Papers and Originals

Value of Chemoprophylaxis and Chemotherapy in Early Chronic Bronchitis

A Report to the Medical Research Council by their Working Party on Trials of Chemotherapy in Early Chronic Bronchitis*

Brit. med. J., 1966, 1, 1317–1322

In order to discover whether progression of chronic bronchitis may be delayed by control of recurrent infection it was decided in 1957 to carry out a controlled double-blind trial of chemoprophylaxis and chemotherapy on cases of chronic bronchitis with a history of recurrent infection but with mild disability, and to observe the associated changes of respiratory function. To obtain the necessary numbers of subjects chest physicians in various parts of the country were invited to participate, and they agreed upon a plan (approved by the then Antibiotics Clinical Trials Committee of the Medical Research Council). This report is concerned with the frequency and severity of illnesses and changes in ventilatory capacity during the first five years of the trial.

Methods

Recruitment of Cases

The trial was carried out on men aged 40–59 in full employment who had a productive cough (grade 2, Medical Research Council, 1960) and who had had at least two chest illnesses with increased phlegm, and a total absence from work of at least three weeks during the previous three years. The forced expiratory volume in one second (F.E.V) had to be over 1.4 litres. Men were excluded if they suffered from any other disabling condition.

Considerable difficulty was encountered in recruitment. Most men attending chest clinics for chronic bronchitis have F.E.V. levels below 1.4 litres. Most men with high values of F.E.V. had infrequent illnesses, while those with recurrent illnesses usually had low values, and this was the most common reason for rejection of otherwise suitable patients. It was hoped that each of the 13 participating physicians would obtain 60 cases within the first year, but only one clinic reached this number despite recruitment over two years (see Table I). There is evidence that different clinics recruited rather different types of subject.

Therapeutic Regimen

Oxytetracycline was chosen for prophylaxis, initially in a dose of 0.5 g. once daily in the morning from mid-September to mid-April each year. It was hoped that if this small and economic dose proved effective it might be more practicable on a national scale than a larger, more expensive dose. Boxes of "yellow tablets," containing either oxytetracycline tablets or indistinguishable dummy tablets according to a scheme of randomization, were prepared and issued to clinics by the Medical Research Council's Pneumoconiosis Research Unit at Cardiff. After three years the oxytetracycline appeared to be having little effect, so the dose was increased to 0.5 g. twice daily during the fourth year and to 1 g. twice daily in the fifth year (see Diagram).

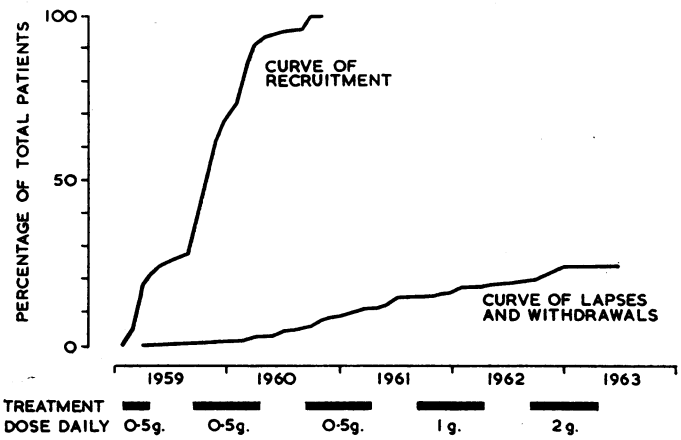

Diagram showing recruitment, withdrawal, treatment periods, and dosage.

For fear that variations in the treatment of exacerbations might conceal the overall effect of oxytetracycline prophylaxis, it was thought desirable to specify treatment, and this permitted comparison of two regimens for treating exacerbations. One, chloramphenicol (0.5 g. q.d.s.), was chosen because it was widely regarded as the most effective drug against bronchial infection and it was considered that the slight risk of blood dyscrasia would be outweighed by the possibility of early control of infection ; the other, a sulphonamide (sulphamethoxypyridazine, 0.125 g. q.d.s.), while never shown to be effective in purulent exacerbations of bronchitis (Kilpatrick and Oldham, 1954 ; Edwards *et al.*, 1957 ; Francis *et al.*, 1964), might protect against pneumonic complications. These drugs, in white capsules, in boxes containing one week's supply, were also issued from Cardiff. Patients were told that if they developed a chest cold they should consult their doctor, and if he considered that they had an exacerbation of bronchitis they should take the white capsules for one week.

