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AN INVESTIGATION OF THE BRONCHIAL  
MUCOUS MEMBRANE AFTER LONG-TERM  
TREATMENT WITH BECLOMETHASONE  
DIPROPIONATE (BECOTIDE®)

By

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Topical treatment of bronchial tubes with Beclomethasone Dipropionate (B.D.) has turned out to be extraordinarily effective in the treatment of bronchial asthma (3, 4, 5, 6, 8). Until now no side-effects of long-term treatment have been reported, and systemic side-effects are hardly to be expected. However, local atrophy of the bronchial mucous membrane similar to that resulting from treatment of the skin with steroid ointments may occur.

When experimenting with animals Dr. D. M. Harris (Personal communication, 1973) found no changes in the lungs of dogs treated with large doses of B.D. No reports of bronchial examination of humans after long-term treatment are available.

Therefore, we wished to examine the bronchial tubes of patients who have received long-term treatment with B.D. In this trial 12 patients were examined, all of them having been continuously treated with 400  $\mu$ g B.D. a day for 6 months. After this period, bronchoscopy with biopsy was performed. The case histories of the 12 patients are briefly reported with the results of the bronchoscopies and the microscopy diagnoses.

Before starting the B.D. treatment, bronchoscopy and bi-

opsy were not performed as a thorough examination had already been made by Glynn & Michaels (7). They examined 18 patients with bronchial asthma, 7 of these being treated with prednisone. In 6 of the 18 patients squamoid changes were found, and in 2 patients thickening of the basement membrane. Furthermore, they found infiltration with eosinophilic cells and lymphocytes. In all cases the muscle tissue was normal.

## CASE HISTORIES

### *141209-0663 (Microscopy No. 3758/73)*

63-year-old man who has been suffering from bronchitis with attacks of dyspnoea for 10 years. He has been treated with prednisone for periods during the last 2-3 years. For 6 months, he has been treated with B.D. with good effect, and he has only had a few slight attacks since starting treatment. The patient is allergic to dust and feathers.

Bronchoscopy shows conditions to be normal everywhere.

Microscopy shows normal epithelium cells with the cilia preserved, and pathological cell infiltrations.

### *140355-0961 (Microscopy No. 2669/73)*

This is a 15-year-old boy who has suffered from asthma since he was 2. He is allergic to dust and dog hair. In recent years he has been chronically weak and has been emaciated with frequent attacks of asthma. Since starting B.D. treatment he has been absolutely well, and has had no attacks.

Bronchoscopy was carried out after 6 months' treatment. The mucous membrane is dry; there is a sparse secretion; and on the left side, abnormal discharge of the bronchial tubes of the superior lung was found.

Microscopy shows normal bronchial epithelium with normal-looking cilia. Normal microscopy.

### *171030-0352 (Microscopy No. 3954/73)*

Woman, 42 years old, has been suffering from asthma for 20 years. She is allergic to dust, animal hair and feathers. She had frequent attacks. The patient has received steroids for certain periods. She has been without symptoms since the start of B.D. treatment.

Bronchoscopy was done after 6 months' treatment, and a normal state was found.

Microscopy shows normal epithelium with distinct cilia. The basement membrane seems slightly thickened. Sub-mucous tissues are somewhat oedematic with only a few lymphocytes and no eosinophilic granulocytes. Normal muscles.

*231022-0518 (Microscopy No. 4080/73)*

50-year-old woman who has been suffering from asthma for 18 years. The patient is allergic to dust and feathers, and has had frequent asthma attacks. She has been put on B.D. treatment with good effect. However, she has had a few slight attacks.

Bronchoscopy was done after 6 months' treatment. The primary bronchus looks anaemic, but the mucous membrane is normal; in some areas it is coated with a thick, white secretion.

Microscopy showed normal cells, (the tissue preparation was bad). Some thick, tenacious basophilic mucus was present with many inflammatory cells. The epithelial cells were normal with abundant cilia. The collagen seems normal.

*050517-0431 (Microscopy No. 4274/73)*

Man, 56 years old, who has been suffering from serious asthma for 2 years; he was treated with prednisone, 5 mg twice a day, but he is now on a Becotide treatment with good effect. He has been entirely symptom-free for the last few months.

When bronchoscopy was done after 6 months' treatment, normal conditions were found.

