an adverse hyperkinetic factor, and gradual involution of the muscular pulmonary arteries.

In Eisenmenger's syndrome with aorto-pulmonary or interventricular shunt, this favourable cycle is prevented by a powerful hyperkinetic factor which maintains the pulmonary artery pressure at systemic level. So long as pulmonary hypertension is maintained vasoconstrictor tone is not inhibited and the muscular pulmonary arteries do not involute.

Obliterative pulmonary vascular disease due to reactive "endarteritis fibrosa" is secondary and is rarely found in infancy.

Thrombo-obstructive lesions are relatively late and may not be demonstrable before adult life.

The different behaviour of cases with atrial septal defect may be explained by the relatively slow involution of the right ventricle after birth. The pulmonary vascular resistance may well fall to normal before right ventricular diastolic tone is reduced sufficiently to allow a critical interatrial shunt, and, once the resistance is truly normal, flows up to 24 litres per minute do not cause pulmonary hypertension.

The practical application of these observations to the treatment of the Eisenmenger syndrome is discussed.

This analysis was begun in 1948 and two attempts at synthesis were made previously; the first in conjunction with Dr. J. B. Lowe in 1950, the second with Dr. H. Gilmour in 1953; and, though both attempts proved unsatisfactory owing to lack of sufficient data, I want to express my great indebtedness to these two colleagues.

Details of necropsies on cases well investigated during life were sent to me by Drs. I. M. Anderson, D. Evan Bedford, Wallace Bridgen, Maurice Campbell, William Evans, Frances Gardner, C. J. Gavey, Ronald Gibson, Frederick Jackson, and Walter Somerville; I am very grateful to all of them for their trouble and generosity.

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LOCAL TREATMENT OF BRONCHIAL ASTHMA WITH HYDROCORTISONE POWDER

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The fact that bronchial asthma can be greatly improved by systemic treatment with cortisone and its derivatives is well established. This treatment, however, demands high dosage and thus has the disadvantage of causing cortical atrophy, and of other risks. Its continued use must therefore be limited to patients whose life is endangered by the asthma or where invalidism is threatening.

If a similar therapeutic effect could be achieved by local instead of systemic treatment the dosage could be expected to be much lower, and the risks connected with high dosage would be avoided. A local effect of hydrocortisone has been well known for some time in allergic disorders of the eye and of the skin. In hay-fever a similar effect has been reported more recently and has been confirmed (Herxheimer and McAllen, 1956; Godfrey, Maunsell, and Pearson, 1957; Lake, Logan, and Peters, 1957; Morris-Owen and Truelove, 1958; Findeisen, 1958). Some of these reports include a number of cases in which pollen asthma was present and which were benefited by the treatment. Apart from

these, reports on the local treatment of bronchial asthma with cortisone derivatives are scanty, and, in their conclusions, tentative only.

In this paper we report a number of therapeutic trials undertaken at different centres with the aim of contributing to this question.

Methods

Although the method of selecting patients differed in the three places of trial (London, Cardiff, and Berlin), the treatment was always the same. The patients were advised to inhale one capsule of micronized hydrocortisone snuff from a powder inhaler. A capsule containing 15 mg. of hydrocortisone and 85 mg. of lactose was placed in this inhaler; half of the contents of a capsule was inhaled orally in the morning and half in the evening. The dose of 15 mg. was chosen on the assumption that only a small part of this amount would be distributed systemically and that this part would be well below the body's own hydrocortisone production, which has since been shown to be about 14 mg. a day (Cope and Black, 1958). In many cases the patient served as his own control. In a few cases he was given hydrocortisone powder for a certain time (two weeks), followed by a similar period without powder; in most cases the hydrocortisone period was followed or preceded by an equal period of placebo snuff. In one group no attempt at control was made, and the groups of controlled patients and others will be reported separately.

The greatest difficulty was the selection of patients for the trial. Only those whose condition was a chronic one and moderately severe could be used—that is, the condition had to be fairly uniform throughout the year and severe enough to require continuous treatment. In addition, patients must have been under observation for some years, so that the variations in their condition were well known to the medical observer. Such patients are comparatively rare, as those with frequent and violent ups and downs must be excluded. Their exclusion is an absolute necessity for a trial like this, because violent spontaneous variations might be attributed to the trial substance. But even if patients are selected who conform to the conditions mentioned, there is no safeguard against intercurrent upper respiratory infections with their almost unavoidable temporary deterioration and subsequent improvement, which may mask the influence of the trial substance.

