Failure of Inhaled Corticosteroids to Modify Bronchoconstrictor or Bronchodilator Responsiveness in Middle-Aged Smokers with Mild Airflow Obstruction

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We have compared the effects of three-month periods of treatment with an inhaled corticosteroid, budesonide 600 
µg twice daily and with placebo on bronchial responses to inhaled histamine and to bronchodilators in a double-blind crossover trial in 14 middle-aged male smokers (mean age, 59.6 years) with mild airways obstruction (mean FEV₁ 2.42 L, 80 percent predicted [range, 48 to 110 percent]). Responsiveness to inhaled histamine was assessed monthly by the provocative concentration (mg/ml) reducing FEV₁, by 20 percent (PC20). Bronchodilator response to a combination of inhaled salbutamol (5 mg) and ipratropium (0.5 mg) was assessed before and after three months’ treatment. Compliance with treatment was checked by weighing aerosol canisters, and by measuring plasma budesonide and metabolites. There was no significant change in FEV₁ (budesonide mean 2.38 L [SEM 0.17] vs placebo 2.40 L [0.17]), vital capacity (budesonide mean 3.69 L [0.17] vs placebo 3.81 L [0.17]) or in bronchodilator responsiveness (mean increase over baseline FEV₁, budesonide 11.6 [2.7] percent vs placebo 10.5 [3.2] percent). There was a small overall reduction in bronchoconstrictor responsiveness over the period of the trial, but there was no effect of 12 weeks of budesonide treatment compared with 12 weeks of placebo treatment (mean log PC20 during budesonide 0.595 [SEM 0.063], placebo 0.591 [SEM 0.053]). Following the three-month crossover trial, six men continued for nine more months to receive budesonide in a single-blind trial and the results were compared with those in six men who took no active treatment for the subsequent nine months. No improvements in baseline spirometry, home peak flow measurements, bronchoconstrictor or bronchodilator responsiveness were observed after 12 months of budesonide treatment. Thus, a regimen of budesonide treatment that consistently attenuates bronchial responsiveness in asthmatic subjects had no effect in these men; larger and longer trials will be required to establish whether a subgroup of smokers shows a favorable response.

(Chest 1992; 101:350-55)

In subjects with asthma, inhaled corticosteroids consistently attenuate nonspecific bronchial hyperresponsiveness (BHR) to inhaled bronchoconstrictor drugs such as histamine or methacholine. In contrast, there is much less information on the effects of inhaled corticosteroids on BHR in nonasthmatic smokers even though corticosteroids are frequently used empirically in the treatment of smokers with chronic obstructive pulmonary disease (COPD). Two recent studies have failed to show any change in BHR associated with this treatment in patients with COPD.

We have performed a double-blind crossover trial of the effects of inhaled corticosteroids on (1) bronchial responsiveness to inhaled histamine and to inhaled bronchodilators and (2) baseline spirometry and peak flow measurements in 14 middle-aged male smokers with BHR and mild-to-moderate airflow obstruction. After the double-blind trial over six months, 12 of the men continued for an additional nine months in an open trial of budesonide or placebo to obtain pilot information on longer-time effects. Preliminary results of this trial have been reported.

MATERIALS AND METHODS

Subjects

Fifteen middle-aged male smokers with measurable BHR to inhaled histamine without overt asthmatic features were recruited from those attending a long-term follow-up study of the effects of smoking started in 1974; their rate of change in FEV₁ over the preceding 12 years was therefore known. At initial recruitment and at subsequent follow-up, all men were encouraged to give up smoking. These men were found to have BHR to inhaled histamine in 1982. In that study the majority of smokers, exsmokers, and never-smokers were not responsive to the doses of histamine used. Men with episodic wheezing attacks occurring at rest, or at night, men who had been receiving bronchodilator treatment, or men who had ever received the diagnosis of asthma were excluded from the study; because positive skin tests to common aeroallergens are found in about a third of the general population, these were not used to exclude subjects. Mean carbon monoxide transfer coefficient was slightly reduced at 1.27 (SEM, 0.06; range, 1.0 to 1.7) mmol/min × kPa−1 × l−1. Skin reactivity to extracts from nine commonly inhaled antigens (grass pollen, cat and dog dander, mixed feathers, Alternaria sp, Cladosporium sp, Aspergillus fumigatus, house dust, and Dermatophagoides pteronyssinus) was assessed by

