and FP has been extensively compared in several studies using sensitive measures of HPA axis function. The first published comparison measured AUC plasma cortisol and the corticotrophin-releasing hormone provocation test in children.

Treatment with 100–200 μg/d FP Diskhaler, 800 μg/d BUD pMDI with large volume plastic spacer, 2.5–7.5 mg/d oral prednisolone, or placebo was given after a run-in period during which the patients did not receive corticosteroid therapy (434). Neither BUD nor FP treatment had any significant effect on the AUC plasma cortisol nor the corticotrophin-releasing hormone-induced plasma cortisol level. By comparison, oral prednisolone exerted a significant effect on both these measures of HPA axis function. As this study compared fixed doses of all three drugs, no conclusion can be made about the systemic potency ratio.

In healthy adult volunteers, the effects of single doses of FP (250 μg, 500 μg, and 1,000 μg via Diskhaler) were compared with placebo and with 800 μg BUD via Turbuhaler (419). The suppression in the $AUC_{0–20h}$ values for plasma cortisol, relative to placebo, induced by each single dose was 8% (FP 250 μg); 19% (FP 500 μg); 28% (FP 1,000 μg); and 16% (BUD 800 μg). A follow-up study compared the effects of 1,000 μg FP and 800 μg BUD, after single doses and after seven consecutive twice-daily doses (509). The single doses were comparable, but FP demonstrated a significantly greater suppressive effect on $AUC_{0–20h}$ plasma cortisol than BUD after seven consecutive doses.

Several further comparative dose–response studies of the effect of FP and BUD on the HPA axis have recently been reported. One randomized, crossover study compared twice-daily treatment with FP Diskhaler (100, 200, 500, and 1,000 μg) with BUD Turbuhaler (100, 200, 400, and 800 μg) for 7 d in 80 healthy volunteers (510). Multiple plasma cortisol samples were taken in 24-h periods prior to randomization and during the last two dosing intervals with each drug; these were expressed as $AUC_{0–24h}$. Plasma cortisol levels were also measured during the 12–24-h period following the last (14th) dose. A dose–response effect for systemic activity was demonstrated for both inhaled corticosteroids, with significant differences in cortisol suppression between the two drugs. The estimated systemic potency ratio for FP Diskhaler:BUD Turbuhaler was 1.7:1.0 (range 1.3–2.4:1.0). The rate of recovery of serum cortisol at the end of the dosing period was also different: a significant suppression of plasma cortisol concentration 12–24 h after the last dose was seen only in those patients receiving the highest dose of FP.

In a randomized, comparative, crossover study of nine healthy volunteers, BUD was given by Turbuhaler in a dose of 800 μg/d for 7 d, followed by double the dose (1,600 μg/d) for 7 d (420). The effects were compared with those of FP Diskhaler, 750 μg/d for 7 d, followed by 1,500 μg/d for 7 d. Both doses of both drugs led to a significant attenuation of post-tetracosactrin serum cortisol levels. No dose–response effect or difference between the two corticosteroids was seen.

A recent efficacy comparison of FP Diskhaler and BUD Turbuhaler in children aged 5–16 yr with moderate-to-severe asthma also included an assessment of 24-h urine cortisol excretion after 5 wk of treatment with equal doses of BUD Turbuhaler or FP Diskhaler (180). There was no significant difference between the effects of the two drugs.

The effects of FP Diskhaler (200 μg/d and 400 μg/d) were compared with those of BUD Turbuhaler (200 μg/d and 400 μg/d) over 2-wk periods in a placebo-controlled, randomized, double-blind, double-dummy crossover study in 48 children aged 6–12 yr (424). The 24-h urinary cortisol values were significantly reduced when compared to placebo in those receiving 200 μg/d and 400 μg/d FP and 400 μg/d BUD, but not in those receiving 200 μg/d BUD. No significant difference in urine cortisol values was detected between either FP or BUD at 200 μg/d, nor between either FP or BUD at 400 μg/d.

In the comparisons of the studies cited above, BUD and FP were administered by different inhaler devices, which differ in output characteristics and in the extent of drug delivery to the intrapulmonary airways (177, 511, 512). Other studies have compared the systemic potency of FP and BUD when both drugs were administered by their respective pMDIs (which also differ in delivery characteristics). In a placebo-controlled, randomized, seven-way crossover study in 21 healthy men, FP pMDI was given in twice daily doses of 200, 375, and 1,000 μg and BUD pMDI was given in twice daily doses of 200, 400, and 1,000 μg (513). The duration of treatment was 4 d and the plasma cortisol $AUC_{0–24h}$ was measured over the last 24-h period. The systemic activity of FP pMDI was found to be 3.7 times greater than that of BUD pMDI.

In a single-dose study of adult patients with asthma, inhaled doses of FP pMDI (500 μg, 1,000 μg, 1,500 μg, and 2,000 μg) and of BUD pMDI (400 μg, 1,000 μg, 1,600 μg, and 2,000 μg) led to different degrees of adrenal suppression at each respective dose level. FP 500 μg produced greater suppression than BUD 400 μg in overnight urine cortisol values (514). Single doses of 400 μg, 800 μg, and 1,250 μg of FP and BUD, each delivered by pMDI with large volume plastic spacer, have also been compared in children with asthma (515). The overnight urine cortisol/creatinine ratio was significantly suppressed by all doses of FP versus placebo, but by no doses of BUD. The overall estimated potency ratio for systemic effects for FP pMDI with spacer: BUD pMDI with spacer was similar to that estimated from the adult study: 2.9:1.0. The percentage suppression at the 800 μg dose was 60.2% for FP; no suppression was seen with BUD. A number of other comparative studies have reported the results of single morning measurements of serum cortisol in patients receiving BUD and FP (195, 196, 198, 200–202). However, this measure is not suitable for accurate comparison of the systemic potency ratio of different drugs.