After two years it was found that some men were using white capsules repeatedly, and it was agreed that for chloramphenicol this might be dangerous. It was therefore arranged that after three such courses in any one period of 12 months subsequent boxes contained penicillin V (250 mg.) instead of chloramphenicol or sulphonamide. After one year such patients reverted to a new box of the original drug. Penicillin was substituted in the course of the trial on 13.4% of occasions on

* The members of the Working Party were: Dr. C. M. Fletcher (chairman), Dr. J. D. Ball, Dr. L. W. Carstairs, Dr. A. H. C. Couch, Professor J. M. Crofton, Dr. J. R. Edge, Dr. Gordon Edwards, Dr. E. L. Feinmann, Dr. M. R. Geake, Dr. G. Gemmill, Dr. J. C. Gilson, Dr. W. H. Helm, Dr. W. M. Macleod, Dr. E. N. Moyes, Professor J. G. Scadding, Professor O. L. Wade, Dr. C. H. Wood, and Mr. P. D. Oldham (secretary).
This report was prepared by Dr. C. M. Fletcher and Mr. P. D. Oldham.

which the capsules were taken. Since this substitution was distributed fairly equally among the different treatment groups, it is unlikely that it will have had much effect upon the results.

The trial was of the factorial kind, as follows:

		Prophylaxis	
		Oxytetracycline	Dummy
Therapy	Chloramphenicol ..	I	II
	Sulphonamide ..	III	IV

The expectation was that group I would receive prophylaxis and therapy, group II would receive therapy but no prophylaxis, group III would receive prophylaxis but no special therapy, and group IV would receive neither prophylaxis nor special therapy. All four combinations of the two prophylactic and two therapeutic regimens were allocated at random within each clinic. Balanced numbers in the four groups were achieved by arranging that each group of 12 men recruited by each clinic contained in random order three on each of the four régimes.

The overall effect of oxytetracycline prophylaxis, independent of therapy, can be shown by comparing groups I and III with II and IV, that of chloramphenicol therapy irrespective of prophylaxis by comparing groups I and II with III and IV, while a differential effect of prophylaxis, according to whether chloramphenicol therapy was given or not, should also be detected. Advice on smoking, occupation, and other treatment was left to individual physicians, but use of chloramphenicol or sulphonamides was discouraged.

Investigation and Records

At the first attendance a standardized questionary was filled in, a chest *x*-ray film taken, a clinical examination carried out, and the F.E.V. measured. Men found suitable for the trial were given serial numbers and issued with the appropriate boxes of tablets. A specimen of sputum coughed up during the first hour after rising (Elmes *et al.*, 1959) was assessed for purulence and volume before starting treatment. Complete standardization of F.E.V. technique was not ensured, since consistency within clinics was more important than consistency between clinics for observing the progression of individual men.

At subsequent clinics a form was completed on which were recorded tablets taken, symptoms of intolerance, sputum volume and type (mucoid, mucopurulent, or purulent), dyspnoea grade (Fletcher, 1952), and smoking habit. Illnesses were recorded in respect of date of onset, number of days off work, number of days spent in bed, date of apparent clinical recovery, and whether or not the sputum had increased. Physicians recorded whether or not the illness appeared to have been an exacerbation of bronchitis. Treatment was also noted.

Occasional samples of urine, taken from the men without any explanation, were sent to the Research Laboratories of Pfizer Limited to have oxytetracycline assayed by standard bio-assay. Of 303 samples from men in groups I and III only 58 (19%) showed no evidence that the drug had been taken. Since the patients were advised to take the drugs in the morning and most of the clinics were held in the evening, more than 80% of the patients probably took the pills they were asked to take for prophylaxis.

Comparison of Treatment Groups

Table I shows certain characteristics of the patients of each clinic on recruitment. In age there is fair uniformity. One clinic, F, had patients with a consistently high F.E.V. The frequency of mucopurulent or purulent sputum varied widely from a majority in clinics B and J to a minority of men in clinics E, F, G, H, K, M, and N, while at clinics A, C, D, and L about half the patients had mucoid sputum. Some of this interclinic variation in sputum purulence may be due to observer-variation, but since standardized assessment was attempted by written instructions the frequency of purulence may have varied between the clinics as much as Table I suggests. In smoking habits the variation was not large. There were more non-smokers, ex-smokers, and light smokers than in the general population (Todd, 1962), presumably because many patients had reduced their smoking because of bronchitis.