The investigation was started first at University College Hospital with the selection of a group of 12 patients, most of whom we had known for a number of years, and whose condition was stable. They were all under continuous standard treatment, usually on antihistamine drugs at night, sometimes combined with ephedrine or aminophylline during the day. As a stand-by the patients used inhalations of isoprenaline; the number of inhalations required by them during an average day and an average night was fairly constant, so that a change in the condition would be immediately reflected by a change in the number of inhalations. We were fairly confident that these patients would permit a good if provisional impression of the efficiency of the snuff. The patients in this group acted as their own controls.

The second group, containing 53 patients, was formed at Cardiff. It consisted of chronic cases—some of the allergic type and some of the infective type. Nineteen patients were controlled—that is, they had placebo capsules at some time or other, often for several periods—and 34 were uncontrolled—that is, no attempt was made to find out whether they were better or worse without the snuff. Four patients in the controlled group had only mild perennial asthma, but it became severe seasonally. All four of them were mould-sensitive.

The third group, comprising 14 patients, was selected in Berlin after some experience had been gained with the previous groups. They were chronic asthmatics of moderate severity, and in all but three its allergic character was certain.

In every patient the presence or absence of hypersecretion was noted. It was regarded as present if the patient continually had viscous sputum with difficulty of expectoration and therefore required potassium iodide as an expectorant at regular intervals. Patients who required potassium iodide only after acute exacerbations of their asthma are not included in this category.

Results (Table I)

First Group.—Five of the 12 patients were better with the snuff than without it. Their condition had improved so much that other anti-asthmatic medication was required only occasionally. In three others the improvement was moderate: the symptoms were definitely less severe, but

TABLE I.—Results of Treated Cases

Patient	Age and Sex	Age at Onset of Asthma	Skin Tests	History of Allergy	Hypersecretion	Result of Treatment
London (12):						
Be ..	44 M	20	Pos.	Pos.	No	Neg.
Cr ..	28 M	2	"	"	Yes	Pos. +
God ..	30 M	8	Neg.	Neg.	No	Neg.
Goo*	37 F	20	Pos.	Pos.	"	Pos. + +
Ha ..	36 M	17	"	"	"	Pos. +
La ..	31 M	23	"	"	Yes	Neg.
Le ..	26 M	2	"	"	No	Pos. + +
Li ..	29 F	25	"	"	"	Pos. + +
Ru ..	53 M	4	"	"	"	Pos. +
Sw ..	51 M	35	"	"	Yes	Pos. + +
Wo†	43 M	34	"	"	"	Pos. + +
Ra ..	31	3	"	"	"	Neg.
Cardiff (19):						
Al ..	26 F	22	Neg.	Neg.	No	Pos. + +
An ..	54 F	51	"	"	Yes	Neg.
Ba ..	31 F	2	Pos.	Pos.	"	Pos. + +
Ha ..	60 F	46	Neg.	Neg.	"	Pos. + +
Je ..	32 M	3	Pos.	Pos.	No	Pos. + +
Jo ..	39 F	24	"	"	"	Pos. + +
Ke ..	45 F	32	"	Neg.	"	Pos. + +
Le ..	30 F	17	"	Pos.	"	Pos. + +
Lo ..	48 F	43	Neg.	Neg.	Yes	Pos. + +
Ma ..	59 F	53	"	"	"	Pos. +
O'N ..	74 F	69	Pos.	"	"	Neg.
Pe ..	27 F	5	Pos.	Pos.	No	Pos. + +
Ric ..	37 M	12	"	"	"	Pos. + +
Ria ..	49 F	16	"	"	Yes	Neg.
Sc*	27 M	3	"	"	No	Pos. + +
Si ..	58 F	38	"	"	Yes	Pos. + +
Th ..	54 F	51	Neg.	Neg.	No	Neg.
Zo ..	58 F	49	"	"	Yes	Pos. + +
Xi ..	60 F	23	Pos.	Pos.	No	Pos. + +
Berlin (14):						
Ca ..	50 F	29	"	"	"	Pos. + +
El ..	37 F	4	Neg.	Neg.	"	Pos. + +
En ..	23 M	13	Pos.	Pos.	Yes	Neg.
Fo ..	30 M	5	"	"	No	Pos. + +
Grö ..	24 F	13	"	?	Yes	Pos. + +
Ha ..	53 F	41	"	Pos.	"	Neg.
Hu*	26 M	23	"	Neg.	No	Pos. + +
Ka ..	52 M	15	"	?	"	Pos. + +
Kl ..	31 F	8	"	Pos.	Yes	Pos. + +
La ..	41 M	9	Neg.	Neg.	"	Neg.
Le ..	22 F	19	"	"	"	Neg.
Ra ..	22 F	4	Pos.	Pos.	No	Pos. + +
Sc ..	32 M	7	"	?	"	Pos. + +
So ..	15 M	13	"	Pos.	"	Pos. + +

