CORTICOTROPHIN IN TREATMENT OF ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS

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The exacerbations of chronic bronchitis in patients admitted to hospital with severe emphysema are associated with a high mortality despite the advent of antibacterial therapy. Even when the exacerbations are due to pathogenic bacteria that are sensitive to the antibacterial drugs used, the patient may die of respiratory insufficiency in the critical period before the infection is overcome.

Some of the reasons for the rapid deterioration and high mortality have been discussed in recent papers on the physiology of respiration before and during acute respiratory infections in the emphysematous subject (Cardon *et al.*, 1951; Westlake, 1954; Riley, 1954; Westlake *et al.*, 1955). Between attacks the less severely emphysematous patient may be able to maintain normal arterial oxygen and carbon dioxide tensions, or may have only a mild degree of anoxaemia on exertion. Others live permanently in a state of chronic respiratory failure, this being the term used to describe the anoxaemia and hypercapnia that occur when the respiratory drive is insufficient to maintain normal gaseous tensions in the arterial blood. In both these groups of patients, and especially in the latter group, an infection that would be regarded as trifling in the non-bronchitic subject may rapidly precipitate acute respiratory failure.

Briefly, this may be attributed to three main factors: (1) Decrease in bronchial lumen, which is probably the most important factor, and to which bronchospasm, mucosal oedema, and increased bronchial secretions contribute in varying degree. (2) Anoxaemia which impairs the sensitivity of the respiratory centre and leads to further hypoventilation. (3) Increased metabolic demands of fever and respiratory exertion.

The decrease in bronchial lumen has the triple effect of increasing the work of breathing, lowering the efficiency of gaseous exchange, and impeding the expectoration of sputum. Considerable improvement in pulmonary function would occur if an effective method of increasing bronchial lumen were available. A controlled trial was therefore carried out to determine whether corticotrophin would have this effect in patients with acute exacerbations of chronic bronchitis who were in respiratory failure.

Methods

Patients admitted to the medical wards between October, 1954, and April, 1955, with exacerbations of chronic bronchitis were assessed for their suitability for including in the trial. Only those who were so severely ill that they had anoxaemia and carbon dioxide retention with an arterial plasma carbon dioxide tension of 45 mm. Hg or above were accepted. Bronchitic patients who had clinical or radiographic evidence of lobar consolidation, tuberculosis, or malignant disease were excluded. Cases of status asthmaticus

and of chronic asthma without a history of chronic bronchitis were also excluded.

A radiograph of the chest was taken in all patients, and a specimen of sputum was obtained for direct microscopy, culture of any pathogenic organisms, and testing for their antibiotic sensitivity. All patients had an initial arterial blood sample taken before any oxygen therapy was given, and the oxygen saturation, pH, and carbon dioxide tension were determined by methods described previously (Westlake, 1954). These afforded a valuable guide to the severity of the illness and were essential criteria for the diagnosis of respiratory failure.

The patients were allotted alternately to one of two groups. The first group was given corticotrophin gel in a dosage of 15 units six-hourly by intramuscular injection for a minimum of six days and for an average of two further days in reduced dosage. The other group was used as a control group, but it was not thought necessary to give injections of "dummy" solution as the patients were receiving injections of antibiotic drugs. In all other respects the management of the two groups was identical. The initial antibiotic regime consisted of soluble penicillin, 500,000 units, and streptomycin, 1 g., intramuscularly six-hourly for 48 hours. Further antibiotic therapy depended on the results of the sputum examination. If *Haemophilus influenzae* was present, streptomycin was continued in a reduced dosage of 1 g. 12-hourly together with the penicillin. If only pneumococci were present, streptomycin was stopped and penicillin alone was given. The antibiotic therapy was continued until the sputum became mucoid and contained no pathogenic bacteria. Intensive antispasmodic therapy was given by the inhalation of 1 ml. of 1% isoprenaline two-hourly during waking hours by Collison inhaler, and in some cases supplemented by aminophylline administered intravenously or per rectum. Repeated intravenous injections of nikethamide (5-8 ml.) were given to those patients who were stuporous and failing to cough. Continuous oxygen was administered via a "polymask" at flow rates of 1-3 litres a minute. Postural drainage was performed regularly where possible. Digoxin, mersalyl, and a low-sodium diet were used where cardiac failure was prominent. No sedatives were given to any patient.