Overall, the available studies indicate that the systemic potency ratio of BUD to FP depends upon the inhaler devices compared and on whether the assessment is made on the basis of single or repeated dosing. The systemic potency ratio between FP pMDI and BUD pMDI on a microgram-for-microgram basis has usually been found to be around 3:1; i.e., three times as much BUD is required to produce the same degree of systemic effect as a single dose of FP. For dry powder inhalers, this ratio seems to be around 1.5:1 in adults and around 1:1 in children.

Other comparisons. In one study, the effect of 1 wk's administration of increasing doses of BDP, flunisolide, and TAA (all delivered via pMDI) on 24-h urinary cortisol excretion was compared. A linear, dose-dependent suppression was seen for all three drugs, suggesting equal systemic effect by all three drug–inhaler combinations (207).

Conclusions. As emphasized earlier, the importance of studies of HPA axis function lies in their usefulness in comparing the systemic effect potential of different inhaled corticosteroids (and inhalers), rather than in any major concern about the risk of adrenal suppression in patients receiving inhaled corticosteroids. In contrast to the clinical effect assessments, the studies summarized allow some conclusions to be drawn:

- All the currently available inhaled corticosteroids have the potential to produce suppressive effects on the HPA axis, and the effect is dose-dependent.
- The ratio for systemic effects on the HPA axis between FP and BUD pMDI is approximately 3:1 on a microgram-for-microgram basis; i.e., three times the dose of BUD is required to achieve the same systemic effect as a dose of FP. For the dry powder inhalers, this ratio seems to be around

1.5:1 in adults and around 1:1 in children. The risk of HPA axis effects with BDP pMDI seems to be somewhat higher than that with BUD pMDI, but there is inadequate information to calculate an accurate systemic effect ratio for BDP pMDI versus BUD or FP.

Markers of bone formation and degradation. The clinical relevance of changes in markers of bone formation and degradation has been discussed earlier. Only a few studies have directly compared the effect of different inhaled corticosteroids on bone markers.

One study compared 2,000 μg/d BDP pMDI with large-volume plastic spacer and 1,800 μg/d BUD pMDI with large-volume plastic spacer over a 4-wk treatment period. Beclomethasone dipropionate led to a significant increase in hydroxyproline excretion and a significant decrease in serum ALP, but neither marker was significantly affected by BUD (516). A further study also found that BDP had a greater effect on markers of bone turnover than did BUD (505). Significant changes in urine hydroxyproline and serum ALP were seen with BDP but not with BUD. In addition, serum osteocalcin was found to be significantly lower in the BDP group, and the reduction was dose-dependent.

The effects of BDP and BUD, both administered via pMDI with a large-volume plastic spacer, were compared in premenopausal women (517). Serum osteocalcin levels were significantly depressed by 2,000 μg/d BDP, but not by placebo or 1,600 μg/d BUD. There was no suppression of osteocalcin at half these doses with either drug.

In a randomized, comparative, crossover study in nine healthy volunteers (514), inhaled 800 μg/d BUD was given by Turbuhaler for 7 d, followed by double the dose (1,600 μg/d) for 7 d. The effects were compared with those of FP Diskhaler, 750 μg/d for 7 d, followed by 1,500 μg/d for 7 d. P1CP and 1CTP levels were measured. The data suggested that both drugs may provoke a short-term reduction in bone resorption; no difference was detected between the drugs. In contrast with this finding, a comparison of FP (1,000 μg or 2,000 μg/d) with BUD (1,600 μg/d), both drugs given by pMDI to patients with severe chronic asthma, showed no significant changes from baseline values in markers of bone metabolism in response to either drug (195).

A recent open crossover study in children compared the effects of BDP Diskhaler and BUD Turbuhaler, both administered at a dose of 800 μg/d for 14 d. Serum osteocalcin levels were unaffected by either treatment, but changes were seen in P1CP, PIIINP, the urine creatinine corrected cross-link assays for pyridinoline (uPyr/cr), and deoxypyridinoline (uDPyr/cr). The suppression was more marked with BDP than with the equal dose of BUD (518). Another double-blind, crossover study in 48 children did not find any adverse effects on these markers in children treated with either BUD Turbuhaler or FP Diskhaler, both given in daily doses of 200 μg and 400 μg (519).

The existing data do not allow any firm conclusions to be made about possible differences between the various inhaled corticosteroids in effect on markers of bone formation and degradation. The majority of the direct comparisons, though, suggest that BDP may have a higher systemic effect than BUD.

Knemometry. Knemometry has made it possible to compare systemic effects of different inhaled corticosteroids in children (520). Significant dose–response relationships with increasing doses of inhaled corticosteroids have been demonstrated (424, 475). Crossover designs have the greatest power to detect differences between treatments (520). Correctly standardized, the chance of detecting a 20% difference in lower leg growth rate is greater than 80% if 20 children are studied (520). Furthermore, the method is normally more sensitive in detecting systemic effects of exogenous steroids than urine cortisol excretion measured at home (423). However, the clinical implication of knemometry findings still needs further study. It was found that daily treatment with 2.5 mg prednisolone totally stopped lower leg growth (478). This indicates that knemometry is too sensitive and probably amplifies or exaggerates the growth-retarding effects of exogenous steroids. On the other hand, it also means that if an exogenous steroid has no adverse effect on lower leg growth in a knemometry study, it is most unlikely that such treatment will be associated with any growth suppression during long-term treatment.

BUD from a Turbuhaler and FP from a Diskhaler have been recently compared in a dose–response study (424) comparing placebo with 200 μg and 400 μg of each drug–inhaler combination. It was found that, microgram for microgram, the two drug–inhaler combinations had similar systemic effects, and that 200 μg/d did not adversely affect lower leg growth rate. In another study, 200 μg/d FP Diskhaler was found to have significantly less effect upon lower leg growth rate than BDP 400 μg/d from Diskhaler (480).