Pos. + + = Considerable improvement. Pos. + = moderate improvement.
* "Dry" asthma.

† Relapsed after being on placebo for two months.

other anti-asthmatic remedies were still required, though not so much as before. In the remaining four the result was plainly negative. Of the five considerably improved patients, two had hypersecretion, and another, who had one of the rare "dry" asthmas, showed an extremely impressive improvement. She had been known to us for 12 years, and her history of perennial asthma with peaks in April and August had been longer. She had required frequent injections of adrenaline, these being replaced later by isoprenaline inhalations. A few years ago her condition gradually deteriorated, and she was put on maintenance doses of corticotrophin. She never expectorated any mucus except during rare and short periods of upper respiratory infection. When she was put on hydrocortisone snuff she was soon able to leave off corticotrophin and the frequent isoprenaline inhalations. At the time of writing she was free of asthmatic symptoms with 10 mg. of hydrocortisone snuff a day.

Second Group.—Of the 34 uncontrolled cases, 15 showed or reported an improvement which was judged to be moderate. Often this improvement did not last long and was followed by a respiratory infection and deterioration which took a long time to subside. As no control was possible in these cases, we do not regard them as evidence for the efficacy of the snuff. Of the 19 controlled cases, 13 showed a considerable improvement, in two the improvement was only moderate, and in four there was no improvement. The four patients with seasonal mould allergy are among those with considerable improvement. They were free of symptoms so long as they took the powder. A fifth patient with a very long history of asthma belonged to the dry type, and he also became completely symptom-free. His asthma was so severe that his chest had become deformed and his nutritional state impaired. It was most surprising to see that he no longer required any antispasmodic treatment.

Third Group.—Of the 14 patients, 10 improved considerably; five of them had no symptoms so long as they took the snuff, whilst the other five still had to use antispasmodics, though much less than before. Of the four not improved two belonged to the infective type. Only two of the improved patients had hypersecretion and continued to require potassium iodide. The patient with dry asthma improved a great deal.

Discussion

Although more than two-thirds of our patients have benefited from the treatment, the interpretation of this result requires caution. These patients were not average asthmatics, but a selected group. Many of them were selected because, according to our initial experience, they were likely to respond to the treatment. In contrast to these, the 34 patients who formed the uncontrolled part of the Cardiff experiment were unselected patients. Here the number of failures (19) exceeds the number of patients improved (15), and it is by no means certain that all the positive cases would have been proved positive if they had been in a controlled trial. It follows that this treatment cannot be expected to help the average chronic asthmatic but only certain types, and our investigation has aimed at defining these types as clearly as possible. From Tables II and III it can be seen that we have treated more allergic (33) than infective (12) cases, and that 82% improved in the

The allergic type without hypersecretion is likely to do best: there was only one failure in 22. Our experience with the three completely "dry" asthmatics is in accordance with this. The improvement of these three patients in spite of their long history was particularly impressive, because their condition was far more severe than that of the average patient in our trial. In the presence of hypersecretion, however, only half of the patients improved, whether of the infective or of the allergic type. As hypersecretion is more frequent in the infective type, the less favourable response in this type may be due to the hypersecretion. There are too few patients in the group of infective type without hypersecretion to be certain on this point.

