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Chronic bronchitis—measurements and observations over 10 years

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Johnston, R. N., McNeill, R. S., Smith, D. H., Legge, J. S., and Fletcher, F. (1976). *Thorax*, **31**, 25–29. **Chronic bronchitis—measurements and observations over 10 years.** A total of 111 patients with chronic bronchitis were selected for study in 1963. By 1974 only 54 patients were available for clinical examination, chest radiography, and pulmonary function measurements. There was a significantly higher mortality compared with men of the same age and in the same locality, and this was due to cardiorespiratory failure and bronchial carcinoma. Reduction of cigarette smoking, declining atmospheric pollution, and antibiotic treatment have reduced the 24-hour sputum volume of these patients. The initial one-second forced expiratory volume (FEV_1) and vital capacity were significantly lower in those patients who later died from cardiorespiratory failure. The duration of antibiotic treatment and the smoking record have not significantly affected the decline of the FEV_1 with advancing age. The transfer factor (diffusing capacity) for carbon monoxide (TF) has declined more in those who continued to smoke. Of the 54 patients 14 had radiological evidence of emphysema initially. This has shown little change over 10 years.

The results of long-term prospective studies in chronic bronchitis have only recently become available (Burrows and Earle, 1969; Bates, 1973; Ogilvie *et al.*, 1973; Howard, 1974). In an earlier study (Johnston *et al.*, 1969), we reported evidence suggesting that chemoprophylaxis for two, three or five years in patients with chronic bronchitis reduced the decline in one-second forced expired volume (FEV_1), but our numbers were too small to be statistically significant. We have continued our earlier study and now report further observations over a 10-year period.

PRESENT STUDY

From patients attending the chest clinic in 1963 we initially selected 120 men aged 38–60 (average age 52 years) who were working and had a history of productive cough for at least three years and two or more respiratory illnesses causing absence from work during that period. Nine patients were excluded because of incorrect preliminary assessment, leaving 111 who are the basis of this study. We had already excluded patients whom, because of the degree of their disability, we considered unlikely to remain employed over the next five years and also those with any other significant disability, for example, systemic arterial hypertension (BP > 160/90 mm Hg) or a history of intolerance to antibiotics. All patients were seen monthly during the winter.

At the October visit each winter we assessed the grade of breathlessness and classified the patient's employment. The smoking history was recorded, and, if the patient was still smoking, he was advised to stop. The patient brought a 24-hour sputum sample collected during the preceding day in a graduated jar, and the volume and macroscopic appearance of this were recorded. The presence of pus was noted, and classified according to the method of May (1965).

Posterior-anterior radiographs in inspiration and expiration and both lateral views were taken in 1963, 1969, 1972, and again in 1974. (AP tomograms at the hilar level and 2 cm behind this were taken in 1963.) The following features were recorded—reduction in calibre of the peripheral pulmonary arteries, a homogenous and more translucent background, localized air trapping on the expiration films, bullae, increased lung volumes, increase in the transverse diameter of the heart, evidence of right ventricular enlargement, and finally an overall 'artistic' assessment of emphysema. These readings were repeated after an interval of six months and 10 years, and a comparison was made between the initial and final films for evidence of change in the extent of emphysema. The

films were read by a radiologist who had no clinical knowledge of these patients.

PULMONARY FUNCTION Tests were carried out in the autumn of 1963, and the spring of 1969, 1972, and 1974. Vital capacity (VC) and FEV_1 were measured from the best of three recordings on a fast-moving kymograph by means of a low-resistance spirometer. Functional residual capacity (FRC) and residual volume (RV) were measured by the closed-circuit helium dilution method. All volumes were corrected to body temperature and pressure saturated with water vapour. Duplicate measurements of the diffusing capacity for carbon monoxide (TF) were made by the single-breath method of Ogilvie *et al.* (1957). Patients were not tested during an exacerbation of bronchitis. In 1972 and 1974 the FEV_1 measurements were obtained from the best of three attempts using a dry wedge spirometer. During the winters of 1971–1973 monthly measurements were made of the resting pulse, the indirect arterial carbon dioxide tension ($Paco_2$), and the peak expiratory flow rate (PEFR).

At the beginning of the study an oxygen electrode was not available, so the oxygen saturation percentage (Sao_2) was measured by a Kipp haemoreflector. In 1972 and 1974 the arterial blood studies had included measurements of the arterial oxygen tension (Pao_2) using an oxygen electrode. The $Paco_2$ was measured indirectly by the rebreathing method of Campbell and Howell (1960), assuming a difference of 6 mmHg between mixed venous and arterial tensions. Since the RV/total lung capacity (TLC) is already a percentage we have expressed this as a + or − difference compared with the predicted RV/TLC.

