It is confirmed that little reliance can be placed on statements concerning a past history of rubella. In this series about one-third of all firm statements were proved to be wrong on subsequent laboratory investigation. The histories, mostly obtained from parents, were most accurate for the 1–5 years age group. Similar findings have been reported by other workers (Vesikari *et al.*, 1968). This lack of correlation between statements concerning a past history of rubella and serological studies may be ascribed to the difficulty in diagnosis of rubella which is often simulated clinically by other infections (Krugman, 1965). Ignorance of infection may also be due partly to the occurrence of subclinical attacks, and, to a certain extent, failure to remember the occurrence of clinical infection many years in the past.

The results of this and previous serological studies of children seem to raise a number of important problems concerning vaccination against rubella. Several vaccines have been developed and the results of preliminary clinical trials published (Proceedings of the 23rd Symposium on Microbiological Standardization, Rubella Vaccines, 1969). Before these vaccines become freely available the age at which they are to be administered must be decided. As yet, insufficient data have been published concerning the possible transmission of vaccine strains of rubella virus across the placenta and the teratogenic effects of these strains on the fetus. Consequently, the vaccination of adult women will involve the prevention of pregnancy immediately before and after administration of the vaccine. If children are to be vaccinated, it must be taken into consideration that the majority are already naturally immune by the age of 10–15 years, and mass vaccination at this stage may be regarded as impracticable or uneconomical. The selection of children on the basis of past histories cannot be relied on, and the alternative screening of all children to detect immune status prior to vaccination would be very laborious. The vaccination of infants below the age of 5 years may be more logical, as this age group has the lowest level of natural immunity. In this case, however, vaccine-induced immunity may not be sufficient to afford protection into adulthood, and it may be necessary to revaccinate in later years.

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REFERENCES

Chagnon, A., Davignon, L., and Pavilanis, V. (1969). In *Proceedings of the 23rd Symposium on Microbiological Standardization, Rubella Vaccines, London, November 1968.* Basle, Karger.
Dudgeon, J. A. (1967). *Public Health (London)*, **81**, 268.
Enders-Ruckle, G., and Lindemann, L. (1969). In *Proceedings of the 23rd Symposium on Microbiological Standardization, Rubella Vaccines, London, November 1968.* Basle, Karger.
Field, A. M., Vandervelde, E. M., Thompson, K. M., and Hutchinson, D. N. (1967). *Lancet*, **2**, 182.
Hillenbrand, F. K. M. (1956). *Lancet*, **2**, 64.
Hutchinson, D. N., and Thompson, K. M. (1965). *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service*, **24**, 385.
Krugman, S. (1965). *Archiv für die gesamte Virusforschung*, **16**, 477.
Lennette, E. H., Schmidt, N. J., and Magoffin, R. L. (1967). *Journal of Immunology*, **99**, 785.
Peetermans, J., and Huygelen, C. (1967). *Presse Médicale*, **75**, 2177.
Public Health Laboratory Service (1968). *British Medical Journal*, **3**, 203.
Sever, J. L., *et al.* (1965). *Pediatrics*, **35**, 996.
Stewart, G. L., *et al.* (1967). *New England Journal of Medicine*, **276**, 554.
Tóth, M. (1968). *Acta Microbiologica Academiae Scientiarum Hungaricae*, **15**, 119.
Vesikari, T., Vaheri, A., and Kauppinen, M. A. (1968). *Annales Medicinae Experimentalis et Biologiae Fenniae*, **46**, 109.
Watson, G. I., and McDonald, J. C. (1963). *British Medical Journal*, **2**, 419.

Five-Year Winter Chemoprophylaxis for Chronic Bronchitis

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Summary: Seventy-nine patients with chronic bronchitis were randomly allotted to four treatment regimens—placebo throughout the winter months for five years; tetracycline for the first two winters and placebo for the next three; placebo for the first two winters and tetracycline for the next three; and tetracycline for five winters. In addition all groups received a five-day course of tetracycline for any acute exacerbation. There was a significant reduction in the number of exacerbations among the more susceptible patients—that is, those who suffered more than one exacerbation each winter. Though the average decline in F.E.V.$_1$ over the five-year period was less in the treated groups this was not statistically significant. There was no significant difference between the groups in respect of lung volumes, diffusing capacity, and blood gases.