Only a few earlier experimental observations in this field are on record. Foulds *et al.* (1955) in a preliminary communication reported an uncontrolled trial of 15 patients with hydrocortisone snuff, of whom 12 improved. Herxheimer and McAllen (1956) have observed that, in 4 out of 10 hay-fever patients who also suffered from pollen asthma, the asthma disappeared after nasal insufflation of hydrocortisone snuff, and they assumed that this was because the snuff was inhaled into the bronchi. Morris-Owen and Truelove (1958) have made similar observations. Brockbank and Pengelly (1958) reported improvement in 17 out of 24 asthmatics with hydrocortisone snuff, but prednisolone snuff had no effect in six out of seven patients. Franklin *et al.* (1958) have also reported success with topical hydrocortisone, given as a suspension, in a majority of patients. These two groups of authors do not specify the type of asthmatic patient used in their studies. For this reason it is not possible to compare our results with theirs.

Our experience shows that the result of topical treatment in any group of asthmatics will mainly depend on the type of asthma involved. Originally we had hoped that the topical treatment of bronchial asthma might replace steroid systemic therapy in most cases and might thus avoid the dangers of continuous large systemic maintenance doses. This hope has not materialized. Only a minority of patients appear to be benefited by corticoids given topically.

It is particularly disappointing that the hypersecretory type, which is normally more difficult to treat, does not respond well. The reason for this is not clear. One might think that the blockage of many bronchi and bronchioli may prevent the action of the corticoid snuff, or that the mucus covering the mucous membrane may prevent its action. If the mucus is the principal obstacle, it should be possible to achieve success by its removal or reduction. In order to test this we have attempted to decrease the hypersecretion in four severe cases by systemic prednisone, and then to replace the systemic prednisone gradually by local hydrocortisone. In three of these cases, however, this substitution was not successful: three of the patients became gradually worse on reducing systemic prednisone from 10–12.5 mg. a day to 5 mg. a day or lower, and the previous systemic maintenance doses had to be resumed. This negative outcome is in contrast to the positive result of Franklin *et al.* (1958) in six out of seven cases. However, these authors have used a prednisolone suspension and not hydrocortisone snuff in their cases, and their type of patient may have been different from ours. Further experiments will be needed to elucidate this question.

Summary

A total of 79 chronic asthmatic patients were treated with hydrocortisone powder, 45 of them in a controlled trial.

In 33 of these 45 patients a definite improvement of symptoms occurred. This improvement was seen mainly in patients with evidence of allergic aetiology and in those without hypersecretion.

Improvement was seen to a much less extent in infective asthma than in allergic asthma.

Cases of "dry" asthma responded dramatically.

TABLE II.—Results Separated for Allergic and Infective Asthma

	Total	Improved	Unimproved
Allergic asthma	33	27 (82%)	6 (18%)
Infective asthma	12	6 (50%)	6 (50%)

TABLE III.—Results Separated for Asthma With and Without Hypersecretion

	Improved	Unimproved
<i>Patients with hypersecretion</i>		
Allergic	6 (55%)	5 (45%)
Infective	4 (50%)	4 (50%)
Total	10 (53%)	9 (47%)
<i>Patients without hypersecretion</i>		
Allergic	21 (95%)	1 (5%)
Infective	2 (50%)	2 (50%)
Total	23 (89%)	3 (11%)

allergic group as against 50% in the infective group. If we divide our patients into those with hypersecretion and those without, we find that of the 19 patients with hypersecretion only 53% improved, whereas 89% of the 26 patients without hypersecretion showed an improvement.

Although our figures are too small to permit definite conclusions, they show that the allergic type is more likely to respond than the infective type, and that the presence of hypersecretion is a handicap to the success of the treatment.

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BRONCHIAL ASTHMA AND CHRONIC BRONCHITIS TREATED WITH HYDROCORTISONE ACETATE INHALATIONS

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Foulds *et al.* (1955) reported good results in 12 out of 15 patients with asthma who were treated with inhalations of hydrocortisone acetate in fine-particle powder. Brockbank and Pengelly (1958) and Helm and Heyworth (1958) carried out short-term controlled trials which showed that a statistically significant number of patients responded well to these inhalations as compared with the number responding to inhalations of placebo powder.

