intervals for four hours after the administration of each analogue.

The results show that the placebo did not improve the asthmatic condition, whereas all the active compounds effected some improvement. From the analysis of the group results, quite distinct time-response curves for the different analogues were obtained. Isoprenaline had the quickest but most transient action. Ephedrine and methoxyphenamine had the most prolonged action, but were the slowest to take effect. Orciprenaline occupied an intermediary position. In general, orciprenaline 20 mg. gave the best results as regards duration and magnitude during the four hours of observation.

The maximum response occurred 60 minutes after isoprenaline, 120 minutes after orciprenaline, and 210 minutes after both ephedrine and methoxyphenamine.

We are indebted to the staff of the Department of Respiratory Physiology for carrying out the investigations described in this report, especially Mr. James Booth, S.R.N., Mr. Peter Wilkes, S.R.N., Mr. Norman Curnock, S.R.N., Mrs. Sheila Clarke, S.R.N., and also Mrs. K. Tattersfield, who prepared the graphs.

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BRONCHODILATORS AND CORTICOSTEROIDS IN CHRONIC BRONCHITIS AND EMPHYSEMA

BY

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Many patients suffering from chronic bronchitis and emphysema are disabled by respiratory insufficiency even during remission from exacerbations of acute infection. Impaired breathing capacity due to increased airway resistance is an important factor in the causation of this disability. Expiration may be prolonged, wheezy, and accompanied by rhonchi. In this respect the pattern of breathing resembles that seen in bronchial asthma. The value of bronchodilators and corticosteroids in the treatment of asthma is now well established. The points of resemblance seem close enough to justify a trial of these drugs in bronchitis and emphysema, notwithstanding certain differences which are believed to exist in the mechanisms of airway narrowing. While expiratory airway narrowing in bronchitis and emphysema is doubtless irreversible, inasmuch as it is due to destruction of pulmonary elastic tissue and consequent rise in transpulmonary pressure, bronchodilators and corticosteroids might conceivably widen the bronchial lumen in so far as narrowing is due to oedema or hyperaemia of the mucosa or to secretion of mucus.

Bronchodilators, such as isoprenaline sulphate, are widely used in the treatment of chronic bronchitis by patients who complain of shortness of breath.

As to the value of steroids in chronic bronchitis and emphysema, some statements of a general nature have been made; in the main they are non-committal in their recommendations, suggesting that steroids are perhaps worth trying (Nicholson, 1955; Birch, 1960). Bickerman *et al.* (1955) claimed good results in emphysema and other non-asthmatic pulmonary conditions, but the criteria of diagnosis and of improvement were not defined, nor was the cause of the emphysema stated, and doubts must arise whether this was chronic bronchitis as it is seen in England. Davies and Williams (1955) treated six cases with "good results" in two. Moyes and Kershaw (1957) found that prednisolone given with tetracycline was no more effective than oral aminophylline with tetracycline. As the aminophylline dosage was small by present standards, it may be inferred that prednisolone played no active part. Lorriman (1959), investigating six chronic bronchitics, obtained improvement in one case, a worsening in another, and no material change in the remainder on prednisolone. Cullen and Reidt (1960) made ventilatory, blood-gas, and diffusion studies on 14 patients who obtained no benefit from steroids. Clifton and Stuart-Harris (1962) gave steroids to 28 patients, in two-thirds of whom a 20% increase in ventilatory capacity was obtained, and in a quarter a 60% increase, but these authors express doubt regarding the ultimate benefit.

This paper describes a trial of isoprenaline sulphate aerosol and of oral prednisolone in the treatment of patients suffering from chronic bronchitis and emphysema showing impairment of breathing capacity during remission from acute infection.

