A comparison of responses to bronchodilator drugs in chronic bronchitis and chronic asthma

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Isoprenaline by inhalation, adrenaline by inhalation, subcutaneous adrenaline, intravenous aminophylline, and subcutaneous atropine were administered to two groups of 18 patients suffering from either chronic bronchitis or chronic asthma using a Latin square design. Prednisolone was then given to both groups of patients for six days. The responses to the drugs were assessed by recording the F.E.V.₁₋₀ before and 20 minutes after the administration of the short-acting drugs and daily during the period of prednisolone therapy. No significant differences were found between the responses to the short-acting antispasmodic drugs in the group of patients suffering from chronic bronchitis and only an insignificant improvement in the mean F.E.V.₁₋₀ occurred during the period of prednisolone administration. Significant differences between mean responses to the anti-spasmodic drugs of the group of patients suffering from chronic asthma were observed. The mean F.E.V.₁₋₀ response following subcutaneous adrenaline was 44%, which was significantly better than the 23.7% improvement after adrenaline inhalation ($P=0.005$) and the mean improvement in F.E.V.₁₋₀ of 17.1% after subcutaneous atropine sulphate ($P=0.001$). A dramatic improvement in the mean F.E.V.₁₋₀ of 49.5% occurred after six days of prednisolone administration. It is tentatively suggested that a good response to subcutaneous adrenaline and a poor response to subcutaneous atropine, as judged by improvement in the F.E.V.₁₋₀, may be an indication that a good response to prednisolone can be expected in wheezy patients.

The objective responses to bronchodilator drugs are commonly used in the assessment of patients with airways obstruction. Isoprenaline given by inhalation is considered by many physicians to be the most efficient short-acting bronchodilator drug and would therefore appear to be the drug of choice for assessing the degree of reversible airways obstruction. The response to isoprenaline and other bronchodilator drugs, however, varies according to the severity of 'bronchospasm' at the time of the test (Hume and Gandevia, 1957; Hume and Rhys Jones, 1961). Some clinicians prefer adrenaline to isoprenaline. It has been reported that the injection of adrenaline has little or no advantage over the inhalation route in asthmatic patients not in severe status asthmaticus (Kennedy, 1961).

Aminophylline is frequently used in the treatment of wheezy patients, but little information is available about its efficacy compared with other bronchodilator drugs.

Cholinergic drugs have long been known to have bronchodilator properties (Finnegan, 1950),

and it has been suggested that there are different responses to atropine in asthma and in chronic bronchitis, the variation in response having some correlation with the response to corticosteroid drugs (Altounyan, 1964).

There is now no doubt about the benefit of corticosteroid drugs in the treatment of some asthmatic patients (Thursby-Pelham and Kennedy, 1958; Somner, Rogan, and Grant, 1960; Phear, Ball, and Page, 1960), but their place in the treatment of wheezy chronic bronchitis is less clear. It is sometimes difficult to differentiate clinically between patients with wheezy chronic bronchitis and patients suffering from chronic asthma, and because of this it is common practice to give a trial of corticosteroid drugs to most wheezy patients. By doing this a few patients thought to have chronic bronchitis are found to respond dramatically—as judged by the objective assessment of ventilatory function tests—and it is likely that this small group of patients have chronic asthma as their dominant disease and not chronic bronchitis. It may be argued that corticosteroid

drugs can, in fact, be dangerous when given to patients suffering from chronic bronchitis, especially in relation to hospital infection. Also a patient's stay in hospital is usually lengthened when corticosteroid drug assessment is performed. It would therefore be of considerable value if some indication could be obtained of a wheezy patient's probable response to corticosteroid drugs from the results of tests using simple bronchodilator drugs.

With these points in mind, it was decided to assess the effects of some commonly used bronchodilator drugs and prednisolone in patients suffering from chronic bronchitis and chronic asthma.

MATERIAL

Two groups of wheezy patients were selected for study. Group 1 consisted of 18 patients suffering from chronic bronchitis. All had cough and sputum occurring on most days for more than three months in the year for at least two years, and all complained of distressing wheeze and breathlessness. These patients were selected from the many chronic bronchitic patients admitted to the Respiratory Disease Unit at Edinburgh over a period of two years. They were chosen because of their distressing wheeze and because I thought that such a group might show more objective response to bronchodilator drugs than an unselected group of patients with chronic bronchitis. There were 12 men and 6 women in this group. Their ages ranged from 36 to 71 years (men 45 to 71 years and women 36 to 67 years). Eleven patients were cigarette smokers at the time of the study. Four patients had been cigarette smokers but had stopped prior to the study. Three of the women had never smoked.

Group 2 consisted of 18 patients with chronic asthma who were not at the time of the study being treated with corticosteroid drugs. In the selection of this group of patients, certain features of their history were used to diagnose chronic asthma as opposed to chronic bronchitis. Particular attention was paid to the mode of development, nocturnal exaggeration of symptoms as opposed to wheeze on getting up in the morning, and the smoking habits.