TABLE I.—*Characteristics of Patients in Different Clinics at Time of Entry into the Trial*

Location	Clinic	No. of Patients	Mean Age	Mean F.E.V. (litres)	Percentage with Mucopurulent or Purulent Sputum	Smoking Habits (%)			
						Non-smoker	Ex-smoker	Smokers of 1–14 g. Tobacco Daily	Smokers of 15 g. or More Tobacco Daily
London ..	A	31	49·6	2·108	55	6·5	12·9	51·6	29·1
Edinburgh	B	18	49·1	1·860	100	6·7	20·0	46·7	26·7
Leeds ..	C	54	50·0	1·974	67	1·9	13·0	53·7	31·5
Gateshead	D	58	49·4	1·864	54	3·4	12·1	44·8	39·7
Burnley ..	E	57	51·2	1·921	16	5·4	10·7	44·6	39·3
London ..	F	53	50·8	2·494	20	0	13·2	50·9	35·8
Southampton	G	42	50·6	1·840	22	7·1	9·5	52·4	31·0
Worcester	H	50	50·3	1·904	30	2·0	26·0	50·0	22·0
Edinburgh	J	18	50·2	2·040	81	12·5	18·8	43·8	25·0
Belfast ..	K	65	49·1	2·145	30	9·2	21·5	38·5	30·8
Chorley (Lancs) ..	L	27	52·0	2·175	64	0	15·4	50·0	34·6
Barrow ..	M	8	48·8	1·788	33	12·5	12·5	50·0	25·0
Norwich ..	N	16	54·5	2·063	6	12·5	31·3	50·0	6·3
All clinics ..		497	50·3	2·032	41	4·9	15·9	47·7	31·4
		All men aged 36–59 in 1958*				8·7	14·2	28·8	48·3

*Estimated from Todd (1962,.

The differences in these characteristics among the treatment groups both for all patients recruited and for those remaining on full treatment were not material. The patients in each group were nearly evenly distributed in age over the whole permitted age-range of 20 years, while the standard deviations of the distributions of F.E.V. within groups were between 0.5 and 0.6 l.

Lapses from Treatment

Of the 497 original men 124 (25%) did not continue to the end of the trial on full treatment. Many of these contributed information for several years before withdrawal. In this report only results from the 373 patients on full treatment throughout the trial are given. Table II shows that in over 60% of lapses the reason for withdrawal was failure to cooperate, which is not surprising in a trial on relatively fit working-men whose only motive for attending regularly was to avoid future illness. Withdrawals of treatment for all reasons except side-effects were evenly divided between the four treatment groups. These side-

TABLE II.—*Numbers of Patients Failing to Complete Treatments*

Treatment Group	No. Recruited	No. Withdrawn or on Partial Treatment							No. Remaining (%)
		No. Dead	Side-effects Attributed to Treatment	Severe Progression of Bronchitis	Other Disease (All Lung Cancer)	Uncooperative	Change of Address	Total	
I	120	2	6	1	—	17	3	29	91 (76)
II	125	1	3	2	—	26	—	32	93 (74)
III	130	3	8	4	—	21	4	40	90 (69)
IV	122	2	—	1	2	15	3	23	99 (81)
I and III	250	5	14	5	—	38	7	69	181 (73)
II and IV	247	3	3	3	2	41	3	55	192 (78)
I and II	245	3	9	3	—	43	3	61	184 (75)
III and IV	252	5	8	5	2	36	7	63	189 (72)
Total	497	8	17	8	2	79	10	124	373 (75)

effects were more common in groups I and III, receiving oxytetracycline.

In four instances minor side-effects experienced by subjects in groups I and III were attributed to chloramphenicol or sulphonamide rather than to oxytetracycline. Even so, 11 side-effects attributed to "yellow tablets" were divided significantly unevenly—10 to oxytetracycline and one to dummy tablets. No alarming side-effects were associated with nearly 400 courses of chloramphenicol given during the trial. The overall lapse rate, about 6% per annum in the course of the trial, was not materially different in the four treatment groups. There is no reason to suppose that the results obtained on the 373 men remaining are not representative.

Results

Number of Illnesses

During the five years of the trial 1,214 separate illnesses were thought by the physicians to be exacerbations of bronchitis. Two patients became ill and remained unable to work, and since it was impossible to distinguish the end of one exacerbation from the beginning of another they are excluded from the analyses. Table III shows how the 1,214 illnesses were distributed among the other subjects in the four treatment groups. In each group most patients had no illness, one illness, or two illnesses, but substantial numbers experienced eight or more. One man in group III had 22 illnesses and one in group II had 16.