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Introduction

Optimal antibiotic regimens for chronic recurrent mucopurulent bronchitis are difficult to assess, being complicated by the plethora of antibiotics available. It is still uncertain whether patients on chemoprophylaxis during the winter months fare better than those receiving prompt treatment of acute exacerbations. Further, can the lung function of these patients be preserved better by chemoprophylaxis ?

The British Tuberculosis Association (1960) report on chemotherapy in chronic bronchitis compared the effect of tetracycline 250 mg. b.d. with penicillin V potassium 312 mg. b.d. and a placebo in 226 patients. Treatment with penicillin or tetracycline reduced the loss of working days by about half compared with the controls. Neither drug significantly reduced the number of exacerbations, but both reduced their duration. The British Tuberculosis Association (1961) reported 519 patients who received in regimen A maintenance starch capsules with intermittent oral penicillin for exacerbations ; B, maintenance tetracycline with starch capsules for exacerbations ; C, maintenance penicillin with again starch capsules for exacerba-

tions; and D, maintenance placebo with tetracycline for exacerbations. The number of exacerbations was somewhat reduced in all except those in regimen A, with no significant difference between those on daily compared with intermittent tetracycline. Only those receiving daily tetracycline showed a significant reduction in duration of exacerbations compared with the other three regimens. Johnston (1962), in a review of the reports at that time, concluded that tetracycline was the drug of choice in a dose of at least 1 g. daily.

The Medical Research Council (1966) report, in which 373 patients were studied over a period of five winters, indicated that oxytetracycline prophylaxis appeared to have no effect on the number of acute exacerbations of bronchitis; but there was a reduction by one-third of the total amount of time lost from work, though this estimate had a large range of uncertainty and it was even possible that it had no effect at all. Calder *et al.* (1968) have reported in more detail 27 patients from one centre included in the Medical Research Council report. These patients were treated for a further two winters with oxytetracycline 500 mg. b.d. and suffered significantly fewer exacerbations of their bronchitis than those receiving a placebo. The duration of exacerbations was not analysed. In neither of these trials was there any significant reduction in the rate of decline of the forced expiratory volume (F.E.V.).

Malone *et al.* (1968), in a recent study on the treatment of acute exacerbations of chronic bronchitis, emphasized the need for early treatment, strict selection of patients, and close treatment supervision. They concluded that ampicillin and methacycline hydrochloride were no more effective than tetracycline, and drew attention to the economy of tetracycline and particularly oxytetracycline.

Present Study

In 1963 we began a five-year study of winter chemoprophylaxis and chemotherapy for patients suffering from chronic bronchitis.

Selection of Patients

From patients attending the chest clinic we selected men aged 38–60 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. We excluded patients who we considered unlikely to remain employed over the next five years and those with any other significant disability or a history of intolerance to antibiotics.

At the October visit each winter we assessed the grade of breathlessness; classified the patient's employment as heavy, medium, or light; and noted any undue exposure to dust, fumes, or damp. 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 which had been 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 May (1965)—that is, M=mucoid, Tr.=trace of pus, +=25% of pus in specimen, ++=50% pus in specimen, +++=75% of pus in specimen. Each winter, and immediately preceding the start of treatment, patients submitted two consecutive early morning sputum specimens. Films were examined for pus cells and eosinophils. The specimens were subjected to a pancreatic digest method and inoculated on blood agar. Sensitivity tests to the standard antibiotics were carried out. Specimens sent by post at the start of exacerbations were treated similarly, and at the end of each winter period two early morning sputum specimens were examined as before.

