patient at a given time, and the diuretic response to any drug must be influenced by this clinical state. In 16 of our patients any likely advantage in diuretic action was given to mercurials as they were given before chlorothiazide. It is evident from our results that a significant diuresis was obtained with subsequent chlorothiazide, and our preliminary observations suggest that this drug is at least as potent as parenteral mercurials, or more so. In the patients who were given chlorothiazide initially the diuretic response was excellent. Our study of this small series of patients has convinced us that chlorothiazide is the most potent oral diuretic now available. If subsequent trials confirm our findings we will have an efficient diuretic which has the merits of practicability and ease of administration. Our patients were grateful that a change had been made from repeated injections, particularly as most of them noticed that the effect was usually better. The practical advantage of the oral method in domiciliary practice is obvious. Toxic manifestations did not appear in a single case, and, in particular, no gastrointestinal disturbances occurred.

The most important side-effect of oral chlorothiazide is hypokalaemia (Bayliss *et al.*, 1958; Slater and Nabarro, 1958). In the dosage used by us the serum electrolyte levels were not markedly affected, but it is known that if continuous daily therapy is instituted hypokalaemia occurs. Further work on the electrolyte changes following prolonged treatment is necessary, as this would seem to be the only serious disadvantage to the use of chlorothiazide in general practice. None of our cases was given supplementary potassium, but it must be stressed that the dose of chlorothiazide never exceeded 2 g. in one day, and that it was never given for more than four consecutive days at intervals of three to four days. Only one patient received as much as 20 days of intermittent therapy. We do not therefore wish to imply that supplementary potassium is unnecessary during treatment with chlorothiazide, but it is possible that this can be avoided if its administration is interrupted by free periods according to the procedure we adopted.

Summary

Oral chlorothiazide was given in doses of 1 g. twice daily to 20 patients with heart failure. In 17 of these 2 ml. of a mercurial diuretic was given parenterally and in 16 it was given initially. To compare the value of these diuretic agents varying courses of intermittent therapy were used. The response obtained was measured as the diuretic index over a two-day period.

Chlorothiazide produced a good therapeutic effect in all cases, and our results suggest that it is as effective as the parenteral diuretics, or more so.

In the short and intermittent courses of treatment which we used only a slight fall in serum potassium was recorded in five patients. Toxic effects were not observed in any of our patients.

We are grateful to Messrs. Merck, Sharp and Dohme Ltd. for supplies of chlorothiazide ("saluric").

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Endemic Goitre, a select bibliography on world distribution, has been published by the Chilean Iodine Educational Bureau (Chile House, Ropemaker Street, London, E.C.2). It contains over 1,000 references to the literature of the last 150 years, arranged on a geographical basis. There are also author and country indexes.

TREATMENT OF HAY-FEVER WITH LOCAL HYDROCORTISONE HEMI- SUCCINATE SODIUM

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During recent years various analogues of hydrocortisone have been used by local application to the nasal mucosa in the treatment of hay-fever. Owing to the relative insolubility of the free alcohol and acetate derivatives, previous workers have used these substances either incorporated in a snuff or as nose-drops in weak concentration. Pennypacker (1954) used nose-drops containing the free alcohol of hydrocortisone dissolved in saline in a strength of 0.2 mg. per ml., which represents its maximum aqueous solubility; vasoconstrictors were also included. Herxheimer and McAllen (1956) employed hydrocortisone acetate dispersed in lactose and used as a snuff, the maximum daily dose being 15 mg. Godfrey *et al.* (1957) also used a snuff, but one containing prednisolone in a maximum daily dose of 2 mg.

The development of compounds of hydrocortisone which are highly soluble in water has introduced a new factor into its use as a local therapy. Such compounds are likely to enter the tissues more rapidly and in higher concentration than the less soluble ones. Any beneficial actions of hydrocortisone in its less soluble forms might be expected to occur with greater speed and lower total dosage with these new preparations. In the present study we describe the use of a highly soluble preparation used in nose-drops. This was hydrocortisone hemisuccinate sodium, which has appeared to be effective when used locally in ulcerative colitis, as described in a previous article (Truelove, 1957), in which is also included a brief review of its properties.

Procedure

Hydrocortisone hemisuccinate sodium suffers from a minor disadvantage for use in nose-drops in that it undergoes in aqueous solution a slow hydrolysis with the liberation of hydrocortisone itself, which is liable to precipitation because of its low solubility. The rate of hydrolysis is dependent upon the intensity of light, and the process can be slowed by keeping the solution in a dark glass bottle. Under these conditions the solution is reasonably stable for 48 hours.