TABLE III.—*Distribution of Patients According to Total Number of Illnesses*

No. of Illnesses	No. of Patients in Treatment Group							
	I	II	III	IV	I and III	II and IV	I and II	III and IV
0	18	11	16	18	34	29	29	34
1	15	14	20	17	35	31	29	37
2	17	16	9	12	26	28	33	21
3	13	14	9	16	22	30	27	25
4	9	10	6	7	15	17	19	13
5	8	7	8	6	16	13	15	14
6	4	9	3	6	7	15	13	9
7	2	1	8	7	10	8	3	15
8+	5	10	10	10	15	20	15	20
Unemployed	—	1	1	—	1	1	1	1
Total No. of men ..	91	93	90	99	181	192	184	189
Total No. of illnesses ..	245	330	306	333	551	663	575	639

No obvious difference between the groups can be seen from the extended and skew distributions in Table III, except for a smaller total number of illnesses in group I. Table IV summarizes different aspects of these distributions. In general, group I had the most favourable experience and group II the least, though the wide variation within each group makes this uncertain. While groups I and III (oxytetracycline prophylaxis) fared better by all criteria than groups II and IV (dummy prophylaxis), this is due entirely to group I, which had a significantly different distribution of number of illnesses from all other groups ($P \simeq 0.035$). Chloramphenicol therapy (groups I and II) showed no consistent advantage over sulphonamide therapy in number of illnesses. The advantage of group I appears to be due only to fewer men having many illnesses, a smaller *range* of distribution, and not to consistent reduction in the number of illnesses at all levels. This is shown by analysing logarithms of the number of illnesses (increased by unity), which gives less weight to the larger numbers of illnesses in each treatment group. When this is done the experience of group I is no longer significantly different from the rest ($P \simeq 0.11$). Not every subject used the special capsules for every bronchitic illness. The results for illnesses when capsules were used were very similar to those described for all exacerbations.

TABLE IV.—*Characteristics of the Distributions Shown in Table III*

Group	No. of Subjects	% Having No Illness	% Having More than One Illness	Mean No. of Illnesses per Man		
				All Men	Men having at Least One Illness	All Men (Logarithmic)
I	91	20	64	2·7	3·4	2·0
II	92	12	73	3·6	4·1	2·7
III	89	18	60	3·4	4·2	2·3
IV	99	18	65	3·4	4·1	2·3
I and III	180	19	62	3·1	3·8	2·1
II and IV	191	15	69	3·5	4·1	2·5
I and II	183	16	68	3·1	3·7	2·3
III and IV	188	18	62	3·4	4·2	2·3
All groups	371	17	65	3·3	3·9	2·3

In short, only the combination of oxytetracycline prophylaxis with chloramphenicol therapy appeared to have any effect, and this was to reduce the number of patients having many illnesses. The practical importance of this result is diminished by the fact that, while there was no evidence that the effects of the four treatment combinations varied from clinic to clinic, the overall numbers of illnesses did vary significantly ($P<0.001$). The average was 1.8 in one clinic, 5.5 in another, while five clinics had averages between 2 and 3, four between 3 and 4, and two between 4 and 5. Thus factors other than treatment were associated with greater variation in number of illnesses than any effect of treatment itself.

Duration of Illness

It was impossible to record the total time spent ill by the patients consistently, since the exact time of onset and recovery in an exacerbation of chronic bronchitis cannot always be specified; so we have analysed the number of days lost from work owing to the illnesses, as this was recorded at each patient's attendance. Close agreement was found between dates and durations recorded in this way for illnesses lasting four or more days and those obtained, with the patients' authority, through the courtesy of the Ministry of Pensions and National Insurance. This measure of duration has the merit of reflecting the loss to society of the patients' services.

A convenient relevant way of summarizing the average days off work per illness is to group the illnesses in classes which, after the first, successively double in duration (Table V).

TABLE V.—*Distributions of Average Number of Days Off Work per Illness*

No. of Days Off Work	No. of Patients in Treatment Group			
	I	II	III	IV
*0–	8	4	4	2
1–	1	—	2	2
2–	6	8	9	5
4–	13	15	12	12
8–	20	23	22	32
16–	16	24	17	18
32–	8	4	7	10
64–	1	3	—	—
Unemployed	—	1	1	—
No illness ..	18	11	16	18
Total ..	91	93	90	99

*Includes patients whose illness caused no absence from work, as well as patients averaging less than one day.

Short illnesses are separated, illnesses of "about a week" are classed together, and as duration increases less importance is attached to the exact number of days off work, which for long illnesses may be less reliable than for shorter illnesses.

No marked differences between the treatment groups are seen in Table V, but small differences which are reliably established may represent material advantages in the long run. If the patients with less than one day's absence are counted as having lost half a day the steps of increasing severity in Table V are

placed on a logarithmic scale and the means of these logarithms of duration correspond (after antilogarithms are taken) to the median of the actual durations—that is to say, half the patients had more and half had less than this median duration. These medians or geometric means are more relevant than arithmetic means in describing a distribution as skew as that of our patients' durations of illness.