GLUCOCORTICOID RESISTANCE IN ASTHMA

Although corticosteroids 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 corticosteroids (521–523). Resistance to the therapeutic effects of corticosteroids is also recognized in other inflammatory and immune diseases, including rheumatoid arthritis, inflammatory bowel disease, and human immunodeficiency virus infection (524–526). Steroid resistance has been studied most carefully in asthma, as it is easier to assess the clinical response to steroids in this condition. Steroid-resistant patients, although uncommon, present considerable management problems. Recognition of patients with steroid-resistant asthma is important, since elucidation of the molecular mechanisms may contribute to our understanding of glucocorticoid actions in asthma and may reveal important insights into the pathophysiology of asthma.

Clinical Features

Glucocorticoid resistance in asthma was first described by Schwartz and associates (527) in 1968 in six patients with asthma who did not respond clinically to high doses of systemic steroids and in whom there was also a reduced eosinopenic response. Carmichael and colleagues (528) reported a larger group of patients with chronic asthma who were steroid-resistant. These patients failed to improve their mean PEF by greater than 15% after taking prednisolone 20 mg daily for at least 7 d. They differed clinically from steroid-sensitive patients only in having a longer duration of symptoms, lower morning PEF values, and a more frequent family history of asthma. Steroid-resistant patients are not Addisonian and they do not suffer from the abnormalities in sex hormones described in familial glucocorticoid resistance. Plasma cortisol and adrenal suppression in response to exogenous cortisol is normal in these patients (529).

Complete steroid resistance in asthma is rare, but there are no population studies giving an estimate of the proportion of patients who are resistant. It is likely that most specialists would only have a few such patients in their clinic, and the prevalence is probably less than one among 1,000 patients with asthma. Much more common is a reduced responsiveness

to steroids, so that high inhaled or oral doses are needed to control asthma adequately.

Steroid-resistant asthma must be defined for research purposes so that data from different groups may be compared. It is important to establish that the patient has asthma rather than COPD, "pseudoasthma" (probably a hysterical conversion syndrome involving vocal cord dysfunction), left ventricular failure, or cystic fibrosis (530). Asthmatic patients are characterized by a variability in PEF and, in particular, a diurnal variability of greater than 15% and episodic symptoms. It is also important to identify provoking factors (allergens, drugs, psychological problems) that may increase the severity of asthma and its resistance to therapy.

Distinction between steroid-sensitive (SS) and steroid-resistant (SR) patients with asthma depends on the response to a high dose of oral steroids given for a reasonable period. In research studies, prednisolone is usually given in a dose of 40 mg daily for 14 d with twice daily monitoring of PEF (Figure 19). In SR asthma, patients fail to improve the morning PEF or FEV_1 by more than 15%. Patients with SR asthma show the typical diurnal variability in PEF and bronchodilate in response to inhaled β_2-agonists. A recent biopsy study in patients with SR asthma showed the typical inflammatory infiltrate of eosinophils that are observed in patients with SS asthma (531). It is clearly important to establish that the patient is taking the oral steroid by measurement of plasma cortisol, which is suppressed after high-dose oral steroids in both SS and SR patients (529). Patients with COPD fail to improve lung function after a course of oral steroids but are distinguished from patients with SR asthma in their lack of acute bronchodilator response and absence of diurnal variability in PEF.

Another group of patients with asthma is responsive to steroids but only in relatively high oral doses. These patients are best described as steroid-dependent (i.e., dependent on oral steroids as opposed to inhaled corticosteroids). These patients deteriorate when the dose of oral steroids is reduced. Rarely, a maintenance dose of greater than 40 mg prednisolone daily may be required, and such patients may mistakenly be classified as steroid-resistant. Patients with steroid-dependent asthma usually have severe disease and are presumed to have a high level of inflammation in their airways.

Mechanisms of Steroid Resistance

There may be several mechanisms for resistance to the effects of corticosteroids, and it is important to characterize patients with steroid resistance carefully if the molecular mechanisms are to be elucidated. Although a family history of asthma is more common in patients with SR than SS asthma, little is known of the inheritance of SR asthma. Identification of the molecular mechanisms of steroid resistance may make it possible to screen relatives for a molecular or gene defect in the future. As discussed above, steroid resistance is recognized in several inflammatory and immune diseases. It is likely that a certain proportion of the population has steroid resistance, which only becomes manifest when they develop a severe immunologic or immune disease state. Resistance to the inflammatory and immune effects of corticosteroids should be distinguished from the rare familial glucocorticoid resistance, where there is an abnormality of glucocorticoid binding to GR.

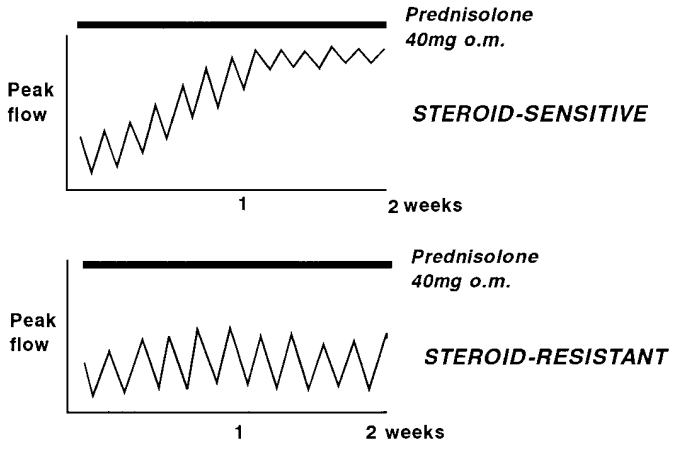

Figure 19. Steroid-resistant asthma is defined by lack of improvement in lung function, such as peak expiratory flow (PEF) after 2 wk of treatment with 40 mg oral prednisone/prednisolone.