There were 14 men and 4 women in this group. Their ages ranged from 32 to 68 years (men 34 to 68 years and women 32 to 44 years). One patient in this group was a cigarette smoker at the time of the study; nine had stopped smoking; seven gave no smoking history; and one was a pipe smoker.

Both groups were chosen on purely clinical grounds. The results of previous ventilatory function tests, if they had been performed, were not taken into consideration. Full details of the patients are given in Tables I and II, and pretreatment F.E.V._{1.0} levels are recorded.

METHODS

The following drugs and methods of administration were used:

- (1) Isoprenaline sulphate 2% inhalation
- (2) Adrenaline HCl 1:100 inhalation
- (3) Adrenaline HCl 1:1,000 subcutaneous injection (0.5 ml.)
- (4) Aminophylline intravenous injection (0.5 g.)
- (5) Atropine sulphate subcutaneous injection (0.6 mg.)
- (6) Saline inhalation.

The inhalations were given using a Wright nebulizer for three minutes with an oxygen flow rate of 8 litres per minute.

The order of drug administration was randomized by the use of Latin squares, the drug sequence for each patient not being known until the morning of the first test. All tests were performed by the author on consecutive mornings between the hours of 8 a.m. and 10 a.m. in order to avoid diurnal variation in tests of respiratory function (Lewinsohn, Capel, and Smart, 1960). The one-second forced expiratory volume (F.E.V._{1.0}) was recorded using a modified Gaensler spirometer (McKerrow, McDermott, and Gilson, 1960). Three recordings of the F.E.V._{1.0} were made before the drugs were given and again 20 minutes after drug administration. The best of the three F.E.V._{1.0} recordings was accepted.

After the six tests had been completed, prednisolone, 40 mg. daily, was given and daily recordings of three F.E.V._{1.0} measurements were made on six consecutive mornings.

Some of the patients were receiving bronchodilator drugs as part of their routine ward treatment, but these drugs were not administered until after the morning test had been performed. The patients who had their own 'inhalers' were instructed not to use them after 4 a.m. and only short-acting preparations containing isoprenaline alone were allowed to avoid any possible carry-over effect of inhalations containing isoprenaline and atropine methonitrate.

RESULTS

The responses to the six drugs used in the first part of the study were calculated as changes in F.E.V._{1.0} expressed as percentages of the pretreatment values. A single pretreatment value was chosen in preference to a mean of all the values in the previous week, because a number of the asthmatic patients showed some spontaneous improvement in their F.E.V. readings during the week before prednisolone was administered, and therefore a mean of all the values during the first week would have tended to exaggerate the prednisolone response. Also during prednisolone therapy the changes in F.E.V._{1.0} over the period of six days were expressed as percentages of the prednisolone treatment values.