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Table 1—Summary of Data

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Height, m</th>
<th>Smokers, cig/day</th>
<th>FEV₁ L</th>
<th>%pred</th>
<th>FEV₁ Post bd L</th>
<th>%Response</th>
<th>1974-1986 ΔFEV₁/HR, ml/min</th>
<th>Histamine, mg/ml</th>
<th>PC20 Positive Skin Tests</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>1.71</td>
<td>30</td>
<td>57</td>
<td>2.34</td>
<td>72</td>
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<td>26</td>
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</tr>
<tr>
<td>2</td>
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<td>1.79</td>
<td>18</td>
<td>34</td>
<td>2.54</td>
<td>75</td>
<td>2.87</td>
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<td>4.5</td>
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<td>5.2</td>
</tr>
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<td>4</td>
<td>66</td>
<td>1.67</td>
<td>20</td>
<td>45</td>
<td>2.92</td>
<td>110</td>
<td>3.12</td>
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<td>5</td>
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<td>12</td>
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<td>55</td>
<td>1.51</td>
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<td>2.0</td>
</tr>
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<td>65</td>
<td>1.72</td>
<td>20</td>
<td>49</td>
<td>1.59</td>
<td>55</td>
<td>2.04</td>
<td>28</td>
<td>10.0</td>
<td>0.7</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>1.72</td>
<td>45</td>
<td>94</td>
<td>2.04</td>
<td>66</td>
<td>2.32</td>
<td>14</td>
<td>21.2</td>
<td>0.9</td>
</tr>
<tr>
<td>9</td>
<td>55</td>
<td>1.68</td>
<td>30</td>
<td>49</td>
<td>2.12</td>
<td>70</td>
<td>2.42</td>
<td>14</td>
<td>17.3</td>
<td>1.6</td>
</tr>
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</table>

Mean (SEM) (1.3) (0.17) (2.7) (5.0) (0.15) (5.0) (0.13) (2.3) (1.49)

*Geometric mean.

prick tests in forearm skin. The response to the test was recorded as positive when the mean wheel diameter was more than 2 mm. Because the trial was to extend over the period January to July, men with nasal sensitivity to pollen (as judged by history or positive skin tests) were excluded.

After the first month, one man who was not complying with treatment withdrew due to lack of time to attend the laboratory. The remaining 14 men completed the six-month trial. Their age, smoking habit, baseline spirometry, bronchial responsiveness, preceding decline in spirometry, skin test results, and drug treatment are summarized in Table 1. Five men were being treated with cardioselective β-blocking drugs for mild hypertension that were continued in unchanged dosage throughout the trial. None was receiving bronchodilator drugs or other treatment. Their mean height-corrected decline in FEV₁ over the 12 years preceding the trial was considerably accelerated, and was three times that found in a group of never-smokers followed concurrently.17

Measurements

At recruitment for this trial, a detailed questionnaire was applied to establish respiratory symptoms, smoking habits, and any history of asthma or allergic disease. At subsequent visits, a separate questionnaire was applied to detect any change in symptoms, smoking habits, treatment, or any recent upper or lower respiratory tract infection or side effects. At each visit fractional concentration of mixed expired carbon monoxide (FeCO) was measured during a period of quiet breathing to corroborate stated smoking habit. No subjects were studied within six weeks of a significant upper or lower respiratory tract infection. If an infection developed, measurements were postponed appropriately and the treatment arm extended.

