Lung function and immunopathological changes after inhaled corticosteroid therapy in asthma

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ABSTRACT: Six patients with asthma (American Thoracic Society (ATS) criteria), maintained on inhaled beta-agonists alone, were treated with inhaled corticosteroid (budesonide 400 μg b.d.) for a period of three months. Prior to steroid therapy, baseline spirometry, bronchodilator response and bronchial hyperresponsiveness were documented and endobronchial biopsies were obtained for immunopathological analysis. Frozen sections of the biopsies were investigated using immunoperoxidase methods, with a panel of monoclonal antibodies selected to reveal the presence and distribution of lymphocyte and macrophage subsets and HLA-DR expression. After three months the studies were repeated.

Studies before steroid therapy revealed a T-cell-dominated inflammation in the bronchial wall of all subjects. Baseline airway obstruction, median (range) forced expiratory volume in one second (FEV) 78.5 (61-109)% of predicted, with a significant bronchodilator response 20.8 (14-33)% and bronchial hyperresponsiveness to histamine geometric mean (sd) PC_{20}FEV_{1} 0.69 (2.5) mg was documented.

Steroid therapy caused a significant reduction in bronchial hyperresponsiveness to histamine, with an increase in geometric mean PC_{20}FEV_{1} to 2.22 (3.2) mg post steroid (p<0.03). Concurrent with a reduction in bronchodilator response and an increase in spirometric variables (improved forced mid-expiratory flow (PEF_{50-75}) p<0.03), there were marked reductions observed in the overall numbers of T-lymphocytes (CD 2, 5, 8), the numbers of CD45RO+ T-cells, and the numbers of macrophages (RFD1+) with the phenotype of antigen presenting cells. In all six subjects, reductions in the quantitative expression of HLA-DR molecules were also seen.

These preliminary results demonstrate that inhaled steroid therapy in asthmatics significantly reduces both the underlying T-cell-dominated inflammation in the bronchial wall and the bronchial hyperresponsiveness in these patients. These data go some way to explaining the efficacy of corticosteroids in this condition.

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Although recognized in about 7% of the population of industrialised countries [1], bronchial asthma is probably underdiagnosed and undertreated [2]. Recent evidence suggests the prevalence and severity of asthma may be increasing [3] and there is also a marked increase in the prescription of drugs for this condition [4]. Increasing disease severity despite increased drug usage suggests that the current treatment of asthma is suboptimal. These considerations, together with recent data suggesting increased asthma mortality [5], highlight the necessity to unravel the pathophysiology of the condition and the mechanism of action of currently available drugs.

Asthma was long considered to be a disease of airway smooth muscle and treatment was directed towards bronchodilation. More recently, the importance of airway inflammation has been recognized [6] and current research is directed at unravelling the precise mechanisms of this inflammatory reaction. We have recently documented a cell-mediated immune response in the asthmatic airway [7] comprising activated lymphocytes and macrophages and have proposed that the presence of this inflammatory reaction may explain the "chronicity" of asthma in many patients.

More specifically, one manifestation of this cell-mediated immune response, (raised expression of HLA-DR in the bronchial wall) was significantly correlated with the degree of bronchial hyperresponsiveness quantified in asthmatic patients as graded by challenge with nebulized histamine, (r=0.84, p<0.001). This relationship constitutes cogent evidence to support the concept that this cell-mediated immune response predisposes asthmatics to bronchial hyperresponsiveness [7].
Parenteral or oral corticosteroids have been the mainstay of treatment for severe asthma for decades and more recently inhaled corticosteroids have been increasingly used with good effect in asthma of moderate severity [8]. However, the mode of action of corticosteroids in bronchial asthma is not fully understood. This study investigates the effects of corticosteroids on the cell-mediated immune response in the airways of asthmatic patients by recording both physiological and immunopathological variables before and after inhaled corticosteroid treatment. In this way, the hypothesis that the well-proven efficacy of corticosteroids in asthma results, at least in part, from a reduction in the T-cell-mediated immune reactivity in the bronchial walls is tested.