The hemisuccinate was therefore supplied by Glaxo Laboratories in the form of tablets. Each tablet contained the equivalent of 2.5 mg. of free hydrocortisone. The nose-drops were prepared each day by the patient dissolving one or more, as ordered, of these tablets in 5 ml. of normal saline contained in a small dark glass bottle fitted with a nasal dropper. Each patient began by using two tablets to the bottle, yielding a concentration of 1 mg. of hydrocortisone per ml. Some patients who responded well to this initial concentration continued their treatment with one tablet in the bottle. Others, in whom the initial concentration was ineffective, used a higher concentration.

The patients began treatment by applying three drops in each nostril four times a day. The nasal droppers yield 1-minim (0.06-ml.) drops—that is, 15 drops per ml.—so that the patients received 2 ml. or less of the solution daily. In

other words, the initial treatment involved the daily use of 2 mg. or less of hydrocortisone.

Patients were instructed to apply the nose-drops while lying supine with the head hanging down in a fully extended position, which was to be sustained for a minute or so, during which time gentle sniffing was practised to disperse the solution throughout the nose.

Selection of Patients

The 22 patients who were treated all had a history of attacks of hay-fever occurring regularly during the grass-pollen season. They were all suffering from marked symptoms of hay-fever, present at least for several days, when treatment was begun.

Some of them had had pre-seasonal pollen injections in previous seasons. Of these, some had never derived benefit from these injections, while others had had some benefit but had not continued with the treatment. Six received injections before the present season, but the onset of hay-fever seemed to indicate that these had been ineffective. The group as a whole is unrepresentative of hay-fever patients in general, as it contained an unduly high proportion who were not responsive to prophylactic pollen injections.

The ages of the patients varied from 17 to 58 years. The length of history was also variable, ranging from 4 to 35 years.

Assessment of Therapy.—All patients were seen immediately before treatment was begun and a note was made of their symptoms. The nasal mucosa was inspected and smears were made from nasal swabs. It was not convenient to see patients daily, but they were generally seen at the end of approximately one week for further re-examination. Most of them were seen several times thereafter, and all of them at least once. From the point of assessing the symptomatic response it was a fortunate chance that the hay-fever season in 1957 coincided with an exceptionally long spell of dry, sunny weather lasting several weeks. For grass pollen the season lasted from early June until the second week in July.

Results

Eleven patients made a rapid improvement on the initial dosage of 1 mg. of hydrocortisone per ml. and became entirely symptom-free in the course of a period ranging from less than 24 hours to a few days. The response was never immediate. In other words, the agent did not behave like a vasoconstrictor. Even in patients who showed the most rapid return to normality the process was a steady one throughout. In those with a more gradual response, spread out over some days, the diminution of the symptoms followed a fairly constant pattern. All showed some improvement in the first 24 hours, with relief of nasal obstruction, although with spasmodic rhinorrhoea still occurring in provoking circumstances. Next followed a stage when the nose was easily irritated but the reaction was limited to a sneeze or two. This passed gradually into normality.

Of the 11 patients who did not respond favourably to the initial dosage, five were tried after a few days on double-strength drops (2 mg. per ml.). Of these, two made an excellent response, which was rapid in one and gradual in the other. The remaining three made no favourable response, and two of them experienced some nasal irritation from the drops.

At this time we inquired about the exact composition of the tablets and learned that the main excipient was sodium chloride, which we judged was acting as an irritant through its osmotic action when the higher doses were employed. It is only fair to add that the tablets were prepared for our use by the makers at high speed because we had decided to make this study only a very short time before the hay-fever season began. Preliminary trials were impossible and the tablets were used as soon as they were made. Nevertheless, the nature of the excipient is a matter of consequence, for we think it is possible that a considerable proportion of

patients not responding to our initial dosage level would do so at higher dosages, which would still be very small in terms of any systemic action. We were precluded from any systematic exploration of this possibility during the present season by the osmotic properties of the tablets.

The subsequent course of those patients who responded well to the treatment is of interest in several connexions. The first is that the strength of the nose-drops could be reduced after a few days of normality without recurrence of symptoms. On the other hand, two patients who reduced the dose after only one day of normality promptly had a mild relapse but recovered immediately they returned to the original dosage.