Forced expiratory volume in 1 s (FEV₁) was measured in the standing position with a dry bellows spirometer that was calibrated daily. The highest FEV₁, from three technically satisfactory forced expiration attempts at BTS was taken as the baseline and compared with reference values.9 The provocative concentration of inhaled histamine reducing FEV₁ by 20 percent (PC20) was then determined with the same equipment and technique as was used in the 1982 study.10 Subjects wore a noseclip and inhaled a 0.9 percent saline solution followed by doubling concentrations of histamine diphosphate (0.5 to 32 mg/ml) generated by a compressed air-driven nebulizer (Wright) at a flow rate of 7.5 L/min through a mouthpiece during tidal breathing for 2 min. The output of the nebulizer, which was checked regularly, was 0.14 ml/min. FEV₁ was recorded at 60, 90, and 180 s. In occasional tests where the value at 180 s was lower than at 90 s, another measurement was made at 5 min to be sure the lowest value was obtained after each inhalation. The challenge was terminated when FEV₁ fell below 20 percent of the lowest post-saline solution value or the 32 mg/ml concentration of histamine was reached. The PC20 histamine was determined by linear interpolation from a log dose-response curve.

After recovery from the effects of histamine, the bronchodilator response was assessed. A solution containing 5 mg of salbutamol and 0.5 mg of ipratropium bromide in isotonic solution was nebulized and inhaled via a mouthpiece and the change in FEV₁, was measured 60 min later.

During the last four weeks of each treatment period, morning and evening peak flow measurements were made at home using a peak flow gauge (Wright).

Venous blood was drawn for total white blood cell (WBC) counts, eosinophil count, and total IgE levels at recruitment and at the end of the 12-week treatment periods with budesonide or placebo. Blood budesonide levels were also checked by a radioimmunounassay technique at the end of each treatment period.

Treatment

Identical canisters with extension tubes which contained either budesonide (200 μg/puff) or placebo were used at a dosage of three puffs twice a day. The dosage of budesonide (600 μg twice daily) was judged to be the largest dose that could be given without producing significant hypothalamic-pituitary-adrenal suppression. Compliance with treatment was checked by weighing canisters at each visit and after 12 weeks of each treatment by measuring plasma budesonide levels in peripheral venous blood.

Design and Analysis of Double-Blind Crossover Trial

After initial measurements, the men started on a 12-week period of treatment with four-weekly laboratory visits. For the last four weeks (weeks 9 to 12) of each treatment, twice daily peak expiratory flow measurements were made at home. All PC20 values were logarithmically transformed before any calculations. The double-blind, two-period, crossover trial was analyzed for a quantitative response and for interactions between treatment and period as set out in the full description of Hills and Armitage.14

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Single-Blind Follow-up

At the last visit of the six-month crossover trial, the men were instructed to continue with their current treatment. The code was subsequently broken and the men continued treatment with either budesonide or placebo in a single-blind trial for the subsequent nine months with three further sets of measurements of baseline FEV₁, bronchodilator and bronchoconstrictor responsiveness at approximately every three months, and four more weeks of home peak flow measurements in the last four weeks of treatment. One man died of myocardial infarction just after the end of the six-month crossover trial and one man moved out of the London area so that 12 men (six receiving placebo and six receiving budesonide) completed the full period of 12 months with the second treatment. All treatment was then stopped.

The studies were approved by the local Medical School Research Ethics Committee.

RESULTS

Double-Blind crossover Trial

Smoking Habits: These were generally similar through the trial (as assessed by stated habits and FeCO); one patient unsuccessfully tried to quit smoking for a few days during the trial. Compliance with Treatment: In the 14 men who completed the trial, canister weights showed a reduction averaging 0.37 g/day with most individuals showing similar values; qualitative measurements of plasma budesonide also confirmed the presence of budesonide in all the men at the end of the appropriate 12-week period. One subject appeared to be using insufficient aerosol during weeks 9 to 12 of placebo treatment. One man consistently appeared to use less aerosol (about 60 percent of mean value) both during placebo and budesonide treatment.