Patients and methods

Six patients were investigated after giving informed consent. The study was approved by the James Connolly Memorial Hospital Ethics Committee. In each case, asthma was diagnosed on the basis of American Thoracic Society criteria [9]. All patients were maintained on beta₂-agonist inhalers, as required for symptomatic relief, and none had received either inhaled or oral corticosteroid treatment or any other drugs for their asthma prior to the present study. None of the patients had a history of respiratory tract infection or acute exacerbation of symptoms for at least two months prior to the study. Chest radiograph on entry was normal in all patients. Median (range) age of the patients was 38.5 (22–63) yrs. Five patients were nonsmokers and one smoked 10 cigarettes daily for the past ten years. Median (range) duration of asthma in the group was 3 (0.5–18) yrs. Three of the six patients were atopic (i.e. showed a positive skin prick response to a battery of eight common antigens, including house dust, house dust mite and mixed pollens). Three of the group had a positive history of asthma in first degree relatives.

Physiology

Baseline pulmonary function tests were recorded at 9.00 a.m. on day 1 of the protocol, using a Gould 2400 computerized system, and the best of three valid attempts was recorded. All patients abstained from their inhalers and from caffeine containing food and beverages for 12 h prior to the study. A standardized bronchial provocation protocol was performed [10] after completing baseline spirometry.

After initial nebulized saline challenge, doubling doses of histamine were administered via a nebuliser (Hudson) driven by oxygen at 7 l·min⁻¹. The aerosols were delivered straight into a face-mask and inhaled by quiet tidal breathing for 2 min. The initial dose of histamine was 0.03 mg. Spirometry was recorded at 30 s and then every 60 s until a 20% fall in forced expiratory volume in one second (FEV₁) was achieved or the FEV₁ returned towards baseline. The provocative concentration of histamine required to reduce the FEV₁ by 20% (PC₂₀ FEV₁) was obtained from a dose response curve. The 20% drop in FEV₁ was calculated using the FEV₁ recorded after three technically correct manoeuvres post-nebulized saline (control).

Computerized spirometry was repeated 24 h later and on this occasion bronchodilator response to inhaled salbutamol (400 μg by metered dose inhaler via a volumatic spacing device) was determined. Spirometry was recorded after 5 min and then every 15 min for 60 min after salbutamol inhalation and the maximum recorded increment in FEV₁ over baseline was used to calculate the bronchodilator response.

Bronchoscopy

Fibreoptic bronchoscopy (Olympus BF10) was performed 2 h after salbutamol inhalation. Premedication was with pethidine 50 mg, promethazine 25 mg and atropine 0.6 mg, by i.m. injection 1 h prior to the procedure.

Local anaesthesia of the airways was obtained with 4 puffs of 10% xylocaine (Astra) aerosol spray (10 mg/puff) applied to the vocal cords and then afterwards with 0.5% lignocaine in 5 ml aliquots as required for airway anaesthesia. Endobronchial biopsy specimens (minimum 2, maximum 4) were taken from sub-segmental bronchi of the right lower lobe in all bronchoscopies using standard Olympus cupped forceps, in identical fashion at each bronchoscopy.

Specimen preparation

The specimens were placed on cork disc, covered in O.C.T. medium, snap frozen in isopentane chilled by suspension in a bath of liquid nitrogen. The frozen specimens were stored at -70°C until analysis. All specimens were cut within one month of freezing. Histological staining (haematoxylin and eosin) was performed on sections from all biopsies. Sections from a representative biopsy were subjected to immunopathological analysis.

Immunopathological analysis

Six micron cryostat sections were cut, air dried for 30 min and then fixed in a 1:1 mixture of chloroform/acetone for 5 min. Toluidine blue (pH 6.5) and haemotoxylin with eosin staining were used to demonstrate histological features. Specific cell types were identified using indirect immunoperoxidase methods [11]. The monoclonal antibodies used were T mix (CD 2, 5, 8), B mix (CD 19, 20), CD45RO (memory T-cells) [12], RFD7 (mature tissue macrophages), RFD1 (interdigitating cells and some B-cells) [13] and RFD1R (HLA-DR) molecules [14]. All test reactions were accompanied by negative controls omitting primary layer reagents (to identify endogenous peroxidase), and positive reagent controls were concurrently performed on sections of human palatine tonsil.
All immunoperoxidase preparations were counterstained with haemotoxylin, with the exception of RFDR1 stains which were not counterstained but used for quantification of optical density. Immunoperoxidase reactions were examined using Bright Field illumination.