Material

The patients, all of whom suffered from chronic bronchitis and emphysema with ventilatory impairment, were drawn from those referred to the out-patient department at Dulwich Hospital, and from patients previously admitted with acute infective episodes. The latter were not submitted to trial until acute infection had subsided. All patients were in remission at the time of testing. The diagnosis of chronic bronchitis was based on a history of at least two years' continuous or intermittent productive cough in the absence of other disease to account for it. The diagnosis of emphysema was based on a history of progressive exertional dyspnoea in the absence of other non-bronchitic pulmonary disease, or significant cardiovascular disease, and on confirmatory physical signs and radiological appearances. Excluded from the trial were patients suffering from bronchial asthma and those over 70 years of age. The term "bronchial asthma" is here taken to mean a condition in which episodic dyspnoea, with wheezing or other evidence of expiratory airway narrowing, occurs unrelated to exertion, bronchitis, left ventricular stress, or inhalation of chemical irritants such as smog. Patients were also excluded whose status was uncertain as regards bronchitis or asthma, or who suffered from both conditions.

Of the 26 patients, 24 were men. The mean age was 58 years (range 45 to 68), and the ages of over half of them lay within the range of 61 to 66. It is believed that this

fairly represents the incidence of the disease within the limits chosen. The mean duration of history was 15 years (range 2 to 42). The onset was acute (bronchitis, pneumonia, war-gas, or smog) in half of the patients, and in the remainder it was gradual or insidious. Effort tolerance differed a good deal among the patients, but there was little variation in the individual patients so long as they were uninfected and unexposed to bad weather. All were wheezy at times, and a few were most of the time. Production of sputum was absent for long periods in only three men, in whom symptoms were due mainly to emphysema. At the time of testing no patients were in cardiac failure due to cor pulmonale, but two had been in failure during pneumonic exacerbations. Four had a secondary polycythaemia (haematocrit greater than 50%). One patient had persistent papilloedema. Electrocardiographic evidence of cor pulmonale was present in five cases. None had previously received steroid therapy.

Methods

The forced expiratory volume in 1 second ($F.E.V._1$) and forced vital capacity (F.V.C.) were measured on a spirometer of the type described by Bernstein *et al.* (1952) with variable-speed kymograph. The largest of three F.E.V.s was selected, unless a progressive rise at any one session indicated a "learning" effect, in which case spirograms were repeated until no further rise was obtained. All volumes were recorded at ambient temperature and pressure, for which no correction was made. Diurnal fluctuations (Lewinsohn *et al.*, 1960) were avoided by testing between noon and 5 p.m.

Each patient acted as his own control. Two to four measurements of $F.E.V._1$ uninfluenced by drugs were made in each case over a control period which varied from five days to three months (mean 33 days). These readings are referred to as "basal" F.E.V.s. The average of the basal F.E.V.s in any individual is called the "mean basal F.E.V." The expected vital capacity (V.C.), based on sex, age, and height, was derived from Needham *et al.* (1954). The expected, or "normal," F.E.V. for each patient was calculated as 83% of his expected V.C. (Tiffeneau *et al.*, 1949; Gaensler, 1951; Kennedy, 1953; Cara, 1953). The mean basal F.E.V. of each patient is expressed as a fraction of his normal F.E.V.

Isoprenaline sulphate 1% aerosol was administered from a conventional hand-operated nebulizer, which delivered 0.2 ml. of solution during 30 inspirations. The isoprenaline was given during the control period immediately after obtaining basal F.E.V. readings, and the F.E.V. was measured again five minutes later.

Prednisolone was given at the conclusion of the control period, and continued for four weeks. The standard scheme was prednisolone 60 mg./day orally in divided doses for three days, then 45 mg./day for four days, and thereafter 15 mg./day for 21 days, tailing off finally. Patients weighing less than 8 st. (51 kg.) received 45 mg., then 30 mg./day during the first week. Spirometry was performed on the 3rd, 7th, 14th, and 28th days of steroid administration. Of the 26 patients, 18 inhaled isoprenaline aerosol after testing, and spirometry was performed to determine the combined effect of both drugs. Patients were invited to declare their subjective assessment of the effect of the drugs.

Results

Control Period.—For each individual in the series the value of the mean basal F.E.V. during the control period has been calculated; these values ranged from 0.51 to 1.95 l., with a mean of 1.04 l. (see Table). Expressed as a percentage of "normal" values, the F.E.V.s ranged from 17 to 73%, with a mean of 39.5%. All spirograms exhibited retardation of expiratory flow rate. There was much spontaneous variation of F.E.V. in most subjects, the average range—that is, the difference between the highest and the lowest for each patient—for the whole series being 0.16 l. In one case the range (over four values) was 0.56 l. The greatest F.E.V. exceeded the smallest by over 10% in 17 cases, and by over 20% in 7 out of 26 cases.