Patients were seen at 28-day intervals, the following data being recorded: any exacerbation of bronchitis *associated with purulent sputum,* the number of days off work, the use of emergency treatment, any other chemotherapy, and any drug intolerance. In addition, the patient brought a 24-hour sputum specimen collected during the preceding day and the volume and appearance were recorded. Patients were provided with diary sheets to record daily any change in chest symptoms and the colour of the early morning sputum. Current weekly consumption of cigarettes was recorded. The patient was asked about any lapse in treatment and the number of tablets remaining were counted to see if there had been any serious omission in therapy. Urine tests for the presence of tetracycline were arranged on two random occasions each winter.

At the end of each winter the following additional information was noted: the grade of dyspnoea, any change of occupation, and the patient's assessment of his chest disability compared with the previous winter. The last was graded as worse (−1), no change (0), slightly improved (+1), and much improved (+2), and the sum of these five assessments by each patient was recorded as the "patient score." The total number of days lost from work because of exacerbations of bronchitis was noted for every patient each winter, and in addition our medical social worker obtained an independent assessment from the Ministry of Pensions and National Insurance of the loss of working-time due to bronchitis.

Pulmonary Function

Tests were carried out on patients in the autumn before the trial started and in the spring following the completion of the fifth winter of treatment. The studies were done on an outpatient basis and patients were not tested during an exacerbation of bronchitis. Vital capacity (V.C.) and the forced expiratory one-second volume ($F.E.V._1$) were measured from the best of three recordings on a fast-moving kymograph by means of a low-resistance spirometer. Functional residual capacity (F.R.C.) and residual volume (R.V.) 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 (DL_{CO}) were made by the single-breath method of Ogilvie *et al.* (1957). DL_{CO} was then divided by the alveolar volume that obtained during the breath-holding period of the test (alveolar volume=inspired volume+residual volume as measured previously by the closed-circuit helium method) and expressed as ml. of carbon monoxide diffusing per minute, per mm. Hg gradient, per litre of lung ($DL_{CO}/V.A.$).

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. Although an electrode was used in the final study, the haemoreflector method was repeated for purposes of comparison. The arterial carbon dioxide tension ($Paco_2$) was measured indirectly by the rebreathing method of Campbell and Howell (1960), assuming a difference of 6 mm. Hg between mixed venous and arterial tensions.

Those results which are expressed as a percentage of the predicted normal values have been derived from the formulae of Needham *et al.* (1954) corrected to body temperature, pressure, and saturation (B.T.P.S.). These normal values were chosen because they were obtained from subjects in an adjacent geographical area in the North-East of Scotland. The $F.E.V._1$ was predicted from the formula for the maximum breathing capacity (M.B.C.) divided by a factor of 35 and the total lung capacity (T.L.C.) from the addition of the predicted values for V.C. and R.V.

Plan of Treatment

The aim was a double-blind study comparing tetracycline 500 mg. b.d. with a placebo administered from October to April for five winters. In addition, an anti-influenza vaccine was

given in October 1964 and again in October 1966. Patients were instructed that when they developed an exacerbation with increasing purulence of the sputum they should post a specimen of sputum direct to the laboratory and start emergency tetracycline 500 mg. b.d. for five days in addition to existing treatment.

The tetracycline and placebo tablets were packed in bottles containing sufficient to last 30 days. These bottles were labelled 1 to 10, with a random allocation of tetracycline to five and a random allocation of patients to numbers 1–10. The first allocation covered the first two winters. A fresh batch was issued at the start of the third winter with a reallocation of tetracycline/placebo to numbers 1–10. The effect was to produce four treatment groups—namely, group "P." who received a placebo throughout, group "T." who received tetracycline throughout, group "T.P." who received tetracycline for two winters and then placebo for three, and group "P.T." who received placebo for two winters and then tetracycline for three. The change in medication at the start of the third winter was unknown to the patients and medical staff.

Results

Of the 120 patients accepted for the trial 41 were excluded—9 because of incorrect preliminary assessment, 7 died, 1 left Dundee, and 24 were defaulters.

Age.—The average age and range for the four groups were: group P. 53 (40–59), group T.P. 51 (38–60), group P.T. 53 (38–60), and group T. 51 (47–58) years.