The number of positive cells were quantified using an image analysis system (Seescan, Cambridge) and the presence and distribution of T-cells, B-cells and macrophage subsets was assessed per unit area (cells per $10^4 \mu m^2$) [15]. HLA-DR expression was quantified by optical density in framed areas of tissue. A minimum of 3 and maximum of 10 fields were analysed on each section. Frames were drawn on the images so that areas of muscle, oedema or damage were not included. The number of positive cells were then point counted in these framed areas. In the majority of cases this analysis covered all of the appropriate areas of the sections which were on average approximately 1 mm$^2$.

Steroid therapy

After the first bronchoscopy, the patients were given budesonide via metered dose inhalers and instructed in their use with a nebulizer spacing device. All six patients were prescribed 400 $\mu g$ (2 puffs) b.d. of budesonide via a nebulizer for a period of three months.

In addition to budesonide, the patients were instructed to continue taking beta$_2$-agonist inhalers for symptomatic relief in similar fashion to their practice before the commencement of the study.

The patients were reviewed in the out-patients department monthly, or sooner if requested by the patient. At the end of three months, the pulmonary function tests, bronchial biopsy, (from the same lung) and immunopathological studies were repeated as outlined above.

Statistics

Wilcoxon matched pairs signed rank test was calculated for all data in accordance with standard statistical practice. All immunopathological studies were performed on coded samples without prior knowledge of the therapeutic or physiological status of the patients.

Historical data [15], on the distribution of immunocompetent cells in normal tissues is included to indicate the relationship between cell proportions in asthmatics before and after steroids and relative values obtained in this laboratory from samples of normal lung.

Results

Physiology

Baseline spirometric variables expressed as % predicted values included a median (range) forced vital capacity (FVC) of 98 (62-113)%; FEV$_1$, of 78.5 (61-109)% and an forced mid-expiratory flow (FEF$_{25-75}$) of 44 (37-61)% with an FEV$_1$/FVC ratio of 66% (60-76). Median bronchodilator response to salbutamol was 20.8 (14-33)% of baseline FEV$_1$ (table 1). All patients demonstrated marked bronchial hyperresponsiveness to histamine with a geometric mean (so) PC$_{20}$FEV$_1$, of 0.69 (2.5) mg (table 2). Thus, on entry to the study the patients exhibited mild airway obstruction with a clinically significant bronchodilator response and marked bronchial hyperresponsive-ness to histamine.

Table 1. - Baseline pulmonary function test

<table>
<thead>
<tr>
<th>Subject</th>
<th>FVC % pred</th>
<th>FEV$_1$ % pred</th>
<th>FEV$_1$ %</th>
<th>FEV$_1$/FVC</th>
<th>FEF$_{25-75}$ % pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>61</td>
<td>32</td>
<td>75</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>72</td>
<td>33</td>
<td>66</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>111</td>
<td>109</td>
<td>22</td>
<td>60</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>92</td>
<td>79</td>
<td>14</td>
<td>76</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>104</td>
<td>78</td>
<td>18</td>
<td>62</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>113</td>
<td>90</td>
<td>19.6</td>
<td>66</td>
<td>61</td>
</tr>
</tbody>
</table>

Mean 94.3 81.5 23.1 67.5 46.5
sp 19.4 16.5 7.8 6.6 9.6
Median 98 78.5 20.8 66 44
Range (62-113) (61-109) (14-33) (60-76) (37-61)

*: percentage change after 400 $\mu g$ salbutamol (metered dose inhaler with volumetric spacing device). FVC: forced vital capacity; FEV$_1$: forced expiratory volume in one second; FEF$_{25-75}$: forced mid-expiratory flow.