Table of Results

Case No.	Pretreatment Values Mean Basal F.E.V.		Response to Drugs	
	Litres	% Normal	Isoprenaline	Prednisolone
1	0·52	25	+29*	+12
2	1·14	40	+10	−25
3	0·89	44	+34	+28
4	0·63	26	+30	+10
5	1·69	73	+22	0
6	1·27	35	+7	+6
7	1·43	49	+5	−7
8	0·80	30	+20	+10
9	0·68	24	+40	+15
10	0·89	30	+19	+9
11	1·02	40	Not obtained	−5
12	0·60	26	+25	+33
13	1·01	30	+47	+13
14	1·39	49	+8	−7
15	1·19	46	+5	+3
16	1·95	69	+23	−3
17	0·59	17	+37	+22
18	0·74	36	+19	+63
19	0·89	30	+23	−19
20	0·84	37	+20	−20
21	1·76	72	+6	+7
22	1·79	61	+7	−3
23	0·51	32	+43	−6
24	1·25	46	+9	+17
25	0·79	30	+27	−5
26	0·76	29	+10	+3
Mean	1·04	39·5	+21·0	+5·8

* The response to drugs is expressed as the percentage change in F.E.V. from basal levels.

Isoprenaline

Isoprenaline sulphate inhalations were given once to each of 11 patients and the percentage change was calculated. In a further 14 patients it was given on two or three occasions. For each individual the F.E.V.s after inhalation were averaged and the percentage change from mean basal was calculated. The results are shown in the Table. In every instance there was an increase in F.E.V. after isoprenaline, the mean increase being 21% (range 5 to 47%). An increase of 25% or more occurred in 8 out of 25 cases. The rise tended to be greater when the basal F.E.V. was below an individual's average. Viewing the series as a whole, the more a patient's basal F.E.V. was depressed below the expected level for age, height, and sex the greater was the tendency to respond well to isoprenaline, but the correlation was not close ($r = -0.5$), and could not possibly be used for prediction of a patient's response.

Patients were usually able to detect subjectively an increase of 20% or more. In the early stages of these experiments isoprenaline tablets were given sublingually, but this mode of administration was abandoned as it soon became clear that the response was usually smaller and less certain than was the case by inhalation.

Prednisolone

The response to prednisolone showed no consistent pattern in relation either to the high dosage during the first week or to the lower dosage during the remaining three weeks. The mean response to prednisolone was therefore taken as the average F.E.V. for the 3rd, 7th, 14th, and 28th

days, expressed as percentage increase over the average basal F.E.V. These results are shown in the Table. In 15 cases there was a positive and in 11 a negative (or zero) response, but many of these changes were small, bearing in mind the large natural variation, and in only 11 patients was the response (positive or negative) greater than 10% and in five greater than 20%. For the whole series the average was only 5.8% (S.E. 3.6%), which cannot be regarded as significant. The few patients in whom there may have been a favourable effect were partly counterbalanced by those in whom the reverse took place.

Although no patient in the trial was suffering from bronchial asthma, six gave a personal or family history suggestive of allergy.

Case 3: worse in summer; not affected by fog.
Case 13: daughter develops rash on contact with dogs.
Case 17: up to 10 years before the trial he was subject to occasional bouts of wheezing.
Case 18: niece has asthma.
Case 21: sneezing attacks in the morning.
Case 24: sister develops rash on contact with cats.

In each there was a positive response to prednisolone, the mean being 25% (S.E. 9%), which must be regarded as significant. If these are omitted from the whole series the mean response in the remainder is zero.

The euphoriant effect of the prednisolone led to a number of grossly inaccurate subjective assessments in patients whose F.E.V.s diminished or remained unchanged. Most of the patients also developed improved appetite and feelings of increased energy and of general well-being.

Isoprenaline sulphate aerosol was administered immediately after F.E.V. measurement to 18 patients taking prednisolone. In all cases increases of F.E.V. occurred that were comparable in size to those obtained with isoprenaline during the control period.