Type of Work.—The type of work and exposure to dust and fumes showed a slight preponderance of heavy work with dust and fumes in groups T. and T.P., but the differences were not significant.

The smoking history and change in smoking habit during the five-year period are shown in Table I.

TABLE I.—*Smoking History*

Group:	P.	T.P.	P.T.	T.	Total
Non-smoker	4	5	9	2	20
Pipe	3	1	1	1	6
70 or less*	8	10	5	15	38
71–140*	2	5	3	3	13
141 or over*		1	1		2
No. of patients	17	22	19	21	79
Change in Smoking Habits During Trial					
No reduction	8	9	4	9	30
50% reduction	3	3	2	3	11
Stopped	2	5	4	7	18

* Weekly consumption of cigarettes.

TABLE II.—*Initial 24-hour Sputum Volume Compared with Treatment Groups*

Volume (ml.)	P.	T.P.	P.T.	T.	Total
0–9	1	3		1	5
10–19	4	9	4	1	18
20–29	4	1	2	3	10
30–39	4	5	4	6	19
40–49	1	2		2	5
50–59			3		3
60–69	3	1	4	6	14
70 or more		1	2	2	5
No. of patients	17	22	19	21	79

TABLE III.—*Initial 24-hour Sputum Appearance Compared with Treatment Groups*

Appearance	P.	T.P.	P.T.	T.	Total
Mucoid	8	12	6	10	36
Trace	7	6	7	8	28
+	1	2	3	2	8
++	1	1	2	1	5
+++		1	1		2
Total	17	22	19	21	79

+ = 25% pus in specimen. ++ = 50% pus in specimen. +++ = 75% pus in specimen.

Initial 24-hour Sputum Volume and Character

These results are recorded in Tables II and III. In 36 (45%) of the 79 patients the initial 24-hour sputum specimens were mucoid, though in only one patient (group P.) were specimens mucoid throughout.

Though group P. is styled placebo these patients were issued with emergency tetracycline, which was used on 90 occasions, giving an average number of emergency treatments per patient of 5·3. The comparable figures were: for group T.P. 3·3, for group P.T. 2·8, and for group T. 2·2. While some patients may have used their emergency treatment unnecessarily we have no evidence that group P. were more careless in this respect. We are therefore comparing a group of patients who received emergency treatment only in group P. with another three groups who received chemoprophylaxis in addition to emergency treatment.

Bearing in mind the number system and the change in drug allocation at the third winter we considered it was valid to accept the patient's assessment of his chest disability. A patient assessment index for the four groups was obtained by dividing the total "patient score" by the number in the group: thus P. = 1·9, T.P. = 2·5, P.T. = 3·4, and T. = 3·2. This index rises in group T.P. (two years' treatment) and further in group P.T. (three years' treatment) but no further in group T. (five years' treatment). Though there is a trend of increasing improvement with duration of treatment these differences are not statistically significant.

Analysis of Number of Exacerbations

The relation of exacerbations to treatment is shown in Table IV. There is a progressive improvement in the average with increasing duration of treatment, but again the differences are not significant.

TABLE IV.—*Number of Exacerbations Compared with Treatment Groups*

No. of Exacerbations in 5 Years	P.	T.P.	P.T.	T.	Total
0	4	6	4	4	18
1	3	5	4	7	19
2	1	2	3	3	9
3	1	1	4	3	9
4	1	1		2	4
5	1	3	1		5
6			2		2
7	2			1	3
8	1			1	2
9		1	1		2
10	1	2			3
11		1			1
17	1				1
21	1				1
No. of patients	17	22	19	21	79
Total exacerbations	87	71	48	45	
Average No.	5·1	3·2	2·5	2·1	

The number of emergency treatments differed only slightly from the number of exacerbations, and the averages were: P. 5·3, T.P. 3·3, P.T. 2·8, and T. 2·2.