The purpose of the present paper is to record the results of two years' experience with inhalations of hydrocortisone acetate powder in patients with asthma and wheezy bronchitis and to suggest some indications for this treatment. An attempt has also been made to estimate the quantity of "inhaled" powder which enters the stomach rather than the tracheo-bronchial tree.

Material

The patients selected had all suffered from asthma or wheezy bronchitis for at least one year, and their condition had been severe enough to necessitate periods off work, except in two patients whose asthma was almost entirely nocturnal. There were 25 men and 28 women treated. The ages varied between 15 and 61 years, the mean being 40 years.

Groups and Definitions.—Bronchial infection was judged to be present if the sputum contained macroscopic pus. Where necessary the pus was examined microscopically to differentiate pus due to eosinophils rather than true pus cells. For convenience of analysis the cases were divided into five groups: (1) recurrent acute asthma without significant bronchial infection; (2) chronic asthma without significant bronchial infection; (3) recurrent acute asthma with significant intermittent infection; (4) chronic asthma with significant intermittent infection but little persistent sputum; and (5) chronic wheezy bronchitis with significant persistent or intermittent infection and more than $\frac{1}{4}$ oz. (7 ml.) of sputum daily. The main difference between patients in groups 4 and 5 was in regard to the daily quantity of sputum, but infection tended to be a more prominent feature in group 5 than in group 4.

Method

All patients with significant bronchial infection when first seen were admitted to hospital for investigation and treat-

ment with antibiotics and routine antispasmodic drugs before receiving hydrocortisone inhalations, and patients whose signs and symptoms cleared completely concurrent with elimination of pus from the sputum were excluded. If the sputum rapidly became purulent again on stopping the antibiotic it was restarted and the patient remained on a small maintenance dose while starting hydrocortisone inhalations. All patients with infection were instructed to start antibiotics again should an exacerbation of infection occur while remaining on the inhalations after discharge from hospital. Patients with severe asthma (without infection) when first seen were admitted to hospital and were treated routinely with antispasmodic drugs for a few days before inhalations were given.

The patients inhaled fine hydrocortisone acetate powder from a "pabracort" inhaler, the powder being in capsules containing 15 mg. of hydrocortisone and 75 mg. of lactose powder, both being ground fine to a mean particle size of 5 microns. The initial dose varied between one capsule three times a day and one capsule daily given as half a capsule twice daily according to the severity of the wheezing at the beginning of treatment. The dose was reduced to the minimum maintenance necessary as soon as improvement occurred. Most patients were able to reduce the dose to half a capsule twice daily within the first week; this was the usual maintenance dose, although some needed to continue with two capsules daily, and some were able to reduce to half a capsule daily.

Treatment was stopped entirely in patients with recurrent acute asthma once the attack had been relieved for a week, and they were provided with capsules and instructed to restart at the onset of symptoms in a dose of between one and three capsules daily according to the severity of the attack. All patients were given any other routine treatment necessary, and this often included an antispasmodic drug before the hydrocortisone inhalation in order to facilitate deep inspiration. Those who responded well but later relapsed while continuing treatment were given prednisone by mouth in addition to the inhalations.

Patients who had failed to make any definite improvement during two weeks' treatment with inhalations were assessed as failures and the treatment was stopped.

Follow-up and Assessment of Results

The assessment of the results of treatment was made on both subjective and objective grounds. All patients had had prolonged routine treatment before starting the inhalations, 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 treatment. 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.

Patients with significant bronchial infection (groups 3, 4, and 5) were instructed to bring a 24-hour specimen of sputum for inspection on each visit.

The results of the inhalation of hydrocortisone acetate powder in bronchial asthma and wheezy bronchitis are shown in the Table.

Of the 53 patients, 43 (81%) improved on hydrocortisone inhalations, whereas 10 (19%) were no better. Of the 43 patients who improved, 13 (30%) relapsed after periods of 1 to 11 months, whereas 30 (70%) maintained the improvement up to the time of writing for between two months and two years. The best results were obtained in group 1 patients with recurrent acute asthma without infection, whereas the results in group 5 patients with wheezy bronchitis were disappointing.

Complications.—There were no definite complications in the present series, but one man had mild dyspepsia for a few weeks which may have been due to the hydrocortisone.