Familial glucocorticoid resistance. Primary steroid resistance due to abnormalities of steroid receptors has been described for androgens, progesterone, and mineralocorticoids, in addition to glucocorticoid resistance (532). In addition, the clinical syndrome caused by the defective D_3 receptor, type 2 vitamin D-resistant rickets, is analogous, with a defect in the cytoplasmic vitamin D receptor. The rare inherited syndrome familial glucocorticoid resistance (FGR) is characterized by high circulating levels of cortisol without signs or symptoms of Cushing's syndrome. Clinical manifestations, which may be absent, are due to an excess of nonglucocorticoid adrenal steroids, stimulated by high ACTH levels, resulting in hypertension with hypokalemia and/or signs of androgen excess (usually hirsutism and menstrual abnormalities in females). Inheritance appears to be dominant with variable expression, but only about 12 cases have so far been reported (532). Several abnormalities in GR function have been described in peripheral blood leukocytes or fibroblasts from these patients. These include a decreased affinity of GR for cortisol, a reduced number of GRs, GR thermolability, and an abnormality in the binding of the GR complex to DNA. The molecular basis of the disease in four patients with a reduction in GR appears to be a point mutation in the steroid-binding domain of GR (533).

Resistance to anti-inflammatory actions of steroids. Resistance to the anti-inflammatory and immunomodulatory effects of corticosteroids differs from FGR described above, as it is not associated with high circulating concentrations of cortisol or ACTH and is not accompanied by hypertension, hypokalemia, or androgen excess. Furthermore, these patients are not Addisonian and show normal adrenal suppression. This suggests that any abnormality is unlikely to be due to the same abnormalities in the steroid-binding domain of GR, as described in FGR. Indeed, chemical mutational analysis of GR has failed to demonstrate any major abnormality in predicted structure in SR compared with SS asthma (534). Steroid resistance may be primary (inherited or acquired of unknown cause) or secondary to some factor known to reduce glucocorticoid responsiveness (corticosteroids themselves, cytokines, or β-adrenergic agonists). There are several possible sites where abnormalities in the anti-inflammatory response to corticosteroids in asthma may arise.

Pharmacokinetic abnormalities. The initial suggestion of Schwartz and colleagues (527) was that defective responses to steroids were due to increased clearance of the glucocorticoid, resulting in reduced clinical and eosinopenic response. There is no evidence for altered bioavailability or plasma clearance of prednisolone or methylprednisolone in patients with SR asthma (535–537). Metabolism of corticosteroids may be increased by induction of P-450 enzymes in response to certain drugs, which may thus lead to a secondary steroid resistance (538).

Cellular abnormalities. Glucocorticoid resistance has been documented *in vitro* in various cells from patients with SR

asthma. Complement receptor expression in peripheral blood mononuclear cells (PBMC) from SR patients is not suppressed by corticosteroids *in vitro* compared to the suppression seen in cells from patients with SS asthma and normal individuals (539). The enhanced expression of activation antigens (CR-1, CR-3, and class II HLA-DR molecules) in PBMC and the growth of colonies stimulated by phytohemagluttinin (PHA) is not inhibited by hydrocortisone in patients with SR asthma, in contrast to complete suppression with low concentrations of hydrocortisone ($10^{-9} - 10^{-8}$ M) in patients with SS asthma and normal individuals (539, 540). Peripheral blood mononuclear cells from patients with asthma generate a neutrophil-priming activity (a 3 kD cytokine not yet identified), which is inhibited by corticosteroids in patients with SS asthma but not in patients with SR asthma (541). However, this resistance appears to be selective because other cytokines, such as IL-1β and GM-CSF, are inhibited by corticosteroids (542). The inhibitory effect of corticosteroids on lipopolysaccharide-induced TNF release in PBMCs is blunted in patients with SR asthma compared with SS asthma, although corticosteroids have an inhibitory effect on IL-1β release, indicating again a selective defect (542). There is also evidence for defective T-lymphocyte responsiveness to corticosteroids in SR asthma. Dexamethasone significantly inhibits PHA-induced proliferation and IL-2 and IFN-γ generation in peripheral T cells from SS but not SR patients (537, 543). There is no difference in the proportion of CD4+ and CD8+ T cells in SR patients, although there is increased expression of CD25 (IL-2 receptor) in SR compared with SS patients, indicating a greater degree of immune activation (543).

These studies in circulating leukocytes suggest that the defect in glucocorticoid responsiveness extends outside the respiratory tract and is therefore unlikely to be secondary to inflammatory changes in the airways. In patients with SR asthma the reduced blanching response to topical corticosteroids applied to the skin further indicates that there is a generalized abnormality that is unlikely to be secondary to local cytokine production (544). The *in vivo* responsiveness of monocytes in SR asthma has been studied using the tuberculin response in the skin. In patients with SS asthma there was suppression of the cutaneous tuberculin response after treatment for 2 wk with oral prednisolone associated with reduced numbers of macrophages, eosinophils, and activated T cells, but this was not observed in patients with SR asthma (545).