The days lost from work owing to exacerbations of bronchitis during the winter months of the trial were recorded first according to the patient's statement, and then compared with the National Health Insurance records. The average number of days lost from work owing to exacerbations of bronchitis were:

Group:	P.	T.P.	P.T.	T.
Patients' statements	55·0	32·5	44·7	47·9
N.H.I. record	55·3	40·4	51·8	42·7

There were very considerable fluctuations in the working-time lost during these exacerbations, and obviously other factors apart from the medical disability determined this result. Our patients were too few in number for any useful conclusions to be drawn from these data.

A further analysis of change of smoking habits in relation to the number of exacerbations showed that neither those who stopped nor those who reduced smoking by 50% significantly influenced the results. An anti-influenza vaccine did not have any significant effect. Thirteen patients obtained lighter work during the trial and eight retired prematurely. These changes are scattered randomly among the treatment groups, except for group P.T. where rather more obtained lighter work.

None of these comparisons showed a *significant* advantage for the groups receiving chemoprophylaxis. If, however, we ignore the previous groupings and analyse the number of exacerbations related to treatment or placebo both during the first two and the latter three years of the trial there is a significant advantage ($P<0.025$) on both occasions. The results are shown in Table V. The effect of chemoprophylaxis was most

TABLE V.—*Analysis of Number or Exacerbations Related to Treatment*

During First Two Winters			During Latter Three Winters		
No. of Exacerbations	Treatment	Placebo	No. of Exacerbations	Treatment	Placebo
0	27	15	0	15	13
1	7	8	1	10	8
2	6	2	2	9	2
3	3	4	3	2	5
4		5	4	2	2
5			5	1	1
6		2	6	1	1
			7–15		7
Total	43	36	Total	40	39

evident on those prone to many exacerbations. Thus all 10 patients who had more than one exacerbation per year on placebo were better when receiving regular tetracycline. These differences were tested further by examining groups T.P. and P.T.—that is, those receiving both placebo and treatment—so that each patient was his own control. The average number of exacerbations was calculated for each patient for the placebo and treatment periods and the differences were compared. The results are shown in Table VI. If treatment had been without

TABLE VI.—*Analysis of Groups T.P. and P.T.*

Response	No. of Patients		
	Group T.P.	Group P.T.	Both Groups
Fewer exacerbations on treatment ..	11	12	23
Fewer exacerbations on placebo ..	2	3	5
No difference	9	4	13
Total	22	19	41

effect then there would be equal numbers in the first two rows of the table. But treatment has produced an 11/2 difference in group T.P. ($P=0.011$), a 12/3 difference in group P.T. ($P=0.018$), and when both groups are combined a 23/5 difference ($P=0.0003$). This analysis discounts treatment order, any carryover effect of previous treatment, and other—for example, climatic factors.

Sputum Studies

Over the five-year period there was a reduction of sputum volume in all groups (P. −8·7 ml., T.P. −4·0 ml., P.T. −14·1 ml., and T. −17·7 ml.). The sputum appearance during the six winter months of the five winters was examined in 73 patients. We have recorded as purulent only specimens containing 25% or more of pus. There was a trend of clearing sputum with increasing duration of treatment, but the differences were not statistically significant:

Group:	P.	T.P.	P.T.	T.
No. of patients	17	19	16	21
No. of specimens ..	479	491	413	580
Purulent (%)	13·6	7·2	9·4	4·5

Streptococcus pneumoniae and *Haemophilus influenzae* were isolated at some time in 72 of the 79 patients (absent in one in group P., three in group T.P., and three in group T.). Coagulase-positive staphylococci resistant to tetracycline appeared in the sputum of four patients in group P., eight in group T.P., eight in group P.T., and four in group T.—that is, a total of 24 patients. In five of the eight in group T.P. but in none of the other groups, these organisms were present in pretreatment cultures. Among these 24 patients these staphylococci may have contributed to clinical relapses in five, but the evidence was doubtful. Thus, coagulase-positive staphylococci occurred no more frequently in those receiving regular winter chemoprophylaxis. Tetracycline-resistant pneumococci appeared in only three patients (one in group T.P., one in group P.T., and one in group T.). Proteus was isolated 114 times in 24 patients. In one patient in group P. this organism was present initially and throughout the trial and was the only pathogen in eight exacerbations.