Clinical assessment of bronchial obstruction is both difficult and unreliable. An objective method of following day-to-day variation in bronchial obstruction was sought which could easily be performed at the bedside. The test of maximum voluntary ventilation (M.V.V.) was chosen. The patients were asked to breathe as fast and as deeply as possible for 15 seconds through a Siebe-Gorman box valve and wide-bore elephant tubing into a Douglas bag. The expired air was then expelled through a gasmeter and measured, the average of three estimations being taken as the M.V.V. and expressed as litres per minute. This method is adequate for estimating the low M.V.V.s of severe emphysema.

The M.V.V. was estimated on admission and on the third, fifth, eighth, and tenth days. During the early stages of the trial the test was done before and after inhalation of isoprenaline, but the differences were small (1-4 litres), so later estimations were done only after isoprenaline. The resting ventilation was also measured on admission before giving oxygen.

Results

In the trial there were 24 patients, of whom 12 received corticotrophin gel in addition to the other forms of therapy described. The relevant clinical details are noted in Table I, together with the results of sputum examination and of initial blood gas analysis, and the resting ventilation. The age distribution was similar in the two groups, and in both groups there were four patients in whom cardiac failure was present. All pathogenic bacteria isolated from sputum were sensitive to either penicillin or streptomycin.

The corticotrophin group had a lower mean initial arterial oxygen saturation and a lower mean initial M.V.V., but the differences did not reach conventional levels of statistical

TABLE I

Corticotrophin								Control							
Case	Age, Sex	C.C.F.	O ₂ Satn.	pH	pCO ₂	R.V. L./min.	Sputum	Case	Age, Sex	C.C.F.	O ₂ Satn.	pH	pCO ₂	R.V. L./min.	Sputum
1	69 M		60.0	7.40	47.9	12.5	Pneum.	2	69 M		60.1	7.40	46.1	13.1	<i>B. coli</i>
3	69 F	+	48.0	7.30	73.5	7.5	A. No path.	4	71 F		56.8	7.33	62.8	9.2	<i>H. infl.</i>
5	68 M		78.5	7.37	52.4	9.8	<i>H. infl.</i>	6	48 M	++	84.0	7.36	58.6	8.9	No path.
7	65 M	++	83.0	7.46	45.2	8.6	"	8	70 M	+	69.2	7.37	53.1	10.4	<i>H. infl.</i>
9	46 F		57.2	7.37	49.8	10.7	Staph.	10	60 M		81.8	7.34	51.7	8.5	No path.
11	63 M	+	44.0	7.24	88.0	6.2	A. No path.	12	60 M		81.5	7.41	53.2	8.5	"
13	58 M		73.8	7.41	48.0	10.3	No path.	14	73 M		81.6	7.40	55.0	10.1	"
15	71 M	+	53.0	7.35	63.5	8.1	"	16	63 M	+	74.0	7.38	60.7	9.7	<i>H. infl.</i> + pneum.
17	55 M		81.4	7.40	47.0	9.1	<i>H. infl.</i>	18	62 M	+	45.6	7.32	77.2	7.6	"
19	60 M		48.3	7.33	71.6	6.6	No path.	20	50 M		72.2	7.39	59.0	5.9	<i>H. infl.</i>
21	59 M		56.2	7.33	58.0	13.2	<i>H. infl.</i>	22	59 M		83.1	7.38	62.2	9.8	<i>H. infl.</i> + pneum.
23	58 M		82.0	7.39	49.5	6.2	A. No path.	24	59 M		86.6	7.40	54.5	11.0	<i>H. infl.</i>
Mean:	61.9	4/12	63.8	7.36	57.9	9.1		Mean:	62.0	4/12	73.0	7.37	57.0	9.4	
S.D.:			14.2	0.034	12.3	2.2		S.D.:			12.6	0.025	9.8	1.7	

C.C.F.=Congestive cardiac failure. R.V.=Resting ventilation. A=Antibiotic therapy prior to admission.