Uunoward Events: One man dropped out after four weeks when it became clear his compliance with treatment was poor. Of the remaining 14 men, only one complained of a side effect related to budesonide (hoarseness, throat irritation, and sore tongue); this led to a short break in treatment and postponement of final assessment.

Five men had respiratory tract infections during the trial, although none was very severe; four occurred during the first or second month of budesonide treatment, one during the third month of receiving placebo. In two men, the total period receiving budesonide was extended by one to two weeks because of these infections.

One of the 14 men died of an acute myocardial infarction a few days after completing the trial; he had been receiving placebo aerosol during the last 12 weeks of the trial, and was the individual who had been poorly compliant with treatment in the final month.

Changes in Symptoms: Apart from transient increases in cough and phlegm (and in two of the men associated mild breathlessness) at the time of respiratory infections, no consistent changes in symptoms were noted.

Changes in Venous Blood: The lowest mean value of eosinophil counts was found at the end of the 12-week period with budesonide (Table 2). There were no significant changes in mean venous blood total WBC counts or IgE.

Changes in Baseline Spirometry and Bronchodilator Responsiveness (Table 3): Mean values of FEV₁, vital capacity (VC), and laboratory measurements of peak expiratory flow (PEF) showed very little variation through the trial. The mean difference between highest and lowest values in the seven baseline measurements of FEV₁ was 0.27 L; the largest differences were 0.44 and 0.55 L. There was no effect of period or drug or drug/period interaction on prebronchodilator values of FEV₁ when comparisons were made after 12 weeks of treatment. Similarly, the percentage of improvement in FEV₁ after inhalation of 5 mg of salbutamol and 0.5 mg of ipratropium bromide was unchanged.

Changes in Bronchoconstrictor Responsiveness to Inhaled Histamine: Mean log PC20 values after 4, 8, and 12 weeks of treatment with budesonide or placebo are shown in Figure 1. There was an effect of period with a significant rise in log PC20 (mean rise 0.192, 95 percent confidence limits 0.047 to 0.337, p 0.014)

Table 2—Effect of Budesonide and Placebo on Total White Blood Cell Counts, Eosinophil Counts, and IgE Levels in Venous Blood*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Budesonide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total white blood cell counts, $\times 10^9$/L</td>
<td>8.99 (0.6)</td>
<td>8.47 (0.5)</td>
<td>8.91 (0.6)</td>
</tr>
<tr>
<td>Total eosinophil counts, $\times 10^9$/L</td>
<td>0.26 (0.04)</td>
<td>0.18 (0.02)</td>
<td>0.25 (0.04)</td>
</tr>
<tr>
<td>IgE levels, $\mu$/ml</td>
<td>1.863 (0.146)</td>
<td>1.851 (0.146)</td>
<td>1.806 (0.146)</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>73</td>
<td>71</td>
<td>64</td>
</tr>
</tbody>
</table>

*Values are mean (SEM) of the 14 men. Measurements were made at recruitment (baseline) and after 12 weeks of treatment with either budesonide or placebo.
Table 3—Effect of Budesonide and Placebo on Laboratory Measurements of Spirometry, Peak Expiratory Flow, and Bronchodilator Responsiveness*

<table>
<thead>
<tr>
<th>Duration, mo</th>
<th>Budesonide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>2.42</td>
<td>2.39</td>
</tr>
<tr>
<td>(pre-bd)</td>
<td>(0.15)</td>
<td>(0.16)</td>
</tr>
<tr>
<td>VC, L</td>
<td>3.96</td>
<td>3.70</td>
</tr>
<tr>
<td></td>
<td>(0.17)</td>
<td>(0.16)</td>
</tr>
<tr>
<td>PEF, L/min</td>
<td>498</td>
<td>511</td>
</tr>
<tr>
<td></td>
<td>(19)</td>
<td>(22)</td>
</tr>
<tr>
<td>ΔFEV₁, post-bd†</td>
<td>10.8</td>
<td>11.6</td>
</tr>
<tr>
<td>(% baseline FEV₁)</td>
<td>(2.3)</td>
<td>(2.7)</td>
</tr>
</tbody>
</table>