TABLE 1A
GROUP 1, CHRONIC BRONCHITIS

Patient Sex/Age	History of Cough and Wheeze	Other Points of Significance	Smoking History	Eosinophils in Blood and Sputum
I.W. F 67	Daily cough 30 yrs. Sputum daily 5 yrs, rarely purulent. Distressing wheeze 3 yrs. Cough and wheeze worse in mornings and at night	Nil	Non-smoker	10% eosinophils of 8,100 total white cell count. No eosinophils in sputum
J.G. F 58	Daily cough 5+ yrs. Sputum daily 5 yrs, mainly mucoid but purulent every winter. Wheeze 5 yrs. No nocturnal exaggeration of symptoms	Nil	20 cigarettes daily for 37 yrs	Normal differential white cell count. No eosinophils in sputum
J.D. M 63	Cough 10+ yrs. Sputum during winter months 10 yrs, frequently purulent. Cough and wheeze worse in mornings. Symptoms less marked during summer months	Nil	20+ cigarettes daily for 50 yrs	Normal differential white cell count. No eosinophils in sputum
W.R. F 47	Cough 40 yrs. Daily sputum 10 yrs, frequently purulent. Daily wheeze 5 yrs, worse when sputum purulent. No nocturnal exaggeration of symptoms	Nil	20+ cigarettes daily for 30 yrs	Normal differential white cell count. No eosinophils in sputum
J.H. F 55	Intermittent cough 20 yrs. Daily cough 5 yrs. Daily sputum 3 yrs, occasionally purulent. Progressive daily wheeze 2 yrs. Cough and wheeze worse in mornings	Nil	10-15 cigarettes daily for 30 yrs	Normal differential white cell count. No eosinophils in sputum
J.L. M 51	Cough 25 yrs. Daily cough 10 yrs. Daily sputum 10 yrs, frequently purulent. Intermittent wheeze 20 yrs. Daily distressing wheeze 5 yrs. Cough and wheeze worse in mornings	Nil	30-50 cigarettes daily for 35 yrs	Normal differential white cell count. No eosinophils in sputum
P.R. M 63	Daily cough worse in winter months 10 yrs. Sputum purulent after colds usually in winter months. Daily progressive wheeze 6 yrs. Cough and wheeze worse in mornings	Nil	15 cigarettes daily for 45 yrs	Normal differential white cell count. No eosinophils in sputum
R.G. M 65	Cough after head colds 10 yrs. Daily cough and sputum 5 yrs. Sputum frequently purulent. Progressive daily wheeze 2 yrs. Cough and wheeze worse in mornings	Nil	20 cigarettes daily for 40 yrs	Normal differential white cell count. No eosinophils in sputum
J.V. M 71	Recurrent cough 16 yrs. Daily cough and sputum 10 yrs. Sputum frequently purulent. Daily wheeze 8 yrs. Cough and wheeze worse in mornings	Nil	15 cigarettes daily for 50 yrs. Stopped 3 yrs before study for financial reasons	Normal differential white cell count. No eosinophils in sputum
E.P. F 36	Winter 'bronchitis' most of life. Daily cough 6 yrs. Sputum daily 5 yrs, mainly mucoid. Daily wheeze 5 yrs. Cough and wheeze worse in mornings. Occasional nocturnal wheeze. Symptoms less severe in winter months	Nil	Non-smoker	Normal differential white cell count. No eosinophils in sputum
J.R. M 57	Cough after colds many years. Daily cough and sputum 6 yrs. Sputum frequently purulent. Wheeze daily 3 yrs. Intermittent mild wheeze when sputum purulent 6 yrs. Cough and wheeze worse in mornings	Nil	20+ cigarettes daily for 30 yrs	Normal differential white cell count. No eosinophils in sputum
D.B. M 57	Daily cough worse in winter months and after colds 20 yrs. Sputum daily 10 yrs, frequently purulent. Progressive wheeze 10 yrs. Cough much worse in mornings	Nil	20+ cigarettes daily for 40 yrs	Normal differential white cell count. No eosinophils in sputum
A.J. M 53	Daily cough and sputum 12 yrs. Sputum purulent only after colds. Daily wheeze 8 yrs, worse when sputum purulent. Cough and wheeze much worse in mornings	Nil	20+ cigarettes daily for 35 yrs	Normal differential white cell count. No eosinophils in sputum
E.C. F 48	Daily cough 20 yrs. Daily sputum 15 yrs, infrequently purulent. Daily mild wheeze 10 yrs, distressing 6 mths. Cough and wheeze worse in mornings	Healed pulmonary tuberculosis	5-10 cigarettes daily for 30 yrs	Normal differential white cell count. No eosinophils in sputum
F.P. M 45	Winter 'bronchitis' 20 yrs. Daily cough 3 yrs. Sputum daily 3 yrs, mainly mucoid. Progressive wheeze 3 yrs. Cough and wheeze worse in mornings	Nil	20+ cigarettes daily for 20 yrs	Normal differential white cell count. No eosinophils in sputum
T.F. M 50	Winter cough most of life. Daily cough 8 yrs. Daily sputum 8 yrs, mainly mucoid. Progressive daily wheeze 5 yrs. Cough and wheeze worse in mornings	Some form of eczema 10 yrs ago	10 cigarettes daily for 32 yrs	Normal differential white cell count. No eosinophils in sputum
M.G. F 58	Winter cough 15 yrs. Daily cough 2 yrs. Daily sputum 2 yrs, frequently purulent. Daily wheeze 2 yrs. Cough and wheeze much worse in mornings	Nil	Non-smoker	Normal differential white cell count. No eosinophils in sputum
C.S. M 64	Winter cough 20+ yrs. Daily cough 2 yrs. Sputum rarely purulent. Daily wheeze 2 yrs. Cough and wheeze worse in mornings	Nil	15+ cigarettes daily for 40+ yrs	Normal differential white cell count. No eosinophils in sputum

TABLE IB

GROUP 1, CHRONIC BRONCHITIS: F.E.V._{1.0} (ml.) BEFORE AND 20 MIN. AFTER ADMINISTRATION OF THE ANTISPASMODIC DRUGS AND SALINE; AND F.E.V._{1.0} IMMEDIATELY BEFORE AND SIX DAYS AFTER PREDNISOLONE THERAPY