Drug Acceptance

Though the number of tablets remaining was checked in front of each patient at every visit, this was not regarded as a completely reliable estimate of drug acceptance. We encouraged patients to report any side-effects or difficulties with their medication. A total of 700 urine specimens from 79 patients were sent to the research laboratories of Pfizer Limited and examined for tetracycline by a bioassay method: 575 (82%) were positive. Further analysis showed that only seven patients were not taking their drugs regularly.

Toxicity

Side-effects most commonly reported were diarrhoea in only seven patients—five in group T.P. and two in group T. These seven patients were all helped by oral nystatin. The only patient who developed a rash was on placebo tablets.

Pulmonary Function

Seventy-eight of the 79 patients who completed the trial were examined at the beginning and end of the study, whereas one was examined at the end only. The mean results, with standard deviations, of the initial tests are shown in Table VII. There

TABLE VII.—*Initial Pulmonary Function Studies*

Test		P.	T.P.	P.T.	T.
$F.E.V._1$ (litres)	Mean	1·61	1·85	1·55	1·60
	S.D. ..	0·67	0·88	0·51	0·66
F.E.V. (%)	Mean	49·5	55·5	48·4	48·1
	S.D. ..	18·5	25·2	17·1	21·3
V.C. (%)	Mean	92·7	93·6	89·5	90·0
	S.D. ..	16·0	21·0	16·2	16·9
F.E.V./V.C. (%)	Mean	43·6	48·9	45·1	45·1
	S.D. ..	11·3	16·1	10·1	16·1
T.L.C. (%)	Mean	110·2	108·3	108·1	114·6
	S.D. ..	14·3	20·4	10·7	19·5
R.V./T.L.C. (%)	Mean	48·2	46·9	50·2	50·7
	S.D. ..	10·4	10·6	8·6	10·7
DLco/V.A.	Mean	3·55	3·39	3·14	3·57
	S.D. ..	1·02	1·07	1·14	0·99
Sa_{O_2}	Mean	94·9	94·4	94·1	93·9
	S.D. ..	2·3	2·3	3·3	1·7
$Paco_2$ (mm.Hg)	Mean	42·5	44·2	42·1	43·1
	S.D. ..	3·9	4·8	3·8	5·3

was a moderately wide range of disability, but this was randomly distributed between the treatment and placebo groups. The distribution of the $F.E.V._1$ between the groups is shown in Table VIII.

The change in pulmonary function over the five-year trial period is shown in Table IX. Where this is expressed as a change in percentage of the predicted value, allowance has been made for the regression due to age, which is built into the

prediction formula. Thus the percentage fall in the F.E.V.$_1$ is additional to a regression of 35 ml. per year, which is included in the formula. There was a greater reduction in mean value for V.C., F.E.V.$_1$, and Sao_2 in the placebo compared with the other treatment groups, but because of the variations within groups this was not statistically significant.

TABLE VIII.—*Initial F.E.V.$_1$ Versus Treatment Groups*

F.E.V.$_1$ (litres)	P.	T.P.	P.T.	T.	Total
<1	4	5	2	4	15
1·0–1·49	6	3	9	5	23
1·5–1·99	3	6	4	4	17
2·0–2·49	1	2	3	5	11
2·5–2·99	2	3	1	1	7
3·0–3·99	1	3		1	5
N.A.				1	1
Total No. ..	17	22	19	21	79
Mean F.E.V.$_1$	1·61	1·85	1·55	1·60	1·66

N.A. = Not available.