Table 2. - PC$_{20}$FEV$_1$, before (B) and after (A) inhaled steroids

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>B</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.7</td>
<td>0.83</td>
</tr>
<tr>
<td>2</td>
<td>0.75</td>
<td>2.8</td>
</tr>
<tr>
<td>3</td>
<td>0.06</td>
<td>0.22</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>1.9</td>
<td>3.5</td>
</tr>
<tr>
<td>6</td>
<td>0.45</td>
<td>3.85</td>
</tr>
</tbody>
</table>

Geometric mean (so) 0.69 (2.5) 2.22 (3.2)
Median 0.72 3.2
Range (0.06-4) (0.22-18)

Comparison of PC$_{20}$ before and after steroids for each subject by Wilcoxon matched pairs signed rank test p<0.03. FEV$_1$, forced expiratory volume in one second; PC$_{20}$FEV$_1$: provocative concentration histamine (mg·ml$^{-1}$) producing a 20% fall in FEV$_1$.

Post budesonide, spirometric values (FVC, FEV$_1$, FEV$_1$/FVC ratio) were not significantly changed but FEF$_{25-75}$ was improved in all patients, from a median 44 (37-61)% to 55.2 (10.49)%; p<0.03 (fig. 1). Bronchodilator response was reduced from median (14-33)% to 11.5 (5-30)% but the difference did not reach statistical significance. There was also a highly significant reduction in bronchial hyperresponsiveness to histamine after treatment, PC$_{20}$FEV$_1$, rising from a geometric mean of 0.69 (2.5) mg to 2.2 (3.2) mg; p<0.03 (fig. 1 and table 2).
served

oid therapy and in two cases no CD45RO+ cells were

cells than in normal bronchial tissue.

reduction in CD45RO+ cells

the six subjects constituted a higher proportion of

reduction in the numbers of infiltrating T-cells was

controls were stained using an identical procedure). All

all specimens showed infiltration of the lamina propria

features precludes detailed study of mast

cells and eosinophils. No more than two of these cells

identified but no epithelioid or giant cells were present.

Two lymphocytes and macrophage-like cells were

propria with mononuclear cells in all biopsies.

Bronchoscopy

Gross findings at bronchoscopy of mucosal hyper-
aemia, oedema and friability were similar on inspec-
tion of the airways both before and after steroid

Histology

Haematoxylin with eosin and toluidine blue staining

of frozen sections showed infiltration of the lamina

pris with mononuclear cells in all biopsies. Both

lymphocytes and macrophage-like cells were

identified but no epithelioid or giant cells were present.

The use of fresh, frozen material without basic lead

acetate fixation precludes detailed study of mast

cells in any of the six subjects [15]; signed rank test

of 3 areas measured; t: taken from a previous study of

five normal biopsies [15] not

repeated here. Wilcoxon matched pairs signed rank test p<0.03

for all T-cells), p<0.03 (CD45RO+ cells).

Small numbers of RFD1+ cells were present in the

biopsies from all six subjects prior to steroid therapy

(table 4). Although a minor population here, i.e.

<50%, cells of this phenotype are absent from normal

bronchial tissue. Compared to normal, larger numbers

of RFD7+ cells were also present in the bronchial

biopsies of all the asthmatic subjects. After steroid

therapy the numbers of RFD1+ cells were reduced in

five out of six subjects, yet identifiable numbers of

these cells remained (p<0.03). In contrast, the numbers

of RFD7+ cells were seen to be increased after

steroids in five out of six subjects, although this

change did not reach statistical significance (p>0.05).

One case showed a reduction in the distribution of

RFD7+ cells back to the normal range (table 4).

Table 3. Distribution of T-lymphocytes in the bronchial

wall before (B) and after (A) three months inhaled steroid

therapy

<table>
<thead>
<tr>
<th>Subject</th>
<th>All T-cells (CD 2, 5, 8)</th>
<th>CD45RO+ T-cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>1</td>
<td>11.9±2.5*</td>
<td>1.1±1.1</td>
</tr>
<tr>
<td>2</td>
<td>13.7±0.5</td>
<td>3.1±0.6</td>
</tr>
<tr>
<td>3</td>
<td>6.2±0.5</td>
<td>5.2±2.0</td>
</tr>
<tr>
<td>4</td>
<td>10.2±0.4</td>
<td>1.9±1.0</td>
</tr>
<tr>
<td>5</td>
<td>4.7±0.1</td>
<td>4.5±0.6</td>
</tr>
<tr>
<td>6</td>
<td>7.5±2.3</td>
<td>1.7±0.2</td>
</tr>
<tr>
<td>Median</td>
<td>8.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Range</td>
<td>4.7-13.7</td>
<td>1.1-5.2</td>
</tr>
</tbody>
</table>

*: Inhaled budesonide for 3 months (see methods for details); *: cells per $10^4 \mu m^2$. Means±3 areas measured on each section;

*: taken from an earlier study of five normal biopsies [15] not

repeated here. Wilcoxon matched pairs signed rank test p<0.03

(All T-cells), p<0.03 (CD45RO+ cells).