Patients Sex/Age		Adrenaline s.c.	Isoprenaline Inhalation	Aminophylline i.v.	Adrenaline Inhalation	Atropine s.c.	Saline Inhalation	Pred- nisolone
I.W. F 67	Before After % improvement	350 600 74.3	240 450 87.5	370 660 78.4	400 325 -18.8	620 700 12.9	320 320 0	350 640 82.8
J.G. F 58	Before After % improvement	1,400 1,570 12.1	1,200 1,450 20.8	1,420 1,400 -1.4	1,420 1,470 3.5	1,050 1,500 42.8	1,500 1,420 -5.3	1,420 1,610 11.3
J.D. M 63	Before After % improvement	740 1,000 35.1	900 1,100 22.2	980 1,050 7.1	950 1,050 10.5	920 1,100 19.6	950 900 -5.3	980 1,150 17.3
W.R. F 47	Before After % improvement	700 700 0	700 800 14.3	760 850 11.8	520 690 32.7	710 890 25.4	720 660 -8.3	710 840 18.3
J.H. M 55	Before After % improvement	950 1,340 41.0	1,000 1,330 33.0	950 1,250 24.0	950 1,300 36.8	1,000 1,340 34.0	1,000 1,000 0	1,000 1,000 0
J.L. M 51	Before After % improvement	760 980 28.9	500 600 20.0	800 920 15.0	700 750 7.1	1,200 1,420 18.3	1,000 1,100 10.0	1,000 760 -24.0
P.R. M 63	Before After % improvement	600 740 23.3	800 1,100 37.5	840 1,080 28.6	850 1,140 34.1	800 1,070 33.7	650 750 15.4	800 900 12.5
R.G. M 65	Before After % improvement	500 660 32.0	520 700 34.6	510 540 5.9	500 650 30.0	500 650 30.0	500 550 10.0	500 540 8.0
J.V. M 71	Before After % improvement	350 380 8.6	350 450 28.6	400 430 7.5	360 540 50.0	390 620 59.0	360 320 -11.1	360 540 50.0
E.P. F 36	Before After % improvement	790 1,490 88.6	1,400 1,500 7.1	650 1,460 124.6	1,070 1,360 17.0	1,040 1,660 59.6	640 650 1.6	1,400 1,790 27.8
J.R. M 57	Before After % improvement	1,360 1,630 19.8	1,230 1,600 30.1	1,010 1,300 30.7	1,010 1,360 34.7	1,450 1,620 11.7	1,060 1,090 2.8	1,360 1,170 -14.0
D.B. M 57	Before After % improvement	440 450 2.3	400 460 15.0	400 480 20.0	420 420 0	410 490 19.5	380 380 0	400 500 25.0
A.J. M 53	Before After % improvement	1,060 1,270 19.8	940 1,220 29.8	1,040 1,260 21.1	1,060 1,230 16.0	1,070 1,400 30.8	1,180 1,250 5.9	1,180 1,130 -4.2
E.C. F 48	Before After % improvement	590 860 45.8	610 920 50.8	420 490 16.7	590 940 59.3	650 1,040 60.0	620 610 -1.6	640 680 6.2
F.P. M 45	Before After % improvement	540 740 37.0	520 760 46.1	500 760 52.0	450 640 42.2	540 800 48.1	450 480 6.7	500 460 -8.0
T.F. M 50	Before After % improvement	1,230 1,520 23.6	1,160 1,390 19.8	1,110 1,320 18.9	1,110 1,260 13.5	1,030 1,590 54.4	1,040 1,030 -1.0	1,280 1,260 -1.6
M.G. F 58	Before After % improvement	1,000 1,380 38.0	1,120 1,540 37.5	1,220 1,660 36.1	1,070 1,220 14.0	1,330 1,660 24.8	1,090 1,140 4.6	1,420 1,360 -4.2
C.S. M 64	Before After % improvement	1,440 1,730 20.1	1,360 1,760 29.4	1,360 1,560 14.7	1,120 1,690 50.9	1,440 1,510 4.9	1,000 800 -20.0	1,360 1,440 5.9