Treatment was maintained for periods lasting from three to seven days after symptomatic normality was achieved and was then suspended. Some patients subsequently suffered a mild relapse in the course of the next few days, but in all cases this responded swiftly to one day's treatment, after which they were again symptom-free for at least several more days. A more pronounced stability of the nasal mucosa was displayed by three patients who had no nasal symptoms after the initial course of treatment. We regard this as a remarkable phenomenon because the hay-fever season was still in progress and symptoms were being experienced by the non-responders of the present series as well as by other patients in this area.

The fact that the patients who responded well to the original course of treatment were able to go through the remainder of the hay-fever season with little or no further use of the treatment was not due to absence of exposure to pollen. Some patients were heavily exposed because of their occupations or their pleasures. For example, one was a golf professional, another was a gardener, and a third, a student by avocation, spent many hours sailing on a river which runs through grassy meadows.

Eye Irritation.—The eye irritation so common in hay-fever was usually completely relieved *pari passu* with improvement in nasal symptoms. There were two exceptions in whom eye irritation continued to occur after protracted outdoor exposure, and these were driven to take an anti-histamine for relief of this symptom; they claimed that this was more effective than when used before starting hydrocortisone treatment.

Chest Symptoms.—Five of the 13 patients who responded favourably to treatment had been accustomed to suffer from mild chest symptoms as a part of their hay-fever. In four of these patients the chest symptoms diminished as the nose improved. In three of these four, during the period of maintenance treatment, chest symptoms returned, in two taking a different pattern from the original one, in that nocturnal asthma occurred instead of morning cough and sputum. These secondary chest manifestations may have been related in some indirect way to the treatment, because they ceased when this was discontinued, the nose throughout remaining normal, even after treatment was stopped. The fifth patient suffered while on treatment from aggravation of an evening asthma which subsided a few days after stopping treatment. One other patient, not usually liable to chest symptoms, developed some cough during treatment.

Nasal Mucosa.—At the beginning of treatment, inspection of the nasal mucosa revealed it to be abnormal in all patients, although the type of change varied from patient to patient. In those who responded to treatment the mucosa was normal in appearance when they were symptom-free. In some who showed the gradual type of symptomatic response the appearance of the mucosa was normal at a stage when mild residual symptoms, such as irritability, were still present. In general, the non-responders showed no change in the mucosa.

Nasal Smears.—Examination of the nasal smears has not been helpful. The appearances during the acute stage were so variable that decisive changes in the cytological picture could not be recognized. Pennypacker (1954) has likewise found the study of nasal smears unrewarding in the same connexion.

Factors Influencing the Clinical Response

We have examined the data in some detail in relation to factors which may have a bearing on the clinical response. We have taken the 13 patients who responded to one or other dosage level as "responders" and regarded the others as "non-responders." We appreciate that this division is somewhat false, because not all patients who failed to respond to the first dosage level were put on to higher dosage. For this reason, as well as the small numbers involved, our inferences should not be regarded as conclusions, but only as clues worth pursuing in more formal later studies.

The age of the patient has little influence on the chance of responding to treatment, although the younger patients did slightly better than the older. The length of the history is possibly of greater importance, because five of the six patients with histories of less than seven years responded well.

The relationship of prophylactic pollen injections to the response to hemisuccinate nose-drops is not straightforward. Those patients who had experienced good results in previous seasons from pollen injections did well with the drops, six out of seven responding, compared with four out of eight among those who had received injections but without benefit, and three out of seven among those never treated by injections (Table I).

TABLE I.—*Relation Between Prophylactic Pollen Injections in Previous Seasons and Clinical Response to Local Hydrocortisone*

Pollen Injections in Previous Seasons	No. of Patients	No. Responding
Given with good response ..	7	6
" " " poor " " " " ..	8	4
Never given .. " " " " ..	7	3

So far as pollen injections before the present season are concerned, patients who had had them did well with the nose-drops, five out of six responding, although, of course, the pollen injections had failed to prevent the occurrence of overt hay-fever. An interesting facet is that, whereas out of eight "responders" who had not received pollen injections in 1957 there were five who had chest symptoms during treatment, no chest symptoms complicated treatment in the five "responders" who had received such injections (Table II).