Abnormality in GR function. In FGR there appears to be an abnormality in GR structure that results in reduced glucocorticoid binding affinity. Glucocorticoid receptor binding has been examined in monocytes and T lymphocytes of SR asthma, and either no difference in GR affinity and receptor density or a relative reduction in GR affinity has been reported (535, 543, 546, 547). Corrigan and associates (535) found some reduction of GR affinity in T cells from patients with SR asthma, but this could not account for the resistance to PHA-induced proliferative responses in cells from the same patients. Sher and coworkers (547) described two types of glucocorticoid resistance: a reduced affinity of GR binding confined to T lymphocytes that reverted to normal after 48 h in culture, and a much less common reduction in GR density (in only 2/17 SR patients) that did not normalize with prolonged incubation. This suggests that there may be different types of steroid resistance in asthma. The small reduction in GR affinity is unlikely to be of functional significance and is not associated with elevated plasma cortisol concentrations, as observed in patients with FGR. The small reduction in GR affinity may be secondary to cytokine exposure, since the normalization of glucocorticoid receptors affinity *in vitro* is prevented by a combination of IL-2 and IL-4 (547) and this combination of cytokines reduces the binding affinity in nuclear glucocorticoid receptors in T lymphocytes, although either cytokine alone has no effect (548). This suggests that steroid resistance may occur in the airways of patients with asthma as a secondary phenomenon due to the local production of cytokines. In patients with SR asthma there is a significant increase in the numbers of BAL cells expressing IL-2 and IL-4 mRNA compared to patients with SS asthma, but no difference in interferon (IFN) mRNA positive cells. After oral prednisone for 1 wk there is a reduction in IL-4 expressing cells and a rise in IFN positive cells in SS asthma, whereas in SR asthma there was no fall in IL-4 positive cells and a fall in IFN positive cells (531). This may indicate that there are different patterns of cytokine release that may contribute to steroid resistance. Although this may account for the increased requirement for corticosteroids in more severe asthma, it is unlikely to account for the reduced steroid response seen in circulating mononuclear cells and in the skin of patients with no response to oral corticosteroids.

There is a marked reduction in GR-GRE binding in PBMCs of patients with SR asthma. Scatchard analysis has demonstrated a marked reduction in GR available for DNA binding compared with cells from patients with SS asthma (549).

Interaction between GR and transcription factors. In the PBMC of patients with SS asthma and normal control subjects, the phorbol ester PMA, which activates AP-1, results in reduced GRE binding. This inhibitory effect is significantly reduced in the PBMC of patients with SR asthma, indicating an abnormality in the interaction between GR and AP-1 (550). This defect does not appear to apply to the other transcription factors, NF-κB and CREB, that also interact with glucocorticoid receptors (550). The abnormality in the interaction between glucocorticoid receptors and AP-1 is unlikely to be due to a defect in glucocorticoid receptors, since the protein sequence of glucocorticoid receptors in patients with SR asthma appears to be normal (534). It is more likely to be due to a defect in AP-1 or its activation. Indeed, activation of c-Fos by phorbol esters is potentiated in the cells of patients with SR compared to SS asthma (550, 551), and preliminary evidence suggests that one of the key enzymes involved in activation of AP-1, namely Jun N-terminal (JNK) kinase, is abnormally activated in these patients (552). The increased basal and cytokine-induced AP-1 activity may lead to consumption of GR, so that steroids are not able to suppress the inflammatory response, either through interacting with GRE or with other transcription factors, such as NF-κB (Figure 20).

An abnormality in AP-1 may also account for the selective resistance to the effects of steroids in SR asthma, since AP-1 is more likely to be important in the regulation of some genes than in others. It would also explain why resistance is seen to the anti-inflammatory effects of steroids, since such resistance can only arise when AP-1 is activated at the inflammatory site, whereas the hormonal effects of steroids at uninflamed sites will not be impaired. Furthermore, there may also be differences in the steroid resistance of different target cells, depending upon the relative balance of transcription factors.

Secondary Steroid Resistance

Although complete steroid resistance is uncommon, there may be a spectrum of steroid responsiveness in inflammatory diseases. This may reflect several mechanisms that are secondary either to disease activity itself or to the effects of therapy.

Downregulation of GR. Downregulation of GR in circulating lymphocytes after oral prednisolone has been demonstrated in normal individuals (553). Whether high local concentrations

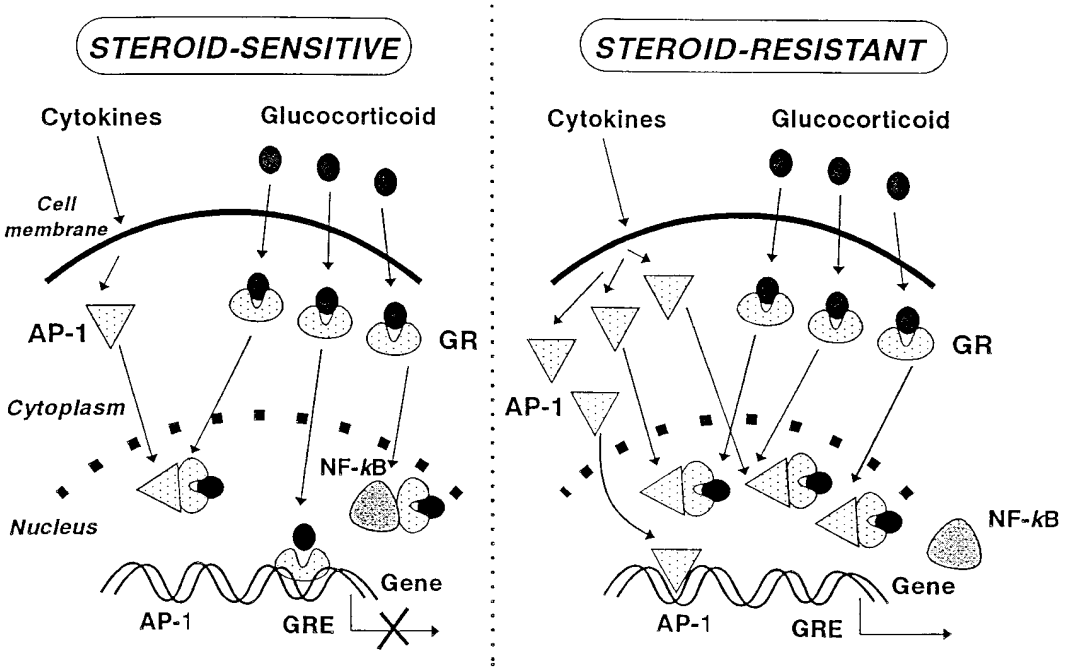

Figure 20. Proposed mechanism of primary steroid-resistance in asthma. Increased activation of activator protein-1 (AP-1) results in the complexing of glucocorticoid receptors (GR), thus preventing the anti-inflammatory action of steroids, either through binding to GREs or through inhibition of NF-κB.

of inhaled corticosteroids reduce GR expression in surface cells of the airway, such as epithelial cells, is not yet certain. It is possible that certain individuals may be more susceptible to the effects of downregulation. If effective GR density is reduced by direct interaction with other transcription factors, such as AP-1 and NF-κB, then the downregulating effect of corticosteroids on GR would be expected to have a greater functional consequence.