TABLE IIA
GROUP 2, CHRONIC ASTHMA

Patient Sex/Age	History of Cough and Wheeze	Other Points of Significance	Smoking History	Eosinophils in Blood and Sputum
G.D. M 38	Recurrent attacks of wheeze as a child and young adult. Daily wheeze 5 mths. No cough or sputum	Family history of asthma	Non-smoker	Normal differential white cell count. No sputum
A.V. F 41	Recurrent attacks of wheeze 10 yrs. Wheeze worse in early summer. Free from symptoms in winter. Daily wheeze 6 mths. Cough only at night. Sputum mucoid and scanty	Nil	10 cigarettes daily until 10 yrs ago. Stopped because of wheeze	Normal differential white cell count. Eosinophils in sputum
J.R. M 55	Daily cough and wheeze 7 yrs. Wheezy as a child. Scanty sputum always mucoid. Distressing nocturnal wheeze and cough	Nil	20+ cigarettes daily until 1 mth before study. Stopped because of symptoms	Normal differential white cell count. No eosinophils in sputum
J.H. M 34	Daily wheeze and cough 10 yrs. Wheeze more distressing than cough. Symptoms fluctuant but no complete freedom from cough or wheeze 10 yrs. Scanty daily sputum frequently purulent. Mild nocturnal exaggeration of symptoms	Nil	20+ cigarettes daily for 20 yrs, 10 daily for 3 yrs. Reduced because of symptoms	Normal differential white cell count. No eosinophils in sputum
M.K. F 44	Daily wheeze 1 yr, gradual onset at menopause. Slight cough at night. Scanty sputum rarely purulent. Wheeze much worse at night	Eczema as a child	Non-smoker	Normal differential white cell count. No eosinophils in sputum
J.B. M 35	Wheeze 19 yrs with frequent exacerbations but no complete freedom. Intermittent cough 19 yrs. Daily cough and sputum 2 yrs. Sputum rarely purulent	Hay fever	5 cigarettes daily for 20 yrs	Normal differential white cell count. No eosinophils in sputum
G.E. M 68	Recurrent cough and wheeze 4 yrs. Freedom from symptoms during spring months. Daily cough and wheeze 6 mths. Sputum mucoid. Cough and wheeze much worse at night	Nil	Non-smoker	Normal differential white cell count. No eosinophils in sputum
R.A. M 62	Recurrent wheeze 20 yrs. Wheeze most troublesome in early summer. Cough associated with wheeze 10 yrs. Sputum mucoid and scanty. Freedom from symptoms during late summer months	Nil	Pipe smoker 2 oz. tobacco per week	Normal differential white cell count. No eosinophils in sputum
D.B. M 40	Recurrent wheeze as a child. Daily wheeze 15 yrs. Daily cough 10 yrs. Sputum scanty but frequently purulent. Nocturnal exaggeration of symptoms	Family history of asthma. Positive skin test for <i>Aspergillus fumigatus</i>	Non-smoker	17% eosinophils of 10,500 total white cell count. Eosinophils in sputum
R.T. M 43	Recurrent wheeze all his life. Daily wheeze with no remission 2 yrs. Daily cough 2 yrs. Daily sputum frequently purulent. Nocturnal exaggeration of symptoms	Various 'allergies'. Family history of asthma	Non-smoker	Normal differential white cell count. No eosinophils in sputum
H.C. F 32	Recurrent wheeze 20 yrs. Daily wheeze 7 yrs. Intermittent cough 7 yrs. Sputum scanty and mucoid. Nocturnal exaggeration of symptoms	Infantile eczema. History of various allergies	Non-smoker	13% eosinophils of 6,700 total white cell count. Eosinophils in sputum
B.McS. M 34	Chronic wheeze 10 yrs with numerous attacks of distressing wheeze. Daily cough 10 yrs. Scanty sputum always mucoid. Nocturnal exaggeration of symptoms	Hay fever	10 cigarettes daily for 16 yrs. Stopped because of exaggeration of symptoms 3 yrs before study	Normal differential white cell count. No eosinophils in sputum
H.B. F 44	Daily wheeze 3 yrs. Intermittent cough 3 yrs. Very scanty mucoid sputum. Cough and wheeze much worse at night	Nil	Non-smoker	9% eosinophils of 6,700 total white cell count. No eosinophils in sputum
G.H. M 44	Recurrent wheeze all his life. Daily wheeze 5 yrs. Daily cough 5 yrs. Daily copious mucoid sputum 5 yrs. Nocturnal exaggeration of symptoms	Nil	20 cigarettes daily for 20 yrs. Stopped 7 yrs before study	Normal differential white cell count. Eosinophils in sputum
C.M. M 52	Recurrent wheeze 10 yrs. Constant daily wheeze 8 mths. Daily cough 6 mths. Sputum daily, numerous bronchial casts. Nocturnal exaggeration of symptoms	? Allergy to house dust. Eczema as a child. Positive skin test for <i>Aspergillus fumigatus</i>	20 cigarettes daily for 30 yrs. Stopped 3 mths before study because of symptoms	7% eosinophils of 7,800 total white cell count. No eosinophils in sputum (bronchial casts not seen in hospital)
K.D. M 35	Recurrent wheeze 10 yrs. Chronic daily wheeze 3 yrs. Intermittent cough 3 yrs. Sputum scanty and mucoid	'Allergy' to aspirin. Family history of asthma	Non-smoker	Normal differential white cell count. No eosinophils in sputum
D.McL. M 40	Chronic daily wheeze 2 yrs. Daily cough 6 mths. Sputum mucoid and copious. Marked nocturnal exaggeration of symptoms	Family history of asthma. Hay fever	Non-smoker for 10 yrs	10% eosinophils of 9,000 total white cell count. No eosinophils in sputum
J.B. F 35	Episodic wheeze all her life. Chronic wheeze 10 yrs. Recurrent cough 10 yrs. Sputum scanty and mucoid. Nocturnal exaggeration of symptoms	Infantile eczema. Hay fever. Family history of asthma	5-10 cigarettes daily for 10 yrs. Stopped 2 yrs before study because of symptoms	7% eosinophils of 7,400 total white cell count. No eosinophils in sputum

TABLE IIB

GROUP 2, CHRONIC ASTHMA: F.E.V._{1.0} (ml.) BEFORE AND 20 MIN. AFTER ADMINISTRATION OF THE ANTISPASMODIC DRUGS AND SALINE; AND F.E.V._{1.0} IMMEDIATELY BEFORE AND SIX DAYS AFTER PREDNISOLONE THERAPY