TABLE II

M.V.V. in Litres per Minute										
Corticotrophin						Control				
Case No.	Day 1	Day 3	Day 5	Day 8	Day 10	Case No.	Day 1	Day 3	Day 5	Day 8
1	23.1	20.4	25.8	—	—	2	15.2	16.0	20.3	21.2
3	16.5	—	15.3	—	28.0	4	21.1	16.3	29.0	36.8
5	12.4	22.4	21.6	24.9	32.5	6	21.9	20.2	17.6	19.1
7	16.0	19.4	23.2	25.3	34.4	8	19.0	27.6	25.8	22.6
9	19.2	19.1	23.4	26.9	29.6	10	12.0	30.9	40.9	48.5
11	12.4	27.4	33.7	34.9	35.3	12	22.6	28.1	32.3	28.3
13	19.5	29.8	36.6	36.9	36.9	14	22.8	34.8	28.8	41.7
15	12.3	14.3	19.1	17.4	20.1	16	22.6	37.0	39.7	37.3
17	27.6	30.9	27.1	28.1	31.8	18	11.7	16.7	—	—
19	13.0	13.5	—	—	25.0	20	12.8	17.1	20.5	17.5
21	19.7	28.5	20.6	27.2	30.1	22	27.0	23.2	40.9	48.1
23	19.8	40.3	40.2	56.5	58.6	24	24.0	24.5	28.4	34.3
Mean:	17.6	24.2	26.3	30.9	32.9	Mean:	19.4	24.4	29.5	32.3
S.D.:	5.5	7.5	6.6	10.5	9.5	S.D.:	4.9	7.7	7.9	10.8

significance (Table I). Comparison of the two groups during and after treatment showed that the addition of corticotrophin gel to standard methods of treatment failed to cause any improvement in the rate of recovery. The mean M.V.V. did not increase significantly on any given day over the mean value for the control group on that day (Table II and Graph).

Mean values of maximum voluntary ventilation in corticotrophin (A.C.T.H.) and control group over 10 days.

The other (Case 1), who received corticotrophin, died on the 10th day in acute respiratory failure, and was found to have gross bullous emphysema and blockage of the bronchi with profuse mucopurulent sputum. Other patients died on the 13th, 16th, and 34th days from respiratory insufficiency. Vestibular damage occurred in one patient who inadvertently received streptomycin sulphate, 4 g. daily for seven days; but after six months of out-patient physiotherapy he has made a complete functional recovery.

Discussion

Although the total number of patients in the trial was small, it is reasonable to conclude from our findings that

corticotrophin is of negligible value in the treatment of the severe exacerbation of chronic bronchitis, even when the acute episode is accompanied by marked wheezing. This conclusion must not be taken as applying to cases with an asthmatic history and severe bronchospasm, since such cases were deliberately excluded from the trial. It is unlikely that a larger dose of corticotrophin gel would have been more effective, for it is known that maximal adrenal stimulation occurs in normal subjects with a dosage of approximately 2 units an hour of this hormone (Bayliss and Steinbeck, 1954; Cope, 1955), and this level should have been achieved with the dosage used in the trial of 15 units of gel six-hourly. If a larger quantity of circulating adrenocortical hormones is required than the adrenals can themselves secrete, then hydrocortisone or cortisone would have to be used rather than corticotrophin.

The value of corticotrophin in status asthmaticus and in chronic asthma has been repeatedly shown in recent studies (Kania and Schmidt, 1954; Ball, 1954; Savidge and Brockbank, 1954; Pearson, 1955; Davies and Williams, 1955). Pearson, in a series of 10 cases of severe asthma treated with either corticotrophin or cortisone, included three patients with a purulent sputum but in whom wheezing was the predominant symptom. These each received 30 mg. of soluble corticotrophin eight-hourly, and the improvement that occurred within 48 hours led him to conclude that "the good effects seen (with corticotrophin) were not counteracted by some degree of bronchial infection."

This conclusion is not shared by Davies and Williams (1955). They treated a group of 44 asthmatic patients with 49 courses of corticotrophin or cortisone, and found that, whilst 87.5% were dramatically improved, three failed to improve, and that these three had a heavily purulent sputum. They also used seven courses of hormone treatment (type unspecified) in six patients with "chronic bronchitis and wheezing," and only two patients showed any improvement, this being classed as "good" rather than "dramatic." They emphasize the importance of distinguishing between asthma and bronchitis before deciding on hormone therapy, and our results confirm this basic difference in response.