TABLE II.—*Liability to Chest Symptoms in the 13 Patients Responding Well to Local Hydrocortisone in Relation to Pollen Injections Before Current Season*

Pollen Injection Before Current Season	No. of Patients	Chest Symptoms
Given .. " " " " ..	5	0
Not given .. " " " " ..	8	5

The three factors which we tentatively suggest may increase the likelihood of a good response to hydrocortisone nose-drops—namely, a short history, previous good response to pollen injections, and pollen injections given before the current season—appear to be independent of one another.

Case 1

A male civil servant aged 32 had had severe hay-fever since 1950. In 1951 he had continuous nasal symptoms, worst in mid-afternoon and again during the night, from mid-May to end of July; "pollaccine" injections were ineffective. In 1953 skin tests were positive to grass and plantain. Mixed pollen injections gave an excellent result; these were repeated in 1954–6 with steadily diminishing effectiveness, but nocturnal symptoms never recurred. The season ran to the end of July in 1955 and 1956. He suffered badly from the side-effects of antihistamines.

Symptoms in 1957 Before Starting Treatment.—Mixed pollen injections were given, as previously, before the season. On June 10 he had an abrupt onset of continuous daytime running of eyes and nose, with nasal obstruction and heaviness, which persisted steadily. On June 19 the nasal mucosa was pale pink, lumpy, sticky, and crusted.

Treatment was begun on June 19 at a concentration of 1 mg./ml. After the first few hours he was symptom-free except for nasal irritability—that is, liability to sneeze once or twice on the slightest stimulus. He was fully normal on June 21. On reducing the dose on June 22 there was increasing coryza. On returning to the full dose on June 23 he became symptom-free. Treatment was continued until June 28, when the nasal mucosa was normal. Treatment was stopped.

A mild relapse began several days after June 28. After one day's further treatment he was again symptom-free for some days. A further one-day course was taken similarly in mid-July, with no further relapse.

Case 2

A golf professional aged 47 first had hay-fever in adolescence, following the subsidence of an asthmatic tendency as a child. He had severe and protracted coryzal attacks, building up rapidly on outdoor exposure from late May to end of June. Morning cough and sputum, with slight chest tightness, occurred when hay-fever was bad, usually in the later part of the season. In 1953–5 grass-pollen injections were given with good results. Major symptoms did not occur in 1956.

Symptoms in 1957 Before Starting Treatment.—He had mild symptoms from the end of May, and severe attacks began in the second week of June. Slight morning cough occurred after particularly bad days. On June 17 the nasal mucosa was sticky and unevenly oedematous, patchily pink, and red in colour.

From June 17 to 23 a concentration of 1 mg./ml. was given and he was free of nasal symptoms from the first day, except for bouts of "half a dozen sneezes" on some occasions on arriving at his place of work (as a golf professional). Morning cough became rather worse in the later part of the week and mild asthma occurred on the evening of June 23. The nasal mucosa was normal on June 24.

He had no further trouble, except for some mild nasal symptoms on June 26.

Discussion

The present study was intended to be a pilot one in order to form some preliminary judgments on the value of nose-drops containing a soluble compound of hydrocortisone in amounts unlikely to have any systemic action. It was hoped also to get some guidance on the best concentration to use if the treatment proved beneficial. The intention was to make use of such information in the design of more formal trials next season if the results looked encouraging.

In the event, hydrocortisone hemisuccinate sodium has proved to be a valuable treatment for about two-thirds of the patients treated, and we think it likely that better results will be obtained when it is possible to use higher concentrations than in the present study, in which their use was precluded only by technical reasons which will be avoidable in future.

The clinical response to this treatment has a distinctive quality. Improvement first reveals itself by the relief of those symptoms, such as nasal obstruction, which usually persist between the episodic coryzal attacks brought on by specific exposure or other irritation. Following this change, the episodic attacks become milder and shorter until they cease. The threshold of irritability of the nasal mucosa is the last feature to return to normal. This is the opposite of what happens with antihistamines, which diminish or suppress the coryzal attacks but often leave the patient with constant nasal discomfort, and, in some cases, with increased nasal obstruction. This difference in response suggests that

antihistamines quickly suppress certain components of the mucosal reaction but leave other components unchanged, whereas hydrocortisone produces a gradual change of the mucosa towards completely normal behaviour.