Patient Sex/Age		Adrenaline s.c.	Isoprenaline Inhalation	Aminophylline i.v.	Adrenaline Inhalation	Atropine s.c.	Saline Inhalation	Prednisolone
G.D. M 38	Before After % improvement	2,800 3,350 19.6	2,420 3,060 26.4	2,200 2,700 22.7	3,200 3,400 6.2	2,250 2,250 0	2,460 2,420 -1.6	2,250 3,260 44.9
A.V. M 41	Before After % improvement	1,350 1,580 17.0	1,350 1,740 28.9	1,140 1,340 17.5	1,460 1,420 -2.0	1,150 1,070 -8.5	1,560 1,470 -5.8	1,140 2,575 125.9
J.R. M 55	Before After % improvement	1,260 1,850 46.8	950 1,510 58.9	1,100 1,550 40.9	1,100 1,500 36.4	1,020 1,240 21.6	1,300 1,310 0.8	1,300 1,610 23.8
J.H. M 34	Before After % improvement	2,150 2,830 31.6	2,390 3,190 33.5	1,900 2,670 40.5	2,400 3,110 29.6	2,000 2,400 20.0	2,100 2,150 2.4	2,400 2,580 7.5
M.K. F 44	Before After % improvement	1,000 1,150 15.0	870 1,100 26.4	1,030 1,310 27.2	950 1,090 15.4	860 1,120 30.2	850 860 1.2	870 2,020 132.2
J.B. M 35	Before After % improvement	1,330 2,460 85.0	1,140 1,730 51.8	880 1,350 53.4	1,040 1,940 86.5	1,180 1,760 49.2	1,360 1,400 2.9	2,150 2,340 8.8
G.E. M 68	Before After % improvement	680 1,480 117.6	900 1,260 40.0	920 1,180 35.6	890 1,150 19.8	820 920 12.2	860 870 1.2	820 1,620 97.6
R.A. M 62	Before After % improvement	590 860 45.8	670 870 29.8	570 790 38.6	610 810 32.8	610 850 39.3	610 610 0	590 940 59.3
D.B. M 40	Before After % improvement	510 650 27.4	520 550 5.9	440 500 18.6	470 500 6.4	560 490 -12.5	550 560 1.8	470 760 61.7
R.T. M 43	Before After % improvement	420 700 66.7	450 520 15.6	420 600 42.8	440 460 4.5	410 620 51.2	400 420 5.0	450 730 62.2
H.C. F 32	Before After % improvement	980 1,560 59.2	900 1,520 68.9	1,530 1,810 18.3	1,610 1,620 0.6	1,430 1,570 9.8	1,430 1,530 7.0	1,800 1,720 -4.4
B.McS. M 34	Before After % improvement	2,060 2,950 43.2	1,790 2,500 39.7	1,840 2,060 13.6	1,840 2,610 41.8	1,920 1,780 -7.3	1,600 1,770 10.6	1,600 1,800 12.5
H.B. F 44	Before After % improvement	1,260 1,610 27.8	1,120 1,280 14.3	1,400 1,600 14.3	1,320 1,410 6.8	1,140 1,190 4.4	1,020 1,210 18.6	1,400 2,010 43.6
G.H. F 44	Before After % improvement	1,480 1,810 26.6	1,430 1,790 25.2	1,500 1,750 16.7	1,470 1,840 25.2	1,400 1,680 20.0	1,460 1,470 0.7	1,480 1,210 -15.4
C.M. M 52	Before After % improvement	1,580 2,550 61.4	2,150 2,670 24.2	2,780 3,200 15.1	1,840 2,260 22.8	1,960 2,050 4.6	1,260 1,340 6.3	1,260 3,280 160.3
K.D. M 35	Before After % improvement	1,990 3,420 71.8	1,850 3,100 67.6	1,280 2,200 71.9	2,310 3,360 45.4	1,440 1,820 26.4	1,340 1,280 -4.5	1,850 2,290 23.8
D.McL. M 40	Before After % improvement	2,410 2,700 12.0	2,510 3,340 33.1	2,400 3,110 29.6	2,750 2,850 36.4	2,580 2,830 9.7	2,440 2,400 -1.6	2,580 3,400 35.6
J.B. F 35	Before After % improvement	1,740 2,050 17.8	1,500 1,900 26.7	1,100 1,870 70.0	1,550 1,740 12.2	1,020 1,400 37.3	1,100 1,100 0	1,550 1,730 11.6

FIG. 1. Group 1, chronic bronchitis. Mean percentage increase in F.E.V.₁₋₀ following the administration of the antispasmodic drugs, saline by inhalation, and prednisolone.

FIG. 2. Group 2, chronic asthma. Mean percentage increase in F.E.V.₁₋₀ following the administration of the antispasmodic drugs, saline by inhalation, and prednisolone.

Figure 1 shows the mean changes in F.E.V.₁₋₀ for the 18 patients in the bronchitic group following the administration of the six test drugs and prednisolone. There is no significant difference between the responses to all five of the active substances used in the first part of the study. The mean improvement in F.E.V.₁₋₀ ranged from 24.1% after adrenaline inhalation to 32.5% following atropine sulphate. There was a mean improvement in F.E.V.₁₋₀ after saline inhalation of 0.2%.

During the six-day period of prednisolone administration slight improvement occurred, which reached a mean value of 11.7% after six days. This improvement is not significant ($P > 0.05 < 0.1$).

Figure 2 shows the mean changes in F.E.V.₁₋₀ for the 18 patients in the asthmatic group follow-

ing the administration of the six test drugs and prednisolone. There is considerable variation between the responses to the six drugs used in the first part of the study. The mean improvement in F.E.V.₁₋₀ following administration of these drugs was 44% after subcutaneous adrenaline, 34.3% after isoprenaline inhalation, 32% after intravenous aminophylline, 23.7% after adrenaline inhalation, 17.1% after subcutaneous atropine sulphate, and 2.3% after saline inhalation. The difference between the mean response to subcutaneous adrenaline and isoprenaline inhalation is not significant ($P = 0.2$), nor is the difference between the mean response to subcutaneous adrenaline and intravenous aminophylline ($P = 0.1$). There are significant differences between the mean F.E.V.₁₋₀ responses following subcutaneous adrenaline and adrenaline inhalation ($P = 0.005$) and subcutaneous atropine ($P < 0.001$).