Summary

A controlled trial has been carried out to determine whether corticotrophin is effective in relieving bronchial obstruction in patients admitted to hospital with acute exacerbations of chronic bronchitis.

In a series of 24 patients, alternate cases were given 60 units of corticotrophin gel daily in addition to antibiotic therapy and all the other usual measures of treatment. No evidence of any beneficial effect could be found either clinically or on physiological testing, and an overall mortality of 21% during the in-patient period was apparently not influenced in either direction by the corticotrophin.

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THRUSH NAPKIN RASHES

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The purpose of this paper is to show that thrush infection of the napkin area is a common condition in babies under 6 months of age in London to-day, and to describe its features and associations. Skin thrush in infancy has been said to be rare (Wright, 1954), but Holzel (1953) thought that it probably occurred more often than was recognized, and reported 11 cases.

Present Investigation

In April, 1954, a severe napkin rash, with the appearance described as typical of thrush, was seen in a week-old baby, and the skin swab showed the presence of *Candida albicans*. Two more examples were seen shortly afterwards, and it was decided to keep a close watch for further cases. During the next year most napkin rashes in babies in the obstetric hospital and attending the infant welfare department were seen by me. When a clinical diagnosis of thrush infection was made, a swab was taken from the rash and cultured for candida. As a control, swabs were also taken from examples of other types of napkin rash, from the perianal area of babies with oral thrush but no lesions in the napkin area, and finally from the buttocks of healthy infants. This last group was composed mostly of babies in the obstetric hospital, and included two who were immediate neighbours in both the nursery and the lying-in ward of a baby with oral thrush.

Swabs were cultured on blood-agar and Sabouraud's medium. Any yeasts isolated were identified by sugar reactions and ability to form chlamydospores. The results are shown in Table I.

Of 47 cases diagnosed as thrush napkin rash, yeasts were isolated from 42. In 39 of these they proved to be *C. albicans*, in two identification was doubtful, and in the remaining case another yeast was found. The presence of candida did not appear to be a chance finding unrelated to the cause of the rash, because no yeasts were grown from 28 infants with other types of napkin rash or from 15 healthy babies. In approximately one-half of infants with

TABLE I.—Results of Cultures for Yeasts from Swabs of Skin of Napkin Area in 102 Babies

Clinical Diagnosis	No. of Cases	No. from which Yeasts were Cultured	No. with <i>C. albicans</i>
Thrush napkin rash ..	47	42	39
Excoriated buttocks ..	20	0	
Ammonia dermatitis ..	8	0	
Oral thrush but no napkin rash	12	5	5
Healthy babies	15	0	

oral thrush candida could be grown from the perianal skin, although no lesions were visible. However, this does not invalidate the bacteriological findings in most of the 42 cases of thrush napkin rash from which candida was isolated, since only 12 had oral thrush at the time.

Thus 42 examples of thrush napkin rash were found in one year. Of 1,300 babies born in the obstetric hospital in that period, 37 were known to have been affected in the first six months of life—an incidence of nearly 3%. This suggests that the condition is common enough to be considered in the differential diagnosis whenever a napkin rash is seen.

Clinical Features

The common sites affected were the buttocks and inner thighs; most cases had lesions in both areas. The rash usually appeared on the prominences of the buttocks, and less frequently the perianal region was involved. In about a quarter of the cases the genitalia were affected and in a few the lower abdomen showed lesions. It is important to realize that thrush infection of the thighs, genitalia, or lower abdomen may occur without involvement of the buttocks.

The early lesions consisted of small dull-red areas, which subsequently coalesced in many instances. Sometimes a large dry red area with circumscribed lesions at the periphery was already present when the case was first seen. On the thighs and abdomen the lesions tended to remain circumscribed. Desquamation of the affected areas occurred, often after the formation of small flat superficial vesicles (Fig. 1). As desquamation proceeded, the peripheral part of the thin white epithelium covering a vesicle frequently remained behind. Small isolated lesions thus denuded of superficial epithelium and surrounded by a white collar are characteristic of thrush infection (Fig. 2).

FIG. 1.—Early thrush napkin rash showing flat superficial vesicles.

FIG. 2.—Thrush napkin rash showing characteristic lesions on inner thighs.