Effects of cytokines. Several pro-inflammatory cytokines, including IL-1 , IL-6, and TNFα, activate AP-1 and NF-κB in human lung (21, 22). As all these cytokines are known to be secreted in asthmatic inflammation, this suggests that these transcription factors will be activated in the cells of asthmatic airways. These activated transcription factors may then form protein–protein complexes with activated GR, both in the cytoplasm and within the nucleus, thus reducing the number of effective GR and thereby decreasing steroid responsiveness (3) (Figure 21). In a model *in vitro* system, increased expression of c-Fos or c-Jun oncoproteins prevents the activation of mouse mammary tumor virus promoter by GR, thus creating a model of steroid resistance (17). Addition of recombinant c-Jun or c-Fos proteins to partially purified GR results in inhibition of DNA binding (17). Phorbol esters, which activate AP-1, result in attenuation of glucocorticoid-mediated gene activation (554). Any reduction in glucocorticoid responsiveness would be greater as the intensity of asthmatic inflammation increased and may contribute, for example, to the failure of oral or intravenous corticosteroids to control acute exacerbations of asthma. Once the inflammation is brought under control with large doses of oral corticosteroids, steroid responsiveness increases again so that lower doses of inhaled or oral corticosteroids are needed to control asthmatic inflammation.

Increased resistance may also be due to the effects of cytokines on GR function, since high concentrations of IL-2 and IL-4 have been shown to reduce GR affinity in T lymphocytes *in vitro* (548). This effect would only be seen in mucosal T cells of patients with severe asthma, and it is therefore difficult to obtain evidence to support this possibility.

Effect of β_2-agonists. High concentrations of β_2-agonists activate CREB in rat and human lung and in inflammatory cells via an increase in cyclic AMP concentration (29, 30, 555). This results in reduced GRE binding due to the formation of GR-CREB complexes. This predicts that high concentrations of β_2-agonists would induce steroid resistance. In patients with asthma, 3 wk of treatment with an inhaled corticosteroid blocked

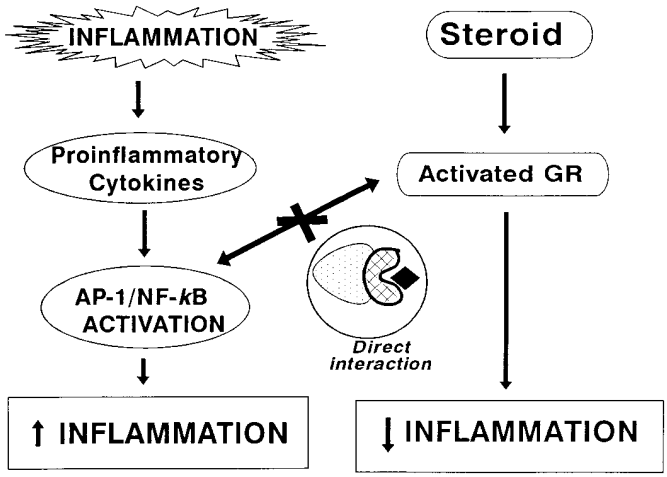

Figure 21. Secondary steroid resistance may arise in the presence of cytokine-mediated inflammation through an interaction between the cytokine-activated transcription factors, such as activator protein-1 (AP-1), and the glucocorticoid receptor (GR), resulting in a reduced availability of GR for control of the inflammatory response. This can only be overcome by increasing the dose of glucocorticoid administered.

the airway response to inhaled allergen, while concomitant treatment with inhaled corticosteroid and a relatively large dose of inhaled β-agonist appeared to provide no significant protection against allergen challenge (556). This suggests that high doses of an inhaled β_2-agonist might interfere with the anti-asthma effect of inhaled corticosteroids. It is possible that some patients who use very high doses of inhaled β_2-agonists (over two canisters per month of metered-dose inhalers or regular nebulized doses) may develop a degree of steroid resistance that is overcome by increasing the dose of inhaled or oral glucocorticoid. This may account for some of the deleterious effects of high-dose β-agonists on asthma mortality and morbidity (557–559). The use of high doses of nebulized β_2-agonists in the treatment of acute exacerbations of asthma may result in resistance to the effects of high-dose intravenous corticosteroids in the treatment of these exacerbations. Steroid responsiveness might be restored by reducing the dose of inhaled β_2-agonists. In an uncontrolled study in steroid-dependent patients with severe asthma, gradual withdrawal of nebulized β_2-agonists resulted in a reduced requirement for oral prednisolone (560).

Premenstrual asthma. In some women there is an increase in asthma symptoms and increased peak flow variability premenstrually, which recovers at the start of menstruation (561). This premenstrual exacerbation of asthma may be very severe in some women, necessitating ventilation. The increase in asthma premenstrually does not appear to respond well to corticosteroids, even in high doses, yet responds well to high doses of progesterone (561). This suggests that there is a form of steroid resistance that is regulated by the levels of endogenous female sex hormones. The mechanisms whereby a fall in progesterone and a rise in estrogen induce reduced glucocorticoid responsiveness in some women with asthma is unknown but may involve some sort of competition for GRE binding sites, since estrogen and progesterone receptors have close structural similarities with GR. Recently an interaction between the progesterone receptor and NF-κB has been described (562). This suggests that a fall in progesterone may increase NF-κB activation, but why only a small proportion of women are affected is not yet certain. It is possible that premenstrual asthma may only occur in women who already have a degree of glucocorticoid resistance.

