and the chance of toxic effect is therefore much less. The optimum dosage is uncertain, but it probably varies from patient to patient.

Little or no benefit is likely to be obtained from this form of treatment in patients with established chronic bronchitis.

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INHALATION OF HYDROCORTISONE ACETATE FOR BRONCHIAL ASTHMA

A SHORT-TERM CONTROLLED TRIAL

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The beneficial effects of oral cortisone in some asthmatic patients have been clearly demonstrated by the Medical Research Council (1956). Hydrocortisone, when given locally as a surface application on the skin or by injection into the joints and tendon sheaths, is of value in many allergic and inflammatory conditions, and when inhaled into the nose as a powder may considerably improve allergic conditions of the nasal mucous membrane, including hay-fever (Foulds *et al.*, 1955); Herxheimer and McAllen, 1956). It would therefore seem reasonable to expect a favourable response in allergic bronchial asthma if, by inhalation, sufficient hydrocortisone could be brought into contact with the surface of the bronchial mucous membrane.

Foulds *et al.* (1955) used hydrocortisone acetate in fine-particle powder for 15 patients with bronchial asthma, with encouraging results in 12. Brockbank *et al.* (1956) found no evidence of benefit in patients treated with inhalations of hydrocortisone succinate solution in a "blind" controlled trial; but in a similar trial, using hydrocortisone acetate powder inhalations, Brockbank and Pengelly (1958) report improvement in a statistically significant number of patients on the hydrocortisone as compared with a placebo powder.

The assessment of benefit from any form of "new" treatment in bronchial asthma is notoriously difficult, since so many factors, including emotion, may be important in precipitating attacks and prolonged natural remissions may occur. It is therefore desirable to submit any method of treatment to a controlled trial before a fair assessment of its value can be made.

The purpose of the present investigation is to test by a controlled trial the short-term effect of the inhalation of hydrocortisone acetate in fine-particle powder in cases of bronchial asthma.

Material and Method

The patients selected for the trial had been subject to bronchial asthma for at least one year, and with one exception the condition had been severe enough to necessitate periods off work. The exception was a patient whose attacks were almost entirely nocturnal. In no instance was the history or the state of the sputum indicative of the presence of considerable recurrent or chronic bronchial infection. Patients who had more than ¼ oz. (7 ml.) of mucoid sputum daily or who had had any previous treatment with corticosteroid preparations or corticotrophin were excluded.

The "double blind" method of trial was used and patients regarded as suitable were placed by random selection by the hospital group pharmacist into either the hydrocortisone or the placebo group. Both groups were treated by the inhalation of powder from capsules with the aid of a "pabracort" inhaler. The capsules contained either 15 mg. of hydrocortisone acetate (ground to a main particle size of 5 microns), together with 75 mg. of lactose or, in the case of the placebo, 100 mg. of lactose, also in fine particle powder. It was not felt necessary to adopt a rigid dosage scheme, since previous experience with this treatment had suggested that the number of capsules used each day probably bore no close relationship to the quantity of powder reaching the bronchial mucous membrane, and that this depended to a considerable extent on the intelligence of the patients and their ability to inspire deeply.

It was noted in this respect that no settled regime of dosage of oral cortisone was adopted in the Medical Research Council (1956) trial in chronic asthma after the first week of treatment.

The starting dose therefore varied between three capsules a day in severe cases that began the trial during an exacerbation, and one capsule a day taken as half a capsule twice daily in those beginning during a relatively mild phase. The maintenance dose was adjusted according to response, the maximum being two capsules daily and the minimum half a capsule daily. Most patients were maintained on one capsule daily. Patients were given any other routine treatment thought necessary, and where severe wheezing was present bronchial dilator drugs were used directly before the inhalation of the trial powder to facilitate deep inspiration.

In patients who remained severely ill and who had failed to improve on general treatment together with trial inhalations after several days, a "blind" change of treatment was made to the other half of the trial, the patient being unaware that any change had been made. In less severely ill patients who were progressing satisfactorily, but in whom the response was not very clear-cut, a "blind" change of trial treatment was made after one to two months.

Results

The assessment of the results of treatment was made both on subjective and on objective grounds. All patients had had prolonged routine treatment before starting the trial inhalation, and this provided a baseline from which the changes in signs and symptoms could be judged. All patients were seen by the same physician at monthly intervals or less while remaining on the trial. Special attention was paid to the symptoms of dyspnoea and tightness of the chest, to exercise tolerance, and to the need for bronchodilator drugs. On physical examination the presence or absence of wheeze was noted and, if present, was assessed as slight, moderate, or severe, on each visit. In patients with recurrent acute asthma, considerable reliance often had to be placed on the history concerning the frequency, length, and severity of the attacks before and during treatment, and a relatively longer period of observation was usually neces-

sary. The assessment of the result of treatment was made in each patient as soon as it was felt that there was adequate evidence one way or the other. The length of treatment before assessment varied between one week in two severely ill patients who had failed to respond, and whose trial treatment was therefore changed, and six months in a patient with recurrent acute asthma who continued to improve on placebo capsules. The mean period before assessment was six and a half weeks. In all patients whose trial treatment was changed, a separate assessment was made at the end of each individual trial period, and the trial remained "blind" until the second assessment had been made.