During the first five winters patients received by random allocation 0, 2, 3 or 5 six-month periods of chemoprophylaxis with tetracycline, 500 mg twice daily. In addition, a similar dose was administered during any exacerbation of bronchitis associated with purulent sputum. For the next five years the antibiotic regimen varied in duration and drug, some patients receiving ampicillin, doxycycline or cotrimoxazole in place of tetracycline.

Of the 79 patients studied in 1968, 56 were available in 1974, and the same clinical, radiographic, and pulmonary function tests were repeated. At the final review in 1974 a detailed account of the duration of winter antibiotic treatment was recorded. The duration of antibiotic treatment varied from 0 to 10 winters, and this figure is the treatment factor. Repeated efforts were made to stop these patients smoking. The majority of these patients have been personally reviewed by the same medical team on 43 occasions between 1963 and 1974. Clinical information is available for 56 patients and complete radiographic studies and pulmonary function results for 54. The weekly consumption of cigarettes, the grade of dyspnoea, the 24-hour sputum volume and character, the antibiotic treatment factor, and chest radiograph report were all linked to the pulmonary function results for the years 1963, 1969, 1972, and 1974.

RESULTS

The changes over a 10-year period are shown in Table I and this records the number of deaths with the principal causes. At least 24 patients have died.

TABLE I

CHRONIC BRONCHITIS—FOLLOW-UP

	1963	1968	1974
No. of patients—total	111	79	56
—untraced		25	4
—excluded			2
Total number of deaths		7	17
Cardiorespiratory		2	7
Myocardial infarction		3	4
Bronchial carcinoma		1	5
Other causes		1	1

The predicted mortality for men of this age and locality is 17 according to data available from the Registrar General's tables. The mortality in our group is higher (χ^2 comparing observed and predicted values shows a significant difference at the 0·005 level) (Table II). We have separated deaths recorded due to myocardial infarction (7) from those described as cardiorespiratory failure, congestive failure or cor pulmonale (9). During the second five-year period only four patients are untraced. A further two patients were not re-assessed because they were too ill with bronchial carcinoma but a third with proven bronchial carcinoma has been included. In addition there are another three patients who have developed solid pulmonary lesions suggesting bronchlal carcinoma in whom histological proof is not yet available. Thus, apart from the six deaths due to bronchial carcinoma, a further six patients have probably developed this disease. No relevant occupational factor has been detected in these 12 patients. Nine

TABLE II

COMPARISON OF OBSERVED DEATHS WITH PREDICTED MORTALITY

	1963–68	1969–74
No. of patients	111	79
Predicted mortality	8	9
Observed deaths	7	17
Excess mortality	0	+87%

patients died of cardiorespiratory disease (excluding myocardial infarction) from three to 10 years after the initial survey. All except one were cigarette smokers but only one smoked more than 140 weekly. This outcome was not related to occupation, smoking, degree of dyspnoea, sputum volume or radiological evidence of emphysema but was related to an initial low FEV_1, reduced FEV_1/VC, an increased RV/TLC, a reduced oxygen saturation of the blood and a raised CO_2 tension (Table III). All but two of the 56 survivors had previously been cigarette smokers. At the start of the survey two were pipe-smokers and 44 were cigarette smokers. By 1974, 21 were still smoking cigarettes, eight of them fewer than initially, four unchanged, and nine more heavily. The two pipe smokers had not altered their weekly consumption of tobacco. Thus our repeated efforts had achieved a 52% cessation, and reduction in another 23%.