Discussion

The mean increase in F.E.V. after inhalation of isoprenaline aerosol was 21%, and an increase of over 25% occurred in 8 out of 25 cases. This accords with Lorriman's (1959) findings of an increase of over 25% in 12 out of 35 cases. Patients were usually able to detect subjectively an increase in F.E.V. of 20% or more. One can conclude that in cases of chronic bronchitis and emphysema with impairment of ventilatory capacity, what is probably a useful improvement occurs in about one-third. The patient's subjective assessment of response is reliable enough to render routine spirometry unnecessary. By and large, the more a patient's F.E.V. was reduced the greater was his response to isoprenaline. Although there is a positive correlation, it is too low to be of value as a means of predicting response to isoprenaline.

For the whole series there was no significant change in F.E.V. during the month's administration of prednisolone. Although the changes that occurred in individuals ranged widely (−25% to +63%), there was no correlation between such changes and the extent of ventilatory impairment during the control period, or the response to isoprenaline, and these parameters were of no value in predicting response to prednisolone.

It is concluded that prednisolone cannot be relied upon to provide a useful increase of ventilatory capacity in more than a minority of patients suffering from chronic bronchitis and emphysema. In clinical practice difficulty may arise from the fact that many emphysematous patients wheeze and on clinical grounds might be thought to be suffering from chronic bronchial asthma, in which condition a good response can usually be expected. If, however, the patient gives a personal or family history of allergy it seems that a moderate response may often be expected. This conclusion was to some extent foreshadowed by Fletcher (1958), who remarked that if corticosteroids appeared to give benefit the patient probably had asthma. The euphoriant effect of the drug may render subjective assessment of the response grossly inaccurate, and it is clear that in order to assess the value of the drug in any individual case ventilatory capacity must be measured by timed spirometry or any other appropriate test of expiratory capacity—for example, peak-flow measurement (Wright and McKerrow, 1959). This should be carried out on separate occasions before starting treatment, and the levels and their spontaneous variation be compared to the levels obtained on several occasions during a course of treatment. This is the only certain way of singling out those bronchitics who respond or in whom an asthmatic component coexists.

This investigation has not been concerned with the chronic bronchitic who is suffering from an acute exacerbation. Felix-Davies and Westlake (1956) have shown that such cases are refractory to corticotrophin, and presumably they are equally so to corticosteroids. Nevertheless it is sometimes extremely difficult to distinguish clinically between the acute infective exacerbation and status asthmaticus, especially if the patient's antecedents are unknown.

Summary

The breathing capacity of 26 patients suffering from chronic bronchitis and emphysema was measured, during remission from acute infection, by timed spirometry, and expressed in terms of $F.E.V._{.1}$. The extent of spontaneous change over a mean period of one month was measured. The greatest F.E.V.s exceeded the smallest by 20% in 7 cases out of 26.

Inhalation of isoprenaline sulphate aerosol yielded a rise in F.E.V. of 5 to 47% (mean 21%). An increase of over 25% occurred in one-third of the patients. The percentage increase tended to be greater the more depressed a patient's F.E.V. was below expected values, though some of those with depressed F.E.V.s responded poorly. Patients' subjective assessment of response to isoprenaline was fairly good.

Prednisolone given orally yielded a small non-significant rise (mean 5.8%) in the whole series. Although patients suffering from asthma were excluded, six patients gave a personal or family history suggestive of allergy, and in these there was a mean rise of 25%. In the remaining 20 patients the mean response was zero.

It is difficult to predict on clinical grounds which chronic bronchitics will respond to corticosteroids and which will not. Patients' subjective assessment of response was poor and often misleading. It is therefore desirable to measure any change occurring with corticosteroids by an objective test of expiratory capacity. Owing to the extent of spontaneous change in F.E.V. that can occur, it is essential to make several measurements during a period of treatment and to precede these by several measurements during a preliminary control period.