It will be seen (first row of Table VI) that groups I and III have medians one and a half to two days smaller than groups II and IV. Analysis of variance revealed no evidence that the

TABLE VI.—*Indices of Days Off Work per Illness in Patients having Illnesses*

Index	Treatment Group			
	I	II	III	IV
(1) Median (or geometric mean)	8·92	10·75	9·27	11·51
(2) Median assuming independence of treatment effects ..	8·85	10·83	9·34	11·43
(3) Arithmetic mean	14·9	17·9	15·4	19·2
(4) Median allowing for variation between clinics	9·36	10·93	9·94	11·48
(5) Arithmetic mean allowing for variation between clinics ..	15·9	18·6	16·9	19·6

effect of oxytetracycline varied according to whether chloramphenicol or sulphonamide accompanied it. Estimates of the effects incorporating this independence are shown in the second row of Table VI. The ratio of the median of group II to that of group I, 1.22, is now the same as that of group IV to group III.

This ratio indicates that taking oxytetracycline led to a 22% reduction in median length of sickness absence, but this reduction is not significantly different from zero ($P \simeq 0.10$; 95% limits lie between a 55% reduction and a 4% *increase* in duration of sickness absence). The equivalent ratio for the effect of chloramphenicol in contrast with sulphonamide is 1.06. This 6% reduction in sickness absence is quite insignificantly different from zero.

In order to estimate the average reduction of sickness absence which might be experienced by a population of bronchitic patients, such as those whom we studied, given one of our treatment combinations, we need estimates of arithmetic means (third row, Table VI). These were obtained by assuming log normal distributions of absence with equal logarithmic standard deviations and using the estimator given by Finney (1941) as extended in the case of pooled standard deviations by Oldham (1953), and show that in a population of bronchitics such as those we have studied oxytetracycline prophylaxis should cause a reduction of three to four days per illness, which could be regarded as useful if it were reliably established. Allowance must, however, be made for the substantial variation of mean duration of illness from clinic to clinic because the proportions on each regimen were not exactly the same. The median lengths of illness in groups I and III are then slightly increased (Table VI, fourth row), bringing them closer to those of groups II and IV. The difference between them is not statistically significant, and the arithmetic means corresponding to these medians (last row, Table VI) show that the average difference of duration of illness associated with administration of oxytetracycline is only 2.7 days.

Analysis of total days off work showed results very similar to those of the average days off per illness.

In summary, the evidence from duration of illness shows that oxytetracycline appeared to cause a considerable reduction but that the estimates are so unsure as to leave a wide range of possibilities open, including even the possibility that it had no effect at all.

Changes in Ventilatory Function

F.E.V. was measured routinely at each clinic visit, and thus up to 25 separate records were produced for each patient. Any systematic differences between clinics in the absolute levels of F.E.V. according to technique used should not have affected the changes of F.E.V. of individuals under the four treatment regimens.

In this paper we report only the gradient with time. For this purpose missed visits were allowed for, but successive clinic visits of each individual were taken as equally spaced in time, though in fact the winter visits were more frequent than the summer visits. Any consequent irregularity will cause only negligible increase of variation about the linear gradient. Linear regression lines were fitted to each patient's records, and the slopes of these are reported as change of F.E.V. in litres per year.

Table VII shows the extended distributions of the changes in the four treatment groups. Four subjects lost over a third

TABLE VII.—*Distributions of Change of F.E.V.*

Change of F.E.V. (l./year)	Treatment Group				All Groups
	I	II	III	IV	
−0·40−	1	—	1	—	2
−0·35−	—	—	1	1	2
−0·30−	—	3	1	6	10
−0·25−	8	4	4	4	20
−0·20−	16	8	15	12	51
−0·15−	16	20	14	14	64
−0·10−	16	28	27	22	93
−0·05−	23	16	14	24	77
0−	9	7	6	9	31
+0·05−	—	5	1	4	10
+0·10−	1	1	1	2	5
+0·15−	1	—	5	1	7
+0·20−	—	1	—	—	1
+0·25−	—	—	—	—	—
Total	91	93	90	99	373

of a litre on average per year, while eight gained a sixth of a litre or more. No differences between treatment groups are apparent, and this is confirmed by the averages shown in Table VIII. The first column shows a weighted average of all the

TABLE VIII.—*Average Change of F.E.V. (Litres per Year) by Treatment Group*

Treatment Group	Weighted Average of Individuals	Crude Average of Individuals
I	−0·086 ± 0·0046	−0·090
II	−0·076 ± 0·0045	−0·076
III	−0·081 ± 0·0051	−0·083
IV	−0·074 ± 0·0046	−0·079
All groups	−0·079 ± 0·0024	−0·082

patients in the trial, the weight depending on the number of satisfactory measurements on each individual and the length of time he was in the trial. Group IV had the smallest loss of F.E.V., group I the largest, but all four lie within a narrow range in relation to the standard errors of the means, which are all around 0.005 l./year. A crude average of individual rates of change of F.E.V. leads to similar figures (column 2) but a changed rank order.