CHANGES IN THE FEV_1 The initial and final FEV_1 measurements have been compared. We had insufficient data for calculation of regression coefficients. The mean FEV_1 in 1963 for the 79 patients was 1·65 (50·4% of the predicted normal): and this had fallen to a mean of 1·4 by 1974 in the 54 patients available for study. The FEV_1 of those 54 patients in 1969 was 1·77 litres. Over the 10-year period the mean fall in FEV_1 for the whole group was 0·34 l. (0·33 l.), for the VC 0·72 l. (0·25 l.), for the TF 1·22 mmol $min^{-1}kPa^{-1}$ (1·04), and for the RV/TLC a rise of 5·1 (3·5). With the exception of the greater fall in VC these changes are in accord with the predicted values (shown above in brackets) for men of this age (Cotes, 1968). The FEV_1 declined by 33% or more in 17 patients while in the remaining 37 patients there was little change. In only three patients were there dramatic falls (1·4 l.→0·5 l.); (2·0→0·8 l.); (1·4→0·6 l.). These 17 patients (mean FEV_1 1·6 l.) have been matched with another 17 with approximately the same initial FEV_1 in which this did not fall (Table IV), and the effects of sputum volume, smoking history, dyspnoea grade, and treatment were compared. The only difference was the higher smoking figure in those showing the greater fall in FEV_1 but this failed to reach significance (P=0·1). Isolated readings of PEFR, resting pulse rate, and P_{CO_2} are useful indicators of disability. However, serial monthly examinations did not give further information. In particular, they did not always deteriorate in exacerbations and, as used here, that is, as monthly tests, have not justified the additional work involved. Examination of the three patients who exhibited a considerable fall in the FEV_1 revealed no consistent pattern. In one the FEV_1 declined more rapidly over the first five years; in the second patient there was a progressive reduction of the FEV_1 over 10 years; while in the third patient there was a slow decline in

TABLE IV

COMPARISON BETWEEN THOSE WHOSE FEV_1 FELL BY 33% OR MORE (GROUP A) COMPARED WITH MATCHED CONTROLS (GROUP B)

Group	Mean Values for 17 Patients in each Group			
	Cigarette Consumption Weekly	Dyspnoea Grade	Sputum Volume (ml)	Treatment Factor
A	*86*	0·5	30·3	4·7
B	*56*	0·5	32·3	4·4

TABLE III

COMPARISON OF PULMONARY FUNCTION DATA (MEAN VALUES) IN SURVIVORS (54) *v* THOSE WHO DIED OF CARDIORESPIRATORY CAUSES (9)

	FEV_1 (litres)	FEV_1/VC %	VC (litres)	RV (litres)	TLC (litres)	RV/TLC %	TF (ml/min/kPa)	SaO_2 %	$PaCO_2$ (kPa)
Survivors	1·77	48	3·66	3·24	6·92	46·6	7·6	94	5·72
C/R deaths	0·87	34	2·57	3·67	6·20	58·56	5·3	89	6·65
P	<0·001	<0·005	<0·001	>0·05	>0·05	<0·001	<0·01	<0·001	<0·001

TABLE V

CHANGES OVER A 10-YEAR PERIOD RELATED TO THE AMOUNT OF ANTIBIOTIC TREATMENT

Treatment Group	No. of Patients	24-hour Sputum volume (ml)	FEV_1 (litres)	FEV_1/VC %	VC (litres)	RV/TLC %	TF (ml/min/kPa)
0—3	26	−7·13	−0·39	−2·04	−0·72	+4·17	−1·32
4—6	15	−21·9	−0·29	−4·79	−0·76	+3·93	−1·30
7—10	13	−8·8	−0·32	−1·46	−0·67	+8·0	−0·58
P		<0·05		<0·05			

TABLE VI

CHANGES OVER A 10-YEAR PERIOD RELATED TO ALTERATION IN SMOKING

	24-hour Sputum Volume (ml)	FEV_1 (litres)	FEV_1/VC %	VC (litres)	RV/TLC %	TF (ml/min/kPa)
Mean change in 33 reduced or stopped smoking	− 14·5	− 0·34	− 0·18	− 0·71	+ 4·39	− 0·71
Mean change in 14 smoking increased or unaltered	− 7·33	− 0·37	− 0·43	− 0·8	+ 6·85	− 2·08
P	< 0·025					< 0·025

the FEV_1 in the first five years with an accelerated decline in the remaining years.

The amount of antibiotic treatment over a 10-year period is not significantly related to the fall in FEV_1 (that is, the trend we reported in 1969 when there was some advantage to those receiving chemoprophylaxis has not been confirmed over the 10-year study) but there has been a reduction in sputum volume in those receiving antibiotic treatment for four to six winters (Table V). Paradoxically, those receiving treatment for 7–10 winters have not shown a greater reduction in sputum volume, probably because of more serious and repeated infections. The effect of smoking is shown in Table VI. Among those who stopped or reduced cigarette smoking (33 patients) there was a significant change only in the 24-hour sputum volume and the TF.

The differences between the initial and final grades of dyspnoea were examined. Ten patients improved, 21 showed no change, and 23 deteriorated. This just represents a significant overall deterioration ($P < 0·05$). The grades of dyspnoea have been plotted against the mean FEV_1 and mean TF (both expressed as percentages of the predicted values) and although these means show trends suggestive of a relation to dyspnoea, they do not reach the level of statistical significance.