Viral infection. It is possible that steroid resistance may evolve as a result of viral infection, since many viruses are capable of activating transcription factors that could interfere with glucocorticoid action. In children with severe steroid-dependent asthma, there is evidence for persistent adenovirus infection in the airways (563). Viruses may activate transcription factors, resulting in increased glucocorticoid resistance. The EIA protein expressed by adenoviruses binds to the anti-oncogene retinoblastoma protein, thus increasing oncogene expression, which may increase glucocorticoid resistance (564).

FUTURE DIRECTIONS

Over the last 5 yr important advances have been made in understanding the mode of action of steroids in asthma at a molecular and cellular level. There have also been changes in the way that inhaled corticosteroids have been used in asthma management, with much earlier introduction in the course of asthma therapy, their use as first-line therapy in chronic asthma and in the development of improved inhaled corticosteroids, such as BUD and FP, that have fewer systemic effects. This has led to a much wider use of inhaled corticosteroids throughout the world in adults and increasingly in children.

New Research into Steroid Mechanisms

The precise mechanism of action of steroids in controlling inflammation in asthma is still not completely understood. It is clear that corticosteroids have effects on the transcription of many genes, resulting in an increased expression of anti-inflammatory proteins and decreased expression of inflammatory proteins. There is evidence that the repression of inflammatory genes is mediated via inhibitory effects on transcription factors, such as NF-κB and AP-1, that regulate the expression of these genes, but there is increasing evidence that corticosteroids may target particular genes more effectively depending on which combination of transcription factors is involved. This may underlie the differing potency of steroids in different cell types and on different genes. Some of these complexities may be accounted for by the fact that GRs interact with other transcription factors through binding to the coactivator molecules CBP and p300 (32, 565, 566). Glucocorticoid receptor dimers bind to specific proteins called steroid-receptor coactivators (SRCs) that are constitutively bound to CBP, which regulates transcription through its association with RNA polymerase and through its intrinsic histone acetyltransferase activity (567, 568). This acetylation allows DNA to unwind from histones, around which it binds in nucleosomes, thus increasing or decreasing transcription by allowing access of RNA polymerase II and of transcription factors to their recognition element in the promoter of genes. Steroid-induced gene repression may be due to activation of enzymes that deacetylate histone, thus increasing the tightness of the DNA loops around histone (and increasing chromatin density). This would exclude the binding of transcription factors to promoter regions of inflammatory genes (569) (Figure 22). Various repressor proteins, such as N-CoR and Sin3, that may be activated by steroids have now been identified (569).

Although corticosteroids regulate the expression of multiple genes, it is important to identify the most important of these in asthma control. It is likely that many genes not yet identified are also regulated by corticosteroids and powerful molecular techniques such as polymerase chain reaction differential display should allow the identification of known and unknown genes that are switched on and off by steroids in different cell types in patients with asthma (570).

Changes in the Use of Inhaled Corticosteroids

"Start high–go low." Previous guidelines suggested that inhaled corticosteroids should be started in a low dose and progressively increased until asthma control is achieved. As inhaled corticosteroids have a slow onset of action, patients who are not controlled lose confidence in the treatment, and this is likely to decrease compliance. It would be more sensible to start at a dose that is likely to be effective and then reduce to the minimal dose needed to maintain control (571). This approach is logical in the light of our current understanding of the mode of action of steroids. Steroids activate glucocorticoid receptors, which act as functional antagonists of transcription factors that regulate increased transcription of genes, such as inflammatory cytokines and enzymes in asthma. If there is active inflammation in the airways, the high level of transcription factors bind to GRs, so that steroids are less effective and cannot effectively gain control of the inflammatory response. Higher doses of steroids overcome this by blocking the activated transcription factors, so that more GRs are available for blocking the inflammatory response. Control can then be maintained with lower doses of steroids. Studies demonstrate that the dose of inhaled corticosteroid can be reduced once control is achieved (228, 281). A recent study lends support to this

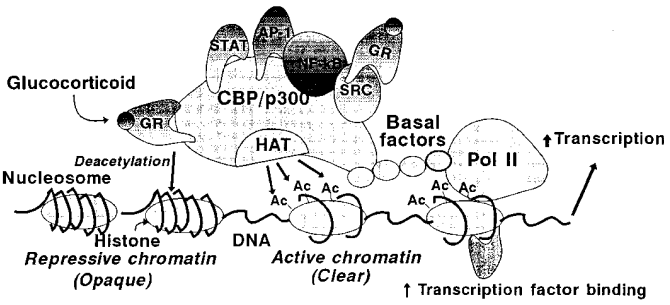

Figure 22. Effect of steroids on chromatin structure. Inflammatory signals may activate transcription factors, such as NF-κB, AP-1, and STATs (signal transduction-activated transcription factors), which all bind to CREB-binding protein (CBP), which has intrinsic histone acetyl-transferase (HAT) activity. Acetylation of histone (Ac-) in the chromatin structure leads to unwinding of DNA, thus allowing access to transcription factors that increase inflammatory gene expression. Corticosteroids activate glucocorticoid receptors that bind to a steroid receptor co-activator (SRC), which results in deacetylation of histone, tightening up DNA coiling (repressive chromatin), restricting access of transcription factors and thus leading to gene repression.

strategy (572). Similar data are available in children (180), but further controlled studies are needed. The "start high–go low" approach is recommended in the recent revision of the British Thoracic Society Guidelines for Asthma Management (573) and in the recent U.S. guidelines (574). It may be seen as similar to the treatment of hematologic malignancies, when there is an initial induction phase but, once in remission, therapy is switched to maintenance therapy to maintain control.