Decline of F.E.V. appears to be unaffected by treatment; the weighted average of all the subjects estimated as 0.079 ± 0.0024 l./ year could be taken as characteristic of each group. This decline is much greater than that observed in the general population, which for non-smokers without symptoms is of the order of 0.03 l./year and for smokers, like most patients in our trial, has been reported as approximately 0.05 l./year (Ferris *et al.*, 1965; Hill *et al.*, 1966).

Changes in Sputum

The effect of chemotherapy on the sputum of our patients may be assessed by changes in sputum volume and purulence. Changes in sputum volume were analysed in a manner similar to that used for changes in F.E.V., and differences between treatment groups were equally unimpressive. Table IX shows

the distribution of sputum purulence in the treatment groups. There is close similarity between groups II, III, and IV. In group I significantly fewer men ever had purulent sputum, but since fewer also had persistently mucoid sputum it is unlikely that this was an effect of chemotherapy, and it must, in spite of the size of the differences, be attributed to chance.

TABLE IX.—*Distribution of Sputum Types*

Type of Sputum	No. of Patients in Treatment Group				All Groups
	I	II	III	IV	
Always mucoid	13	19	21	23	76
Mucopurulent or mucoid	66	45	45	50	206
Purulent at least once ..	12	28	23	26	89
All types	91	92	89	99	371

Discussion

By laying down strict criteria for admission of patients we hoped that we would obtain a uniform sample of men with "early chronic bronchitis." In fact the patients were very diverse in respect of F.E.V., sputum volume and sputum purulence, and in liability to chest illnesses. This heterogeneity contributed to the wide and skew distribution of illnesses, which makes it difficult to interpret the differences between treatment groups in any general terms. In the dosage we used, oxytetracycline prophylaxis had no consistent effect on the number of illnesses. Used with chloramphenicol therapy, it significantly reduced the number of patients having many illnesses, but with sulphonamide it had no apparent effect at all (Table IV). This was as true in the last two years of the trial with a daily dose of 1–2 g. as in the first three years with a dose of 0.5 g. It is difficult, but not impossible, to think how occasional chloramphenicol therapy could reduce the number rather than the duration of illnesses, but this unexpected finding may have been due to chance, despite its apparent statistical reliability.

There is a suggestion that oxytetracycline prophylaxis was associated with a reduction in average length of illness (Table VI), but the estimate of the reduction in average length, allowing for all disturbing factors (about 16% ; Table VI, rows 4 and 5), is so uncertain that in the population from which our sample was drawn the true effect might, on the one hand, be negligible or, on the other hand, it might be a most material reduction of over 30%. Surprisingly, chloramphenicol given in a dose of 2 g. daily in the treatment of exacerbations had no material effect on their duration. This therapeutic failure and the possible effect of prophylaxis on duration rather than on number of illnesses suggests that any effect of prophylaxis may have been not on the initiating causes of exacerbations (which may have been viral agents or meteorological changes) but on secondary bacterial proliferation. It may in fact have been acting as a more immediate type of chemotherapy than an antibiotic taken when the patient felt ill enough to consult his doctor. The relative ineffectiveness of intermittent therapy has been noted previously (Fear and Edwards, 1962).

In view of the small effect of chemotherapy on illnesses it is not surprising that we found no effect on rate of decline of F.E.V. A relationship between this rate of decline and the average level of the F.E.V., frequency of illnesses, and purulence of sputum will be reported in a separate paper.

Though we found difficulty in recruiting patients with persistent cough and sputum, and with chest illnesses but with F.E.V. over 1.4 l., prevalence surveys have shown that in towns about 10% and in the country about 6% of all men aged 40–59 have these characteristics (Holland, 1964 ; Holland and Reid, 1965). Our study suggests that neither chemoprophylaxis nor chemotherapy will, on the average, delay progression of disability in the type of patient we recruited to our trial. But this does not exclude the possibility that there are some men with early obstructive bronchitis who could be benefited. Though the average shortening of our patients' illnesses by prophylactic oxytetracycline was small—amounting to a reduction of time lost from work on the average of not more than some two days per annum per man—this small effect may be due to a large number of men in whose exacerbations infection played little part, and in whom the results were negative, concealing a considerable effect upon a smaller number in which infection was important and was controlled. Unfortunately we do not know how to distinguish those men who might be benefited. When we compared the treatment groups, including only those men who ever had purulent sputum, there was no greater difference between the groups than there was when all the men were considered together, so assessment of sputum purulence is no guide. The effect of oxytetracycline in conjunction with chloramphenicol on the number of illnesses suggests that perhaps it is men with very frequent exacerbations who can be most helped by chemotherapy.