*Values are mean (SEM) of the 14 men.
†Increase in FEV₁ h after inhaling a nebulized solution of 5 mg of salbutamol and 0.5 mg of ipratropium bromide.

between the end of the first period (12 weeks from start of the trial, April) and the end of the second period (24 weeks from start of trial, July). However, there was no significant effect of budesonide treatment (mean difference in log PC20 from placebo after 12 weeks of treatment 0.037, 95 percent confidence interval -0.108 to 0.182, p>0.5) nor any evidence of drug/treatment interaction. Inspection of the mean results after four and eight weeks of budesonide or placebo again showed no significant differences or trends (Fig 1). Grand mean log PC20 for the 42 measurements with budesonide was 0.595 (SEM 0.063) and for the 42 measurements with placebo 0.591 (SEM 0.055). Attempts to detect individual smokers who responded to treatment were difficult because of the effect of season. The largest individual differences in PC20 between treatments—a mean rise of 1.18 doubling doses with budesonide and a mean rise of 1.03 doubling doses with placebo—were both found in the second half of the trial and so were in the direction of the seasonal change. In most smokers, the difference in PC20 between the two treatment periods was less than 0.5 doubling doses.

Peak Flow Measurements during the Last Four Weeks of Each Treatment (Table 4): There were no changes; diurnal variation was small throughout.

Single-Blind Follow-up for Nine Additional Months

Compliance with Treatment: Regular weighing of canisters revealed good apparent compliance in the six men taking budesonide aerosol (mean use 0.36 g/day); again with a narrow range, there was no tendency to decreased use at 12 months compared with three months.

Untoward Events: Three of the six men receiving budesonide had infections during the second winter of the trial and one was slow to recover so that his final measurements were not made until two months after the other men. No side effects of the drugs were encountered.

Changes in Venous Blood: No significant changes were observed in hemoglobin, total WBC or eosinophil counts, or in total IgE in peripheral venous blood.

Changes in Airway Function: At the beginning of treatment, FEV₁ and PEF and bronchodilator responsiveness were similar in the two groups of six men treated with budesonide and placebo, respectively (Table 5). There were no significant changes over the 12 months. Mean PEF in these men commenced at >90 percent predicted.

Analysis of the PC20 results was complicated by the

Table 4—Home PEF Values during Weeks 9 to 12 of Treatment: Budesonide or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Budesonide</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
</tr>
<tr>
<td>AM</td>
<td>L/min</td>
<td>469</td>
</tr>
<tr>
<td></td>
<td>%pred</td>
<td>95.9</td>
</tr>
<tr>
<td>PM</td>
<td>L/min</td>
<td>465</td>
</tr>
<tr>
<td></td>
<td>%pred</td>
<td>95.1</td>
</tr>
<tr>
<td>Mean*</td>
<td>L/min</td>
<td>16</td>
</tr>
<tr>
<td>AM-PM</td>
<td>difference</td>
<td>(2)</td>
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</table>

*Average of the mean daily AM to PM difference over four weeks in the 14 men.
effect of period in the double blind crossover trial. Thus, in the first three months with both budesonide and placebo, there was a small increase in log PC20; in the subsequent nine months, there was no further significant change in log PC20 with budesonide.

**DISCUSSION**

In the present study we were unable to demonstrate any consistent improvement in baseline lung function, home peak flow, bronchoconstrictor responsiveness, or bronchodilator responsiveness in smokers with mild airflow obstruction following three months of treatment with budesonide. These results contrast with the consistent improvement others have found with similar treatment in patients with asthma, but agree with two other recent studies in smokers with chronic airways obstruction.