Most patients should be started on inhaled corticosteroids at a dose of 400 μg twice daily and should be treated with this dose for at least 3 mo (as this is the time when maximal benefit of the inhaled corticosteroid is obtained). The dose of inhaled corticosteroid should then be reduced according to a simple step-down regimen. In a few patients, the initial dose of steroids may be too low and it may be necessary to increase the dose. In patients with more severe asthma it is necessary to start treatment with oral steroids in order to obtain control initially; inhaled corticosteroids should be started at the same time. It is of utmost importance to establish optimal lung function for each patient so that this value can be used to judge subsequent control. It may be that even higher doses of inhaled corticosteroids are justifiable in the initial assessment of asthma to establish the maximal achievable lung function, but it is important that this dose is then tapered down to the lowest dose needed to maintain this level of control.

Earlier introduction of inhaled corticosteroids. There is persuasive evidence that introduction of steroids as soon as possible after diagnosis of asthma results in better lung function and reduced bronchial hyperreactivity than when inhaled corticosteroids are delayed. Further longer term, controlled studies are needed to confirm these important observations. At present it is recommended that inhaled corticosteroids be introduced when patients have symptoms on a daily basis or when they use short-acting inhaled β_2-agonists more than three times a week. It has been suggested, however, that inhaled corticosteroids might be introduced even earlier in the course of asthma, as soon as asthma is diagnosed, since there is evidence that even in patients who have episodic asthma the airways are inflamed. This has led to establishment of a large, multicenter, international placebo-controlled trial to evaluate the efficacy of introducing inhaled corticosteroids early in children and adults with asthma (START). There is no evidence to date that inhaled corticosteroids are curative or modify the natural history of the disease, but it is possible that their earlier introduction might have such an effect.

Asthma often begins during the first 3 yr of life. However, only about one-third of the 40% of children younger than 3 yr who wheeze suffer from asthma. The majority of the remaining two-thirds have virus-induced wheeze that will disappear after age 3. Further studies are needed to know how inhaled corticosteroids are best used in these age groups. These studies must include both efficacy and safety parameters and preferably should be long term.

Monitoring corticosteroid effects. Traditionally, control of asthma is monitored by asthma symptoms, measurement of diurnal variability of PEF, and the use of rescue inhaled β_2-agonists. These are taken as surrogate markers of airway inflammation. However, it is not certain whether these clinical measurements reflect control of inflammation, and this has led to a search for noninvasive markers of inflammation that may be independent of lung function, such as exhaled NO, induced sputum cytology, and exhaled condensate (146, 575, 576). There appear to be some correlations between exhaled NO, sputum and airway mucosal eosinophils, and airway responsiveness, but the correlations are not close (291, 577). Airway hyperresponsiveness has also been used as a measure of asthma inflammation. In a recent controlled study looking beyond symptom control to the treatment of methacholine reactivity, the use of higher doses of inhaled corticosteroids resulted. A reduced frequency of asthma attacks and better asthma control based on peak flow variability was also seen (578).

New Inhaled Corticosteroids

Currently available inhaled corticosteroids are highly effective and have a good margin of safety. However, there is room for improvement in existing drugs, and there are several new steroids in development. Mometasone furoate is a highly potent topical steroid that was developed initially as a dermatologic therapy and has now been shown to be effective in controlling rhinitis when given once daily (579). It is also under evaluation in the treatment of asthma. RP-106541 is another promising new steroid in development.

The recognition that corticosteroids may control inflammation predominantly through suppression of transcription factors may also provide the opportunity for the development of novel anti-inflammatory steroids. It seems likely that the side effects of steroids are largely due to *trans*-activation of genes through binding of the GR dimers to DNA, whereas the anti-inflammatory effects may be due to binding of a single GR to activated transcription factors, such as AP-1, NF-κB, or the co-activator CBP, resulting in gene repression (Figure 23). Some steroids appear to discriminate between these effects; thus, mifepristone and ZK 982993 have a greater potency against *trans*-repression than *trans*-activation (9). Preliminary evidence suggests that both FP and BUD have a greater potency in *trans*-repression than *trans*-activation (580). It is possible that in the future steroids that show an even greater differentiation of these effects might be developed.

The area where most improvement in steroids has been seen is in the development of drugs with greater first-pass hepatic metabolism (FP, BUD, and mometasone), thus reducing systemic absorption from the gastrointestinal tract. However, all of these steroids are still absorbed from the respiratory tract into the systemic circulation. Development of steroids that are inactivated systemically is therefore desirable. It is possible that inhaled corticosteroids may be developed that

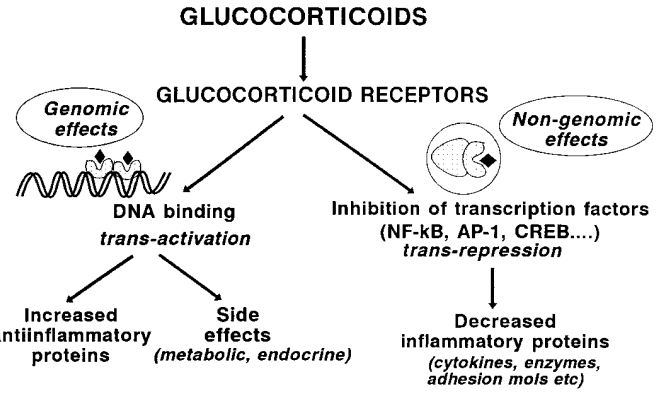

Figure 23. The effects of corticosteroids may be mediated by *trans*-activation with DNA binding and by *trans*-repression, due to inhibition of transcription factors, such as NF-κB, AP-1, etc. Side effects may be mediated predominantly by *trans*-activation and anti-inflammatory effects by *trans*-repression, so it may be possible to design novel steroids that are safer by favoring *trans*-repression over *trans*-activation.

have a potent topical anti-inflammatory effect but are degraded by enzymes of circulating cells such as erythrocytes or leukocytes. Another approach is more selective targeting of inhaled corticosteroids by the use of liposomes (407).

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