More observation of the nature of exacerbations occurring in mild bronchitis is required before effective treatment can be designed. Bacterial superinfection may not play such an important part in exacerbations of chronic bronchitis, at least in its early stages, as is generally believed. In more advanced bronchitis a considerable number of controlled trials have shown a significant effect of both continuous and intermittent antibiotic prophylaxis (Scottish Health Services Council, 1963 ; *British Medical Journal*, 1964).

It may be that these illnesses are due more to exacerbations of bronchial obstruction than to exacerbations of bronchial infection and that prophylaxis and treatment should be designed more to provide relief of obstruction than to control infection.

Summary

To study the relationship between recurrent bacterial infection and the progression of disability from airways obstruction in early chronic bronchitis, a double-blind trial of antibacterial drugs in therapy and prophylaxis was carried out on men aged 40–59 with recurrent chest illnesses and with F.E.V. over 1.4 litres over a period of five years at 13 clinics throughout the country.

Oxytetracycline or dummy tablets were given continually from September to April, at first in a dose of 0.5 g. daily, increasing in the last two years of the trial to 1 g. and finally 2 g. daily. Chloramphenicol (2 g. daily) or sulphamethoxypyridazine (0.5 g. daily) was given as treatment of exacerbations. Combinations of the prophylactic and therapeutic regimens were allocated at random.

Despite careful diagnostic standardization and selection, there was a wide variation in the type of patient at the different clinics. Both number and duration of illnesses considered to be infective exacerbations of bronchitis showed a large variation between clinics and a very skew distribution. This made it difficult to give any simple index of the effect of either prophylaxis or treatment, and adjustment had to be made for interclinic variation.

Oxytetracycline prophylaxis by itself appeared to have no effect on the number of illnesses. In those patients who also received chloramphenicol therapy there was a significant reduction in the number who had many illnesses. Duration of illnesses, measured by time off work, also showed a wide and skew distribution and varied significantly from clinic to clinic. It appeared that oxytetracycline prophylaxis reduced by one-third the total amount of time lost from work owing to exacerbations of bronchitis, but this estimate had a large range of uncertainty.

Ventilatory capacity declined more rapidly in the patients than would have been expected for men of their age and smoking habits in the general population. Neither prophylaxis

nor therapy had any effect on the rate of decline of F.E.V. or on the volume or purulence of sputum specimens.

We wish to record our appreciation to Pfizer Limited for their generous supply of oxytetracycline and indistinguishable dummy tablets, and for their willing cooperation in the analysis of numerous blood and urine samples for oxytetracycline, both before and during the trial; and to Messrs. Parke Davis and Co. for their supply of chloramphenicol, sulphamethoxypyridazine, and penicillin capsules. Numerous members of the staff of the Pneumoconiosis Research Unit assisted with the packing and dispatch of over a million tablets, but the main burden of this work fell on Mrs. J. P. Duimovich, who also kept the statistical records of the trial. We would like to thank the officers of the Ministry of Pensions and National Insurance who provided us with records of the sickness absence of the patients in the trial, and the staff and health visitors of the different clinics for their continual help, especially for the extra evening sessions that were necessary, since the patients were nearly all at work during the day.

The participating clinics and hospitals were: Postgraduate Medical School, Hammersmith Hospital, London W.12; Department of Respiratory Diseases and Tuberculosis, University of Edinburgh; Leeds Chest Clinic; Whinney House Hospital, Gateshead; the Marsden Hospital, Burnley; the Central Middlesex Hospital, London N.W.10; Central Chest Clinic, Southampton; Worcester Royal Infirmary; Corbett Hospital, Stourbridge, Worcs; Department of Therapeutics and Pharmacology, the Queen's University of Belfast; Chorley Chest Clinic, Chorley, Lancs; High Carley Hospital, Ulverston, Lancs; Norwich and East Norfolk Chest Clinic, Norwich.

Communications concerning the Report should be sent to the Medical Research Council, 20 Park Crescent, London W.1.