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SIMPLIFIED ARTERIOVENOUS SHUNT FOR USE IN HAEMODIALYSIS

BY

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Scribner *et al.* (1960) in their first description of an arteriovenous shunt for use in haemodialysis employed a supporting plate. This plate proved unsatisfactory because of the rotatory stresses imposed on the vessel cannulae, and has since been discarded. Various modifications in joining the by-pass to the vessel cannulae have been described (Quinton *et al.*, 1961 ; Sinclair *et al.*, 1961 ; Nayman, 1962). It has been the experience in this unit that a nut-bolt union which some of these designs incorporate is unsatisfactory. The threads on occasion have become filled with blood clot and the manœuvre of screwing the two components together has caused torsional strains on the by-pass and vessel cannulae. Hence it was thought advisable to discard the type of screw union previously described (Nayman, 1962).

The above designs of arteriovenous shunts involve the use of three tubular components (two vessel cannulae and a by-pass shunt) and either two or four junctions.

Principle and Material Used

A model has been designed in this unit which does not require a separate by-pass component and has only a single junction, which is of a non-screw type. The principle involved is to employ only arterial and venous cannulae, which for the purpose of haemodialysis are connected direct to the extracorporeal circuit.

At the termination of haemodialysis a shunt is effected by connecting the arterial cannula direct to the venous one. This technique requires a plastic that is flexible and allows some change in its alignment. Polytetrafluorethylene (" teflon ") is wholly unsuitable because of its rigidity, and has been replaced by polyvinyl chloride. This plastic material does not have the same potential of repelling water that teflon has, but has proved eminently suitable for use in the treatment of acute renal failure, where there is no need for the arteriovenous shunt to be retained in position for periods longer than three to four weeks.

Fashioning of Cannulae Ends

Apposition between the respective vessel cannulae is effected by fashioning the distal ends of each into a right-angled flange, which facilitates a fairly large area of contact without any change in the internal diameter of the cannulae.

The construction of this right-angled flange utilizes the principle of heating the plastic to the required shape and maintaining this shape by cooling. The inherent quality of any plastic material is such that a change in shape has to be brought about in a graduated manner. It has been our experience that the shaping of this right-angled flange is best done in two stages. The first stage entails converting the cylindrical shape into a cone. This is achieved by inserting a heated cone-shaped flaring mandrel into the end of the cannula (Fig. 1,A). The heat causes the plastic to flow on to the mandrel, and when the desired shape is obtained the cannula and mandrel are rapidly cooled (Fig. 1,B).

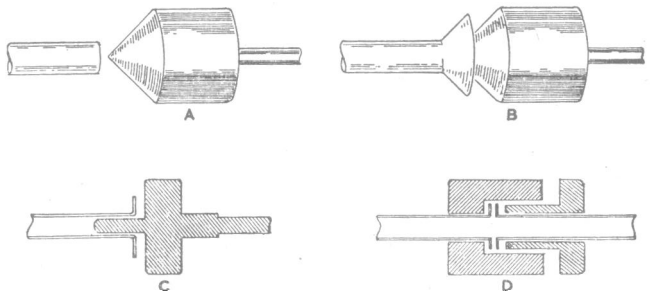

FIG. 1.—Stages of formation of right-angled flange. A: Cone-shaped flaring mandrel prior to insertion into end of catheter. B: Cone-shaped flange formed. C: Section of right-angled flange and right-angled flaring mandrel. D: Section of junction, indicating how apposition of the right-angled flange is maintained by the male and female components.

A right-angled flaring mandrel is now inserted into this cone (Fig. 1,C). The above process is repeated and the cone is now converted into the desired right-angled flange.

These two right-angled flanges have to be maintained securely in position without any danger of leakage, and must be capable of withstanding any stresses occasioned by movement. At the same time this junction has to be so designed that the connexion to the extracorporeal circuit is simple and rapid.

Junction

The right-angled flanged ends are secured in position by a non-screw " perspex " male-and-female junction. The male and female counterparts are each threaded over the vessel cannulae. These fittings are so designed that the external diameter of the male end, the internal diameter of the female recess, and the diameter of the flanged ends of the vessel cannulae are all congruent (Fig. 1,D). The union of the male and female parts will therefore ensure adequate contact of the flanged ends. This is maintained and secured by an appropriately designed spring clip.

This spring clip is fixed to, and in the disengaged position pivots on, the expanded end of the male part of the junction fitting. The other end of the spring is shaped so as to engage over the distal end of the female fitting. When in this engaged position the spring is prevented from slipping