Microscopy shows normal bronchial epithelium, and the cilia are preserved. The basement membrane seems to be slightly thickened. There are no inflammatory infiltrations.

*280128-0490 (Microscopy No. 4459/73)*

Woman, 45 years old, has been suffering from bronchial asthma with serious attacks for 2 years. The patient is allergic to dust, feathers, and mould fungus. She has been treated with B.D. for 6 months, and she has had no attacks in this period.

Bronchoscopy done after 6 months' treatment shows normal conditions.

Microscopy shows bronchial epithelium cells with normal nuclei, no suspect cells, and tissue flakes containing smooth muscles and fibrous connective tissue. Cell formation looks normal. The few epithelial cells seen appear normal, and there is ample collagen present. There are some squames and many exfoliated epithelial cells with clear brush borders. The exfoliation is most likely to be the result of the biopsy procedure. There is ample mucus, rich in eosinophils and small round cells.

*231107-0633 (Microscopy No. 4716/73)*

65-year-old man who has been suffering from bronchial asthma for 6 years. He is allergic to house-dust. During the last year, he suffered from exacerbating asthma with daily attacks. For 6 months he has been treated with B.D., and his asthmatic symptoms have disappeared completely. He has only a slight cough in the morning and function dyspnoea.



*Fig. 1.*

Microscopy shows normal bronchial epithelium, and the cilia are preserved. The basement membrane seems to be slightly thickened, no inflammatory infiltrations (Microscopy No. 4274/73).

Normal conditions were found by bronchoscopy.

Microscopy shows the epithelium with squamous metaplasia and with eosinophils migrating through this layer. There is abundant subepithelial collagen containing patches of inflammatory cells which are mainly lymphocytes. Mucus is abundant and contains eosinophils.

210318-0557 (Microscopy No. 4583/73)

Man, age 54, who has been suffering from bronchial asthma for 12 years, which has been gradually getting worse. He is allergic to dust and animal hair. His asthma is better after 6 months' treatment with B.D., and a Ventolin® inhaler is not needed.

Bronchoscopy shows normal mucous membrane, and trivial secretion.

Microscopy shows normal conditions.

040623-0546 (Microscopy No. 4326/73)

50-year-old man who has been suffering from bronchial asthma for 8 years, and who is allergic to house dust. He has been treated with B.D. for 6 months. The patient has had no real attacks since starting this treatment.



*Fig. 2.*

The same patient as in Fig. 1. Van Gieson's stain confirms the integrity of the sub-epithelial tissues (Microscopy No. 4274/73).

Bronchoscopy gives the impression that the mucous membrane is slightly atrophic everywhere.

Microscopy shows slight hyperplastic respiration epithelium tissue without the nucleus being atypic. It was accompanied by only a very sparse stroma, and there was no certain inflammatory infiltration.

*110112-0429 (Microscopy No. 3869/73)*

Man, age 61, who has been suffering from asthma since his youth. Lately he has complained of exacerbation with frequent attacks and function dyspnoea. He is allergic to house-dust. However, after 6 months' treatment with B.D. he has only had a few, slight attacks of asthma, which have been aborted with a Ventolin inhaler.

Bronchoscopy shows a normal mucous membrane, which is not atrophic (in spite of bad tissue preparation), but gives the impression that the cells are normal with normal cilia.



*Fig. 3.*

Normal respiratory epithelium with a normal sub-epithelial stroma (Microscopy No. 3758).

*140602-0521 (Microscopy No. 3890/73)*

Man, 71 years old, who has been suffering from bronchial asthma for 9 years. He is allergic to dust, animal hair, and feathers. He has started B.D. treatment, but he still has attacks of asthma and function dyspnoea.

Bronchoscopy, after 6 months' treatment, shows normal conditions.

Microscopy shows a regular respiratory epithelial layer with normal cilia.

*200320-1781 (Microscopy No. 4099/73)*

Man, aged 53, who has been suffering from severe bronchial asthma for 15 years. He has been hospitalized many times in status asthmaticus. By allergologic examination he has been found allergic to dust and feathers, and exacerbation is seen during infections. The patient has been treated continuously for 10 years with 5-10 mg/day prednisone. For the last 9 months he has been treated with B.D., and a significant improvement of his state has taken place in that he has not suffered from serious attacks. He has been able to reduce his dosage of prednisone to 5 mg/day.