Table 4. Distribution of macrophage subsets in the bronchial wall before (B) and after (A) three months inhaled steroid therapy

<table>
<thead>
<tr>
<th>Subject</th>
<th>RF-D1+ dendritic cells</th>
<th>RF-D7+ phagocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>1</td>
<td>1.2±1.1*</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>2</td>
<td>2.1±0.5</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>3</td>
<td>2.5±0.1</td>
<td>0.6±0.2</td>
</tr>
<tr>
<td>4</td>
<td>2.4±1.0</td>
<td>2.5±0.8</td>
</tr>
<tr>
<td>5</td>
<td>0.4±0.6</td>
<td>0.3±0.1</td>
</tr>
<tr>
<td>6</td>
<td>3.3±0.5</td>
<td>1.5±0.8</td>
</tr>
<tr>
<td>Median</td>
<td>2.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Range</td>
<td>0.4-3.3</td>
<td>0.3-2.5</td>
</tr>
</tbody>
</table>

*: only one area measured; *: positive cells per $10^4 \mu m^2$ means±3

areas measured; #: taken from a previous study of 5 normal

subjects [15]; NPC: no positive cells. Wilcoxon matched pairs

signed rank test p<0.03 (D1), p>0.05 (D7).

The levels of HLA-DR expression by inflammatory

cells in the lamina propria and the epithelium were

quantified by optical density on biopsies taken prior
to budesonide therapy. All patients exhibited raised
levels compared to normal, which show little or no HLA-DR expression (table 5). HLA-DR expressed in biopsies taken after steroid therapy also recorded and optical density of this reaction was found in all six cases to be lower than that recorded prior to steroids (fig. 2), although still higher than normal. These changes were found to be significant to a level of p<0.03.

Table 5. — HLA-DR expression on the bronchial wall including the inflammatory infiltrate, measured as relative density per unit area, before (B) and after (A) inhaled steroid therapy

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>HLA-DR expression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td>1</td>
<td>1.6±0.4</td>
</tr>
<tr>
<td>2</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>3</td>
<td>3.1±0.3</td>
</tr>
<tr>
<td>4</td>
<td>1.5±0.3</td>
</tr>
<tr>
<td>5</td>
<td>2.3±0.9</td>
</tr>
<tr>
<td>6</td>
<td>1.6±0.4</td>
</tr>
</tbody>
</table>

Median 1.6
Range 1.2–3.1 0.7–1.4

Data are given as mean±standard deviation.
Normal HLA-DR expression in the bronchial wall 0–0.5 [7]. Wilcoxon matched pairs signed rank test p<0.03.

Fig. 2. — Relative density per unit area of HLA-DR molecules expressed by the epithelium, lamina propria and by the inflammatory cells of the bronchial wall in six asthmatic patients measured before (B) and after (A) 3 months therapy with inhaled budesonide (400 µg b.d.). Measurements recorded from immunoperoxidase staining on frozen sections using an image analysis system. Each point represents the mean of multiple areas (minimum 3, maximum 10) measured on sections of each sample. The overall size of the sections from each sample was variable but the average section size would be 1 mm².

Discussion

These results are in accordance with our previous work in demonstrating a chronic cell-mediated immune response in the bronchial walls of patients with clinically stable asthma [7]. They go further in demonstrating that efficacious therapy with inhaled corticosteroids alters all of these immunopathological features. Steroid therapy caused no significant change in spirocentric values with the exception of an increase in FEF₂₅₋₇₅ values after the 3 months' treatment. These findings are consistent with previous reports of corticosteroid treatment in asthma [16]. However, bronchial hyperresponsiveness to histamine was significantly attenuated by budesonide in our patients (p<0.03) and bronchodilator response (FEV₁) to inhaled salbutamol was reduced after budesonide treatment. These results are in keeping with a number of recent reports showing a significant reduction of bronchial reactivity in response to inhaled and oral corticosteroids [17]. However, to date there are little data available to explain how bronchial responsiveness is reduced by corticosteroids. It is clearly important to define this mechanism.