REFERENCES

Brit. med. J., 1964, **1**, 718.
Edwards, G., Buckley, A. R., Fear, E. C., Williamson, G. M., and Zinnemann, K. (1957). *Brit. med. J.*, **2**, 259.
Elmes, P. C., Dutton, A. A. C., and Fletcher, C. M. (1959). *Lancet*, **1**, 1241.
Fear, E. C., and Edwards, G. (1962). *Brit. J. Dis. Chest*, **56**, 153.
Ferris, B. G., Anderson, D. O., and Zickmantel, R. (1965). *Amer. Rev. resp. Dis.*, **91**, 252.
Finney, D. J. (1941). *J. roy. statist. Soc.*, Suppl. No. 7, p. 155.
Fletcher, C. M. (1952). *Proc. roy. Soc. Med.*, **45**, 577.
Francis, R. S., May, J. R., and Spicer, C. C. (1964). *Brit. med. J.*, **1**, 728.
Hill, I. D., Letchner, J., Tinker, C. M., and Fletcher, C. M. (1966). In preparation.
Holland, W. W. (1964). M.D. Thesis. London.
—— and Reid, D. D. (1965). *Lancet*, **1**, 445.
Kilpatrick, G. S., and Oldham, P. D. (1954). *Brit. med. J.*, **2**, 385.
Medical Research Council (1960). Ibid., **2**, 1665.
Oldham, P. D. (1953). *Brit. J. industr. Med.*, **10**, 227.
Scottish Health Services Council (1963). *Bronchitis*. Report of a Subcommittee of the Standing Medical Advisory Committee, p. 29. H.M.S.O., London.
Todd, G. F. (editor) (1962). *Statistics of Smoking in the United Kingdom*. Tobacco Manufacturers' Standing Committee. Research Papers No. 1, 3rd ed. London.

Massive Pulmonary Embolism in Healthy People

H. A. FLEMING,* M.D., M.R.C.P.; SHEILA M. BAILEY,† M.B., B.S.

Brit. med. J., 1966, **1**, 1322–1327

In recent years many reports have indicated an increasing frequency of the diagnosis of pulmonary emboli. Short (1952), Gorham (1961), Barritt and Jordan (1960, 1961), Wilhelmsen *et al.* (1963), Goodwin *et al.* (1963), Morrell *et al.* (1963), Freiman *et al.* (1965), and Sasahara and Stein (1965) are representative examples from a vast literature. Until Thompson and Hamilton's paper in 1962 the occurrence of major pulmonary emboli in ambulant healthy people had received little general recognition. Many clinicians still fail to recognize this condition, and are prepared to make a diagnosis of pulmonary embolism only in the post-operative case, the case in gross heart failure, the bedridden, or the aged. This point is emphasized in the tragic report of Murphy (1963), and by the fact that three of our own severe but fortunately non-fatal cases were also doctors' wives in whom there was considerable delay in diagnosis.

This failure is mirrored in a number of otherwise excellent monographs and conference proceedings on the pulmonary circulation, and even one on pulmonary embolic disease, which have nothing whatever to say on fatal pulmonary embolism in healthy persons.

The frequency with which we made this clinical diagnosis led us to wonder if there were not a number of such patients who died either before diagnosis was made or before treatment could be effectively instituted (Fleming, 1962). This led to the present study of fatal cases, and of cases diagnosed and treated in life.

* Consultant Cardiologist, East Anglian Regional Hospital Board and Addenbrooke's Hospital, Cambridge.
† Research Assistant, East Anglian Regional Hospital Board and Addenbrooke's Hospital, Cambridge.

Material

We first searched the necropsy reports of the Cambridge University Department of Pathology for the years 1946–63. This department carries out all the necropsies in the Cambridge area, and detailed reports are kept.

As this study was concerned only with healthy people all those over 70 were excluded, as were those known to suffer from predisposing disease or to have undergone recent surgery or trauma. Minor surgery or surgery a few weeks previously did not exclude some cases if the association was not obvious to the doctor seeing the patient.

During 1946–63 9,280 necropsies were carried out, the numbers rising steadily from 273 in 1946 to 857 in 1963. Of these about 300 were classified as having massive pulmonary emboli, and about 400 as having small pulmonary emboli. Thirteen of these subjects had died suddenly outside hospital and no other cause of death could be found. Three were over the age of 70, and one had a small abscess in the left upper lobe. These were eliminated from the series, leaving nine cases to be considered here. A further 18 cases fulfilling the criteria of the study had been admitted to hospital before their death. Thus there were 27 fatal cases for consideration—6 males and 21 females. The age range was 23 to 69 years (average 50).

Of the nine cases of sudden death outside hospital eight were women, and all but one had a recorded complaint of some dyspnoea or chest discomfort preceding death. The 23-year-old patient was five months pregnant, and had been treated for venous thrombosis three and a half weeks previously.

In all cases either a large embolus straddled the pulmonary artery bifurcation or both main pulmonary arteries were blocked