Bronchoscopy with biopsy was done after 6 months' treatment.

The microscopy diagnosis showed eosinophilia with subepithelium oedema.



Fig. 4.

The same patient as in Fig. 3. Van Gieson's stain shows ample collagenous tissue (Microscopy No. 3755).

## RESULTS

The individual results are given above and it will be seen that the descriptions are largely within the normal range. Typical results are shown in Figs. 1-4.

The occasional presence of eosinophils, subepithelial oedema, and thickening of basement membranes is no doubt due to the underlying asthmatic state. The occasional appearance of thick mucus is also most likely to be due to this.

The one distinct metaplastic change (Figs. 5 and 6) is suggestive of a chronic irritation, but isolated areas like this do occur in lungs, and consequently any relationship to treatment is equivocal.

Particular attention was paid to the appearance of epithelial layers and the structure of the subepithelial layer. Apart from the changes noted above, no deviations from normal were seen.

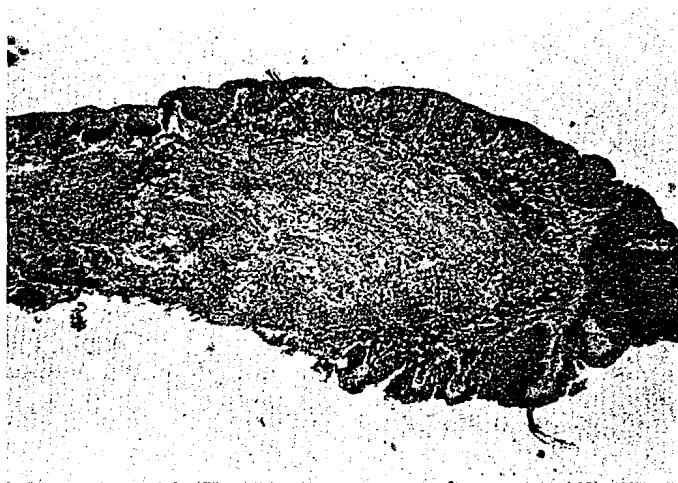


*Fig. 5.*

The epithelium shows squamous metaplasia with eosinophils migrating through this layer (Microscopy No. 4716/73).

#### DISCUSSION

It is known that glucocorticoids are able to produce a reduction in the production of collagen and intercellular substance, and that they may also inhibit the healing of surgical wounds and the development of granulation tissue. There is a paucity of literature on the pulmonary effects of glucocorticoids, and this is presumably because such effects are absent. Spontaneous pneumothorax has been associated with glucocorticoids given during the therapy of tuberculosis (1, 9) and staphylococcal pneumonia (10), but there is little doubt that such associations are by chance. Increases in fat occur in the mediastinum during glucocorticoid administration, but such changes are part of a general metabolic effect. One author (2) noted alveolar epithelialisation and epidermal metaplasia at autopsy in the lungs of a patient on glucocorticoids, but since no further cases



*Fig. 6.*

The same patient as in Fig. 5. The epithelial change is obvious and the migration of eosinophils through this layer easily seen (Microscopy no. 4716/73).

have been reported the significance of such a finding is doubtful. With a topically applied steroid it is pertinent to ask what potential changes might be seen in the respiratory passages and alveoli of the lung. Since diseases of the skin have been widely treated with steroids, it is relevant to consider the changes produced in this layer. Topical steroid therapy has been associated with atrophy or thinning of the skin. It has been suggested that there is an inhibitory effect on fibroblast activity which eventually leads to collagen atrophy and Stevanovic (11) has postulated a quantitative decrease in the amount of ground substance. The loss of supportive tissues leads eventually to dilation and congestion of blood vessels.

It is conceivable that similar changes might occur in the lung with long-term topical treatment with a potent steroid, but the present study revealed no evidence of this.

## CONCLUSION

Biopsies from the lungs of patients treated with B.D. in some cases revealed changes associated with asthma. No adverse effects on lung structure attributable to B.D. were found.

## SUMMARY

Biopsies performed on the lungs of 12 patients treated with Beclomethasone Dipropionate (B.D.) for 6 months did not reveal any damage attributable to treatment. In some, signs of the underlying asthmatic condition were seen, and in one, an area of squamous metaplasia was found.

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