Previous studies using histological methods have described the presence of peri-bronchial inflammation in stable asthmatics [18, 19]. The use of monoclonal antibodies (MoAbs) in immunopathological analysis has allowed the dissection of this inflammatory reaction into its component parts with obvious similarities in other immune-mediated chronic inflammatory diseases [20–22]. By demonstrating, in the present study, that T-cell numbers, CD45RO+ T-cells and dendritic cells (RFDF1+) [13] are all reduced after therapy, one mode of action of inhaled steroids may be revealed. Of particular interest is the reduction in T-cells expressing CD45RO antigen. This molecule is absent on virgin T-cells only to emerge when antigenic stimulation occurs. It is within this subset that the memory cell pool is said to reside. The CD45RO+ molecule is a protein tyrosine phosphatase [23], thought to be essential as a receptor for ligands as yet ill-defined, that promote secondary T-cell responses [24]. The presence of high numbers of CD45RO+ cells, therefore, may be the aberrant feature promoting the chronicity of bronchial inflammation in asthmatics. If this is the case, it would follow that any compound that significantly reduces the numbers of CD45RO+ cells in the bronchial wall might also prove clinically efficacious. For this hypothesis to hold, it is also necessary to establish a direct link between the bronchial T-cell-mediated inflammation in these patients and the bronchial hyperresponsiveness characteristic of asthmatics. This link is found in the level of HLA-DR molecules expressed by the epithelium and inflammatory cells in the asthmatic airways.

Previous studies from this laboratory have revealed a close correlation between raised HLA-DR expression (one manifestation of type IV hypersensitivity) and bronchial hyperresponsiveness [7].
The data presented here show a concurrent reduction in HLA-DR expression and bronchial responsiveness, and thus establish a possible basis for the known efficacy of steroid therapy. It is interesting to note that in vitro studies in this laboratory have demonstrated that culture of alveolar macrophages with physiological concentrations of budesonide causes a significant reduction in HLA-DR expression (Marienayagan and Poulter, submitted, 1990), thus suggesting that the inhaled steroids could have a direct effect on Class II major histocompatibility complex (MHC) antigen expression by the infiltrating cells.

Although our patients were not homogeneous, in that their age, duration of asthma, atopic status, smoking status, and family history of asthma were not uniform, five out of six individual patients demonstrated a significant reduction in both bronchial hyperresponsiveness and airway inflammation. In one patient, bronchial hyperresponsiveness changed only slightly. Although the limited range of the study group may have mitigated against recognition of a differential effect of corticosteroid in atopic or smoking subjects, close scrutiny of our data does not show any such effects. The finding of global efficacy of corticosteroids in this series, despite their individual heterogeneity, is in keeping with clinical experience in a wide variety of patients with asthma, all of whom respond to corticosteroids with few exceptions.

Our data do not conflict in any way with the well-documented importance of type I hypersensitivity responses in acute asthma [25]. We deliberately selected patients free of clinical exacerbations for at least two months in order to exclude the confounding effect of acute type I-associated bronchospasm. However, it is now well-documented that T-cells can release factors chemotactic for granulocytes [26] and, thus, the T-cell infiltration seen prior to therapy may predispose to the recruitment of mast cells and eosinophils, by T-lymphocytes, on exposure to the appropriate antigen. It follows, therefore, that reduction in T-cell reactivity could lead to reduced granulocyte-mediated responses. Because our methods (in particular the use of frozen section specimens) are sub-optimal for the recognition and study of eosinophils and mast cells, the effects of budesonide therapy on these parameters remain to be tested.

In summary, our results demonstrate significant reduction in bronchial hyperresponsiveness in asthmatic patients following 400 μg b.d. of inhaled budesonide, for a period of three months, that is associated with a concurrent reduction of a peri-bronchial, cell-mediated immune response. We therefore suggest that the well-documented efficacy of corticosteroids in asthma may, at least in part, be related to a local immunomodulating effect on the T-cell-mediated reaction in the airways of asthmatic patients.

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References