After prednisolone therapy had been started a significant improvement of 25.5% ($P<0.01>0.001$) occurred after 24 hours and rose to 49.5% after six days' treatment ($P<0.001$).

All patients in both groups had a differential white cell count performed before the administration of prednisolone, and all patients, except for one in the chronic asthma group who had no sputum, had three specimens of sputum examined microscopically for eosinophils. One patient in the chronic bronchitic group had a significant increase of eosinophils in the peripheral blood, though none in this group had eosinophils in the three specimens of sputum examined.¹ In contrast, four patients in the chronic asthma group had a significant peripheral blood eosinophilia, two had eosinophils in the sputum, and a further two had both eosinophils in the sputum and blood eosinophilia.

The eight patients in the chronic asthma group with sputum or blood eosinophilia or both did not respond significantly better to prednisolone than the 10 patients in whom no eosinophilia was demonstrated. The mean improvement in F.E.V.₁₋₀ of the patients with eosinophilia after six days' prednisolone treatment was 53.4%, compared with 47.2% for the patients without eosinophilia ($P>0.8<0.9$).

DISCUSSION

Strikingly different results were obtained in the two groups of patients studied. In the chronic bronchitics (group 1) the similarity of the responses to the short-acting bronchodilator drugs is impressive. There was a slightly greater improvement in the mean F.E.V.₁₋₀ after atropine sulphate, compared with the mean responses to the other drugs, but this was not statistically significant. In an independent study of patients with chronic bronchitis it was found that the improvement in F.E.V.₁₋₀ following the administration of atropine sulphate subcutaneously continued for at least one hour (Fig. 3 and Table III). It is possible that, by recording the F.E.V.₁₋₀ 20 minutes after drug administration the response to atropine sulphate in the present study has been underestimated. This is unlikely in the case of the other drugs used, as in a previous unpublished study of 30 wheezy patients maximum improvement in the mean F.E.V._{0.75} was achieved by 20 minutes and

FIG. 3. Mean percentage increase in F.E.V.₁₋₀ measured at intervals of 10 minutes for one hour after atropine sulphate, 0.6 mg. s.c., in 12 patients suffering from chronic bronchitis (patients not included in present study).

FIG. 4. Mean percentage increase in F.E.V._{0.75} measured at intervals of five minutes for 30 minutes following the administration of isoprenaline inhalation, adrenaline inhalation, subcutaneous adrenaline, and intravenous aminophylline to a group of 30 patients suffering from chronic bronchitis or chronic asthma (patients not included in present study).

no further improvement was observed at 30 minutes after administration of the drugs (Fig. 4). The improvement in the F.E.V.₁₋₀ of bronchitic patients observed after the administration of atropine is not necessarily of therapeutic benefit, as some of the response may be due to drying of bronchial secretions, which in some patients can be harmful because of the danger of sputum retention. Only in a minority of patients with copious bronchial secretions may this effect of atropine be of benefit.

¹ It is possible that the incidence of eosinophils in the sputum varies in the course of the day, and this may be the explanation for the negative eosinophil sputum results in the patients who had a significant increase in the blood eosinophil count.

TABLE III

CHANGES IN F.E.V.₁₋₀ (ml.) MEASURED AT 10-MIN. INTERVALS FOR 1 HOUR AFTER ADMINISTRATION OF ATROPINE SULPHATE, 0.6 mg. s.c., TO 12 CHRONIC BRONCHITIC PATIENTS NOT INCLUDED IN MAIN STUDY

Case		Initial	10 Min.	20 Min.	30 Min.	40 Min.	50 Min.	60 Min.
1	% improvement	770	900 16.9	1,020 32.5	1,030 34	1,000 29.7	1,000 29.7	1,020 32.5
2	% improvement	750	850 13.3	920 23	890 18.7	850 13.3	780 4	750 0
3	% improvement	900	1,010 12.2	1,000 11.1	950 5.5	1,100 22.2	1,090 21	1,130 25.5
4	% improvement	700	850 22	830 18.5	880 25.6	870 24.2	900 28.5	900 28.5
5	% improvement	2,450	2,840 16	2,900 18.4	2,950 20.5	2,990 24	3,100 26.5	3,150 28.5
6	% improvement	1,230	1,590 29	1,900 54.5	2,150 75	2,050 66.5	2,140 74	2,300 87
7	% improvement	370	490 32	460 24.4	500 35	510 38	520 40.5	600 62
8	% improvement	420	520 24	620 47.5	600 42.7	600 42.7	640 52	600 42.7
9	% improvement	650	700 7.7	750 15.4	800 23	840 29	880 35	830 27.5
10	% improvement	750	850 13.4	870 16	950 26.5	930 24	870 16	920 22.5
11	% improvement	800	900 12.6	970 21.4	1,050 31.3	1,030 28.7	1,050 31.3	1,100 37.5
12	% improvement	930	1,070 15	1,160 24.7	1,150 23.5	1,250 34.5	1,200 29	1,220 31
	Mean % improvement		17.9	25.6	30.4	31.4	29.8	35.4