The initial 24-hour sputum volume has been plotted against FEV_1 and TF but there is no relation between these measurements and the volume of sputum.

BLOOD GASES Twelve patients showed a reduction in the arterial oxygen tension (9·3 kPa) in 1974. This was not related to changes in cigarette smoking, the duration of antibiotic treatment or the radiological assessment of emphysema. There was little overall change in the indirect P_{CO_2}. In only five patients was there a rise exceeding 0·4 kPa.

SMOKE CONTROL Smoke control areas came into effect in October 1959 and since then have extended so that by 1974 most of the city is controlled. In 1963 the average daily mean smoke concentration was 100 $\mu g/m^3$ (range 7–681) and the SO_2 concentration 98 $\mu g/m^3$ (range 0–379) while in 1974 the respective figures were 19 (range 1–209) and 59 (range 1–255).

CHEST RADIOGRAPHS The 1964 films were graded as normal in 40 and emphysema in 14 (grade 1, 12 and grade 2, 2). When the 1964 and 1974 film series were compared there was progression of emphysema by one grade in three and by two grades in two.

DISCUSSION

Considering the long period of the survey and the number of attendances for specialized tests, it is not surprising that 29 of the original 111 patients defaulted. It is important to know whether this loss has affected the results in the remainder. We believe this is not so since the mean FEV_1 for the original group was 1·7 l. and the mean FEV_1 of those who defaulted was 1·8 l.

Our patients had already a considerable degree of airways obstruction as measured by the FEV_1 compared with those reported by Bates (1973) (FEV 80% of predicted normal) and Ogilvie *et al.* (1973) (mean FEV_1 2·35 l.). Our patients (who were selected initially as likely to remain in employment for at least five years) have shown a significant excess mortality due to cardiorespiratory failure and bronchial carcinoma. Our results therefore are notably different from Bates' Canadian patients. The value of the FEV_1 in assessing prognosis is again confirmed, and this remains an important test in those with established obstructive airway disease. We believe that where the FEV_1 is 70% or more of the predicted value the prognosis approaches that of the population at large but where it falls to 50% or less there is a higher risk of cardiorespiratory failure and a considerable mortality.

Howard (1974) has drawn attention to the control of atmospheric smoke in helping patients with chronic bronchitis, and those cities which have implemented the Clean Air Act have made a notable contribution to the prevention of this disease. It should be noted that the control of SO_2 pollution is not so successful and further studies are needed to test the importance of this type of pollution.

We have found that emphysema as defined radiologically progresses very slowly over a 10-year period. This is in agreement with the report of Simon (1971). However, in our patients with more advanced obstructive airway disease approximately one-quarter had evidence of emphysema when first examined.

Thurlbeck *et al.* (1970) found that tests of carbon monoxide uptake provide the best correlation with the extent of emphysema at necropsy but even these will not always diagnose the extent of emphysema. In our own series 28 patients had a TF $<85\%$ of predicted and from Thurlbeck's data these should have shown evidence of emphysema. If the RV/TLC ratio were substituted then 26 patients exceeded the predicted values by $+10$. The fact that only 14 patients were reported as showing radiological evidence of emphysema is not surprising since it is recognized that the earlier stages of emphysema are not easily detected. We were unable to show a close relation between the presence of radiological emphysema on the one hand and a combined reduced TF and raised RV/TLC on the other. Among the 14 patients only eight had a TF $<85\%$ of predicted and nine a RV/TLC exceeding $+10$ of predicted. It should be noted that in our patients who continued to smoke there was a significant decline in TF. The fall in TF may be due to some extension of emphysema which cigarette smoking is known to aggravate (Hutchison, 1973).

In our earlier report we observed that chemoprophylaxis and the control of respiratory infections delayed the decline in the FEV_1. This has not been confirmed over the 10-year period and our further results are in line with those of Bates (1973) and Ogilvie *et al.* (1973). This apparent failure may be attributed to the lack of good tests for small airway function in the early 1960s or due to the fact that our drugs were mainly antibacterial and therefore ineffective against viral infections. If it is correct that the effects of cigarette smoking and intercurrent respiratory infections operate primarily on the small airways (and future studies are needed to test these views) these results are not surprising. Our results should not be construed as evidence to encourage the bronchitic to smoke and to neglect the treatment of intercurrent infections. Rather antibacterial treatment is necessary on clinical grounds to control further extension of infection, and smoking should be stopped for at least one very important reason, namely, to prevent bronchial carcinoma.

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