One feature of the results has both practical and theoretical implications. This is the finding that when the nose responds well to the nose-drops the concomitant eye irritation and chest symptoms commonly subside. This parallel change taking place in nose, eyes, and chest has been observed by other workers using hydrocortisone or prednisolone snuff in the treatment of hay-fever (Herxheimer and McAllen, 1956; Godfrey *et al.*, 1957). However, these workers were using enough of the corticoids to raise the possibility that the suppression of manifestations remote from the nose was due to a systemic action. In the present study a similar response was obtained with a daily dose of hydrocortisone which did not exceed 2 mg. in any of the patients concerned. Consequently, the possibility that these secondary manifestations of hay-fever were controlled by a systemic action of the hydrocortisone is remote. In other words, the improvement in the nasal mucosa was itself responsible in some way for the relief of eye and chest symptoms. This implies that these symptoms arose as a secondary consequence of the abnormal state of the nasal mucosa and were not due to the direct action of pollen on the organs concerned.

However, the issue is not clear-cut, because some of the patients who initially lost their chest symptoms developed them again later while on treatment, although the nose was normal. The secondary manifestations of hay-fever may therefore be of multiple pathogenesis. An important practical possibility is that a course of pollen injections before the current season, even when it has not prevented the onset of hay-fever, will protect the patient against a return of chest symptoms after his nose has responded to local hydrocortisone. These two methods of treatment may therefore prove to be complementary.

Leaving aside the question of giving pollen injections before the season, which requires further study, we are able to formulate a provisional plan for the use of local hydrocortisone hemisuccinate sodium in the treatment of hay-fever. This is possible because of two circumstances in the present study which largely compensate for its being uncontrolled. First, when local hydrocortisone is effective a definite improvement occurs within 24 hours, so that little time is lost if it turns out to be ineffective in a particular patient, even allowing for trying more than one concentration. Secondly, the decisive quality of the favourable responses left no doubt that the treatment was indeed efficacious, a conclusion arrived at the more readily because the hay-fever season coincided with a long spell of settled weather, so that external conditions altered little. We propose:

1. A solution containing hydrocortisone hemisuccinate sodium in a concentration equivalent to 2 mg. of free hydrocortisone per ml. should be used, two or three drops being applied to each nostril four times a day (the patient should be told how to use nose-drops efficiently).

2. If a good response is obtained treatment should be maintained for a few days after the nose has become symptomatically normal. The treatment can then be tailed off over a few days. (The only contraindication to maintaining treatment beyond the nasal response should be the development or recurrence of chest symptoms.)

3. After treatment has been stopped further recurrence of nasal symptoms will usually be aborted by one day's treatment.

Summary

Hay-fever subjects in a stage of symptoms have been treated with nose-drops containing hydrocortisone hemisuccinate sodium, a compound which is freely soluble in water.

Among 22 patients treated were 13 who showed a decisively favourable response, with the nose becoming normal in one to four days.

Eleven of these 13 patients responded to a concentration of 1 mg. per ml., with a maximum daily dose of 2 mg. of hydrocortisone. Five patients not responding to this concentration were treated with double this strength, and two responded. Thereafter, any recurrence of nasal symptoms responded to one day's treatment.

The nasal mucosa became macroscopically normal in those patients who responded well to treatment. Nasal smears did not yield helpful information.

Secondary manifestations of hay-fever, such as eye irritation and chest symptoms, usually subsided together with the nasal symptoms. However, chest symptoms sometimes recurred while the patient was under treatment with a normal nose, although they passed off again on stopping treatment, without immediate recurrence of nasal symptoms.

Factors tentatively suggested as improving the chance of a successful response to local hydrocortisone treatment were a short history of hay-fever (less than seven years); pollen injections in past years with good results; and pollen injections before the current season even though, as must be obvious, they had failed to prevent the occurrence of hay-fever.

Some practical and theoretical implications of the results are discussed and a provisional plan for the use of this form of treatment is formulated.

We are indebted to Glaxo Laboratories for making a gift of the nasal tablets.

ADDENDUM.—Since this article was written the provision of a tablet of hydrocortisone hemisuccinate sodium which is rapidly soluble, non-irritant, and non-deliquestent has proved to be technically difficult. The manufacturers have supplied us with slowly dissolving tablets which have proved satisfactory in non-seasonal allergic rhinitis. However, the answer to the problem may be the use of prednisolone phosphate, which is stable in aqueous solution as well as being highly soluble. In non-seasonal allergic rhinitis this compound seems to be roughly three times as active, weight for weight, as hydrocortisone hemisuccinate sodium.

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