TABLE IX.—*Change in Pulmonary Function after Five Years*

Measurement	P.	T.P.	P.T.	T.
F.E.V.$_1$ (%)	−16·5	−9·7	−1·7	−7·2
V.C. (%)	−9·4	−4·8	−5·5	−5·9
F.E.V./V.C. (%) ..	−2·5	−2·4	0·8	−0·6
T.L.C. (%)	−3·7	−0·8	−4·8	−2·1
R.V./T.L.C. (%) ..	3·5	3·4	4·0	4·2
DLco/V.A.	−0·14	−0·09	−0·12	−0·50
Sao_2	−4·13	−3·57	−0·79	−2·83
$Paco_2$	−1·50	−3·00	−3·00	−1·78

In the other measurements the changes in mean value did not appear to favour the treated groups more than the placebo group and there was no statistical difference in results. The percentage fall in T.L.C. and the rise in R.V./T.L.C. was due to greater reduction in V.C. than in R.V. The deterioration in DL_{CO}/V.A. and Sao_2 is in the expected direction, but it is difficult to explain the fall in mean $Paco_2$ in all groups. There was no obvious systematic bias in the measurement, which was carried out with the rebreathing method on both occasions, but one possibility is that the first study was in the autumn of the year whereas the second was in the spring.

Discussion

Bacterial infection in chronic bronchitis is an intermittent complication, is variable and unpredictable, and consequently the results of chemoprophylaxis are difficult to assess. Our results show that, as one would expect, the most susceptible patients in terms of the frequency of exacerbations are those who benefit most from chemoprophylaxis. The level which appears to justify chemoprophylaxis is more than one exacerbation each winter. At levels below this we agree with Malone *et al.* (1968) that early treatment for clearly defined exacerbations with purulent sputum will achieve satisfactory results.

Our repeated observations on 24-hour sputum samples showed a progressive clearing of pus with increasing duration of chemoprophylaxis and a slight reduction in sputum volume, but the results were not statistically significant and the assessment was complicated by continuing intermittent therapy.

Tetracycline toxicity has been negligible. The isolation of tetracycline-resistant coagulase-positive staphylococci among patients on tetracycline prophylaxis has been discussed by Wade *et al.* (1967), who found no evidence of frequent or dangerous proliferation of drug-resistant organisms in the sputum. None of our patients developed a progressive staphylococcal infection.

In the Medical Research Council (1966) trial the rate of decline in F.E.V.$_1$ over a five-year period was unaffected by chemoprophylaxis, but the patients were suffering from early chronic bronchitis and the average F.E.V.$_1$ was just over 2 litres. Their annual decline in F.E.V.$_1$ was 4%, which is similar to that reported by Jones *et al.* (1967) in a more disabled group of patients who were not receiving chemoprophylaxis. In our study the disability of the patients was intermediate and the average annual decline in absolute F.E.V.$_1$ was 5·5% in the placebo group compared with 2·6%, 3·8%, and 3·6% in the other treatment groups. This suggests an advantage for those receiving chemoprophylaxis for two, three, or five years, but the results do not achieve statistical significance. We suspect from our other evidence that probably there is slower deterioration in lung function when chemoprophylaxis is given, but we believe that more frequent serial measurements over a long period of study will be necessary to establish this in patients with moderate disability.

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REFERENCES

British Tuberculosis Association (1960). *British Medical Journal*, 1, 297.
British Tuberculosis Association (1961). *British Medical Journal*, 2, 979.
Calder, M. A., Lutz, W., and Schonell, M. E. (1968). *British Journal of Diseases of the Chest*, 62, 93.
Campbell, E. J. M., and Howell, J. B. L. (1960). *British Medical Journal*, 1, 458.
Johnston, R. N. (1962). In *Symposium Chronic Respiratory Disorders*, p. 76. Edinburgh, Royal College of Physicians.
Jones, N. L., Burrows, B., and Fletcher, C. M. (1967). *Thorax*, 22, 327.
Malone, D. N., Gould, J. C., and Grant, I. W. B. (1968). *Lancet*, 2, 594.
May, J. R. (1965). *Lancet*, 1, 959.
Medical Research Council (1966). *British Medical Journal*, 1, 1317.
Needham, C. D., Rogan, M. C., and McDonald, I. (1954). *Thorax*, 9, 313.
Ogilvie, C. M., Forster, R. E., Blakemore, W. S., and Morton, J. W. (1957). *Journal of Clinical Investigation*, 36, 1.
Wade, O. L., Elmes, P. C., and Bartley, E. (1967). *Thorax*, 22, 265.