We have considered a number of possible explanations for these negative results.

We checked compliance with treatment by regularly weighing metered dose canisters at each visit and by confirming the presence of budesonide metabolites in the blood after 12 weeks and after 12 months of treatment. In addition, we noted a significant fall in blood eosinophil count from baseline values after 12 weeks of treatment with budesonide. Although the lack of subjective benefit would be expected to reduce compliance, the men recruited into this trial were well known to us and appropriate decreases in canister weights were maintained over the full 15-month period of treatments; in the one man who withdrew from the trial, poor compliance was suspected at an early stage from canister weights. Obviously the appropriate canister weights and presence of plasma budesonide might reflect discharge of canisters and compliance in the hours before a laboratory visit; but we suspect that compliance in our men would be better than in a larger, less personally supervised trial. The dosage of budesonide chosen was the maximum we believed we could use without leading to significant impairment of hypothalamic-pituitary-adrenal control of endogenous corticosteroids. Smaller doses over a similar period have been shown to attenuate bronchoconstrictor responsiveness in subjects with asthma.

We found an effect of period on PC20 in our trial; although we avoided studying men shortly after a recognized upper or lower respiratory infection, it seems probable that the attenuation of bronchial responsiveness with period was associated with season. This effect of period will have tended to obscure any drug effect, but formal analysis showed no evidence of drug effect after 12 weeks' treatment or any drug-period interaction. Confirmation of the lack of effect of budesonide was obtained by comparing mean values after four and eight weeks of treatment. Short-term repeatability of PC20 in smokers appears to be similar to that in asthmatic subjects with most values falling within one doubling dilution. The increase in PC20 induced by bronchodilators is also similar. In the present smokers, PC20 was increased by a mean of 2.3 doubling dilutions 1 h after treatment with nebulized salbutamol and ipratropium (results not shown).

The failure of budesonide to improve prebronchodilator or postbronchodilator FEV1 or home PEF was clear cut. PEF values were very close to predicted values and showed little diurnal variation so perhaps there was little room for improvement. This does not apply to FEV1 where a bronchodilator effect could be demonstrated at baseline, which was quite unchanged after 12 weeks (and indeed 12 months) of treatment.

The single-blind follow-up for nine more months of treatment in two groups of six men aimed to obtain preliminary information on longer-term effects. No change was found in prebronchodilator or postbronchodilator airway function. Interpretation of the PC20 results was again complicated by the increase found in the April to June period after the first winter and by more frequent respiratory infections in the second half of the second winter. At best, however, only a very small attenuation of PC20 occurred after 12 months of treatment with budesonide.

In asthma there is a relation between PC20 to histamine and the severity of asthma, diurnal variation in PEF, and the requirement for treatment.
hence, it has been suggested that treatment should aim to attenuate BHR as well as restore normal airway function and suppress symptoms. The significance of the BHR found in smokers is less clear. In smokers there is a weaker relation of BHR to diurnal variation in PEF and a stronger relation to baseline FEV1, than in asthma, so BHR may follow rather than precede the development of airway narrowing. Nevertheless, most previous trials of the response of baseline airway function to oral corticosteroid treatment in smokers with chronic airways obstruction have shown some improvements in at least some subjects. Our failure to detect any change may reflect more rigorous exclusion of subjects with asthmatic features or the lesser degree of airways obstruction in the present subjects. Additional longer trials with a larger number of subjects will be required to assess if budesonide can slow long-term decline in lung function.

ACKNOWLEDGMENTS: This work was supported by grants from the Medical Research Council and Chest, Heart and Stroke Association, and some further financial assistance from A.B. Draco. We are grateful to Vic Aber and Robert Robinson for help with the statistical analysis.

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