TABLE I

	Improved	Not Improved	Total
Hydrocortisone	19	4	23
Placebo	6	9	15
Total ..	25	13	38

The results of inhalation of hydrocortisone acetate powder and of placebo powder in 38 trial periods in 26 patients (14 men, 12 women) with bronchial asthma are shown in Table I. If the χ^2 test with Yates's correction for continuity is applied we get a value for χ^2 of 5.5, which is significant at the 2% level.

These results are perhaps open to the criticism that the treatment of 12 patients was changed from one part of the trial to the other, and that the effect of the first treatment might persist after the change had been made. The exclusion of the results of the second period in treatment in these 12 patients gives the figures shown in Table II. The value of χ^2 for these figures is 4.3, which is significant at the 5% level.

TABLE II.—*Results of Inhalation of Hydrocortisone Acetate Powder and of Placebo Powder in 26 Patients (14 Men, 12 Women)*

	Improved	Not Improved	Total
Hydrocortisone	14	3	17
Placebo	3	6	9
Total ..	17	9	26

Change of Trial Treatment

Twelve patients were changed "blindly" and without their knowledge from one-half of the trial to the other. Six of these changed from the placebo to the hydrocortisone powder; all had been no better on the placebo and one remained unchanged on the hydrocortisone; the other five made definite improvement on the hydrocortisone. Two of these patients had been very seriously ill despite energetic routine measures before the trial started and during the placebo inhalations, but both responded dramatically when changed to hydrocortisone after one week, and on the night the change was made both slept well for the first time for many days. Six patients were changed from hydrocortisone to placebo inhalations; three of these had improved on the hydrocortisone, but the asthma had been relatively mild and the change was made in order to obtain a more clear-cut result. One of these immediately relapsed on the placebo, but the other two maintained their improvement until the trial was terminated after two and three months respectively. Two patients were not improved on either half of the trial. One man, after an initial good response to hydrocortisone in hospital, relapsed on returning home and was therefore assessed as "not improved"; he was changed to the placebo powder, on which he has remained well until the time of writing, a period of two months.

Discussion

It is unfortunate that by chance 17 patients should have been allocated to the hydrocortisone and only nine to the placebo inhalations, but we feel there is little doubt that the inhalations have a beneficial effect for a time in some patients with bronchial asthma. The rapid improvement of five patients when changed from the placebo to the hydrocortisone was especially impressive. For success it is essential that enough powder should contact a wide surface area of bronchial mucous membrane. The powder is therefore ground fine in order to allow penetration to the small bronchioles.

Foulds *et al.* (1955) suggested that there was no advantage in the inhalation of more than 15 mg. of hydrocortisone daily. Although we have made no specific tests on these lines, the method of inhalation is so inexact, and the ability of the patients so variable in spite of careful training, that we feel this quantity may be insufficient in some patients, especially where in the initial stages of treatment chest movements are very poor and respiration is shallow owing to bronchial spasm. One of the four patients assessed as being no better on hydrocortisone, and another who improved slowly, were obese, middle-aged women with severe wheezing and distended chests who found it almost impossible to inspire deeply even with the help of preceding bronchial dilator drugs. We think that in this type of patient at least three capsules—that is, 45 mg. of hydrocortisone powder—should be inhaled daily at first to give a fair chance of success.

The disadvantage of the bigger dose is that the absorption will be higher and toxic effects more likely, and doubt may arise whether any benefit is due to local or general effects. In successfully treated patients, however, the dose can be reduced to one capsule daily (15 mg.) within a few days, and it would seem unlikely that this dosage would produce sufficient general absorption to have significant side-effects or influence on the asthma. There were no complications in the present series.

Summary and Conclusion

A short-term "blind" controlled trial of inhalations of hydrocortisone acetate in fine-particle powder has been carried out in 38 periods of treatment in 26 patients. The number of patients improved in the hydrocortisone group as compared with the placebo group was at a statistically significant level.

It is therefore concluded that hydrocortisone acetate powder inhalations are an effective form of short-term treatment in some patients with bronchial asthma.

We are indebted to the late Dr. W. J. Dunn, Dr. J. Shafar, and the many other doctors for their co-operation; to Dr. J. Edge for helpful criticism; to Dr. E. Tallett, the hospital group pharmacist, for his enthusiastic co-operation throughout; to Mrs. J. Withnell for the secretarial work; and to Messrs. Paines & Byrne Ltd. for providing the "pabracort" inhaler, and the material for the trial.

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The Care of the Elderly is the report of the Ninth Conference of the National Old People's Welfare Council. This was held on April 17 and 18, 1958, in London. The conference included discussions on the future pattern of care for the elderly through health and welfare services (opening speaker, Mr. Derek Walker-Smith, Minister of Health); preparation for retirement (opening speaker, Mr. W. A. Sanderson); the housing of the elderly (opening speaker, Mr. J. R. Bevins, parliamentary secretary to the Ministry of Housing and Local Government); recruitment and training of workers among the elderly; problems of communal homes; visiting; surveys and research; and the changing pattern of comprehensive care (opening speaker, Professor R. E. Tunbridge). This report is obtainable from the National Old People's Welfare Council, 26, Bedford Square, London, W.C.1, price 3s. 6d., quoting ref. no. 534.