The responses to the short-acting bronchodilator drugs in the group of patients with chronic asthma (group 2) differed markedly from the group 1 results. The greatest improvement in the mean F.E.V.₁₋₀ occurred after subcutaneous adrenaline, but this response was not significantly greater than the mean F.E.V.₁₋₀ improvement following isoprenaline inhalation or intravenous aminophylline. The significant difference between the mean F.E.V.₁₋₀ responses to subcutaneous adrenaline and adrenaline inhalation is not in accord with the work of Kennedy (1961), who reports that both methods of administration of adrenaline cause similar responses in asthmatic patients. The inhalation dose of adrenaline used in the present study was large—approximately 3 mg. delivered from the Wright nebulizer to the face mask—and hence it is unlikely that a small dose of adrenaline was responsible for the relatively poor mean response to adrenaline inhalation. Following the inhalation of adrenaline the response is maintained for longer than 20 minutes, and hence the time of F.E.V.₁₋₀ recording can be excluded as a cause of this difference between the mean responses following inhalation and injection of adrenaline.

The patients selected were not severely disabled by their wheeze and breathlessness at the time of the study. None of the chronic asthma patients selected was ill enough to require immediate treatment with prednisolone. The mean F.E.V.₁₋₀ of the asthma patients before the first treatment was 1,340 ml., and only slight daily fluctuation of the mean basal F.E.V.₁₋₀ occurred during the six days of the first part of the study (range 1,300 to 1,400 ml.). As the patients were not in a severe stage of the disease and there was only slight daily fluctuation in the mean pre-treatment F.E.V.₁₋₀ values, it can be assumed that adrenaline inhalation was not given at a time when the patient's asthma was so severe that a poor response could be expected (Hume and Gandeia, 1957; Kennedy, 1961).

Atropine sulphate produced only slight improvement in the mean F.E.V.₁₋₀ in the asthmatic group, and this response is significantly less than the responses to the other active drugs used except for adrenaline by inhalation. This finding is in agreement with previous reports which state that the atropine compounds alone, by aerosol or injection, are of little or no value in the treatment of asthma (Pearson, 1958; Herxheimer, 1959).

When the responses to the active drugs in the chronic bronchitic and the asthmatic groups are compared, the outstanding difference is in the response to atropine—a good response in the bronchitic group and a poor response in the asthmatic group. A good response to subcutaneous adrenaline was observed in both groups. When the responses to subcutaneous adrenaline and atropine in both groups are considered together with the insignificant improvement after prednisolone in group 1 and the good response to prednisolone in group 2, it is tempting to postulate that a significantly better response to subcutaneous adrenaline than to subcutaneous atropine is more in favour of an expected satisfactory prednisolone response than are equally good responses to subcutaneous adrenaline and subcutaneous atropine. The numbers of patients studied were small, however, and some variations of the subcutaneous adrenaline and atropine responses occurred within the groups. This is worthy of further study, since a poor response to aerosol atropine compared with aerosol isoprenaline has been observed in patients whose airways obstruction responds to corticosteroids, and similar responses to aerosol atropine and isoprenaline in patients whose bronchospasm was unaffected by corticosteroid therapy have also been reported (Altounyan, 1964; Gandevia, 1965). Aerosol atropine methonitrate produces a more rapid response in patients regarded as having chronic bronchitis than in patients with uncomplicated asthma (Gandevia, 1965). It is possible that atropine compounds have different actions in different forms of airway obstruction, and further study is necessary.

Prednisolone produced insignificant improvement in the mean F.E.V.₁₋₁₀ in the bronchitic patients. This finding is in agreement with the results of other studies of corticosteroid drugs in chronic bronchitis and emphysema (Freedman, 1963; Cullen and Reidt, 1960; Lorrman, 1959). Some of the patients did, however, experience subjective improvement out of all proportion to the ventilatory improvement recorded.

The mean F.E.V.₁₋₁₀ response to prednisolone of the chronic asthmatic patients, which reached a value of 49.5% after six days' treatment, was not unexpected, as patients suffering from chronic asthma can be expected to respond to corticosteroid drugs (Thursby-Pelham and Kennedy, 1958; Somner *et al.*, 1960; Phear *et al.*, 1960).

The different responses to prednisolone in the two groups are evidence in favour of a correct initial clinical diagnosis of chronic bronchitis and chronic asthma.

Eight of the 18 patients with chronic asthma studied were found to have sputum eosinophilia and/or significant peripheral blood eosinophilia. It has been reported that asthmatic patients with sputum eosinophilia respond well to corticosteroid therapy (Brown, 1958). In this study the patients with eosinophilia did not respond significantly better to prednisolone than did those in whom no eosinophilia was demonstrated.

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