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CHEMOTHERAPY OF BRONCHITIS

INFLUENCE OF PENICILLIN AND TETRACYCLINE ADMINISTERED DAILY, OR INTERMITTENTLY FOR EXACERBATIONS

A REPORT TO THE RESEARCH COMMITTEE OF THE BRITISH TUBERCULOSIS ASSOCIATION BY ITS BRONCHITIS SUBCOMMITTEE*

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An investigation by this Subcommittee carried out from January to April, 1959, showed that the number of working days lost as a result of bronchitis was halved by the daily administration of antibiotic capsules compared with a similar group of patients taking inert capsules (British Tuberculosis Association, 1960). The antibiotics employed were tetracycline, 250 mg. twice daily, and penicillin-V potassium, 312 mg. twice daily. The results are summarized as follows:

	Mean Time Off Work per Day at Risk	Average Time Off Work per Patient
Penicillin group	0.06 day	6.8 days
Tetracycline group	0.06 "	7.5 "
Control group	0.12 "	14.2 "

The variable nature of the response was such that the observed difference between the two antibiotic groups was compatible with either drug having an advantage of some four working days over the other. The number of bronchitic exacerbations appeared to be unaffected by treatment. Bearing in mind the comparatively small dose of tetracycline, it was thought that the main action of both antibiotics had been to suppress infection due to pneumococci, neither regimen having had much effect on *Haemophilus influenzae*. In an attempt to clarify this point it was thought that a subsequent investigation should include a study of the bacteriology of the patients' sputa.

The purpose of the present investigation was, firstly, to ascertain whether these findings held good for another winter and to compare the value of antibiotics

administered prophylactically each day throughout the winter with an alternative prophylactic regimen in which antibiotics were to be given in higher doses for short periods at the onset of symptoms usually leading to a bronchitic exacerbation. Secondly, it was proposed to make a more detailed bacteriological study based on sputum specimens examined under research conditions before, during, and after the end of such treatment.

Methods

In view of the improvement in health which resulted from antibiotic medication in the previous trial, the inclusion in the second trial of a group of patients receiving nothing but an inert substance was considered inadmissible on ethical grounds. The regimens adopted were as follows, being maintained throughout the period of the trial.

Regimen	Daily Capsules. Dose: One Capsule before Breakfast and on Retiring	Intermittent Capsules. Dose: 2 Capsules t.d.s. for 3 Days, then 1 t.d.s. for 3 Days
A	Starch	Penicillin
B	Tetracycline	Starch
C	Penicillin	Starch
D	Starch	Tetracycline

Patients having daily antibiotic capsules were given inert capsules intermittently, and vice versa.

A list of 12 treatments—three of each regimen—was drawn up at random, for each clinic separately. Chest physicians were asked to recruit 12 patients and to forward their names. As these were received they were allocated in turn to the list of treatments. Some clinics recruited fewer than 12 patients, so that there was some imbalance finally in the total number of patients on each regimen.

Daily capsules were pink and indistinguishable from each other. They were to be taken every day throughout the trial, even when "intermittent" capsules were also being taken. The doses of the daily antibiotics were as in the previous trial—namely, penicillin-V potassium, 312 mg. b.d., or tetracycline, 250 mg. b.d.

"Intermittent" capsules (brown) were also indistinguishable from each other. They were presented in bottles each containing sufficient capsules (27) for six days' medication. Each patient was to start taking these at the first appearance of symptoms, which in his particular case were usually followed by an exacerbation of bronchitis. The dose of antibiotics to be taken intermittently was either (1) penicillin-V potassium 624 mg. (equivalent to 1 million units by injection) thrice daily for three days, followed by 312 mg. (equivalent to half a million units by injection) thrice daily for a further three days, or (2) tetracycline 500 mg. thrice daily for three days, followed by 250 mg. thrice daily for a further three days.

Apart from the addition of the intermittent medications, the trial was conducted along lines very similar to that of January–April, 1959. The main difference was that in the second trial the bottles of capsules were distinguished by a code letter whereas in the first trial code letters were unnecessary and were not used.

Central Organization

Penicillin was provided by Messrs. Eli Lilly and tetracycline by Messrs. Lederle. Both the antibiotics and the inert preparation (starch) were encapsulated and bottled by Messrs. Eli Lilly, who dispatched to each

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clinic a box containing one large jar of daily capsules for each patient, labelled with the appropriate letter, together with four small bottles of "intermittent" capsules for each patient, similarly labelled. The identity of the regimens A, B, C, and D were not known to any of those partaking in the trial or to any of the members of the Bronchitis Subcommittee until after the results had been fully analysed.

Graduated sputum pots, specially printed patients' diaries, and instruction sheets were also sent to each clinic, together with a letter to the local bacteriologist giving details of the investigations required in relation to sputum cultures.

Chest Clinic Organization and Clinical Material

The selection of patients for the trial was based on criteria almost identical with those of the first trial, as follows: Patients should be men, preferably wage-earning, aged 30-65, in employment, and with a history of winter cough and sputum for the past three years. During this time they should have been off work at least twice because of bronchitis with purulent sputum, and they must be reasonably intelligent and willing to co-operate even if they thought the capsules were unhelpful.

Patients were not suitable for the trial if their main symptom was wheezing, if they had been in heart failure, or if radiographic changes other than those of bronchitis and emphysema were present. Also excluded from the trial were those known to be sensitive to penicillin and those likely to be off work because of some other disability.

At a preliminary interview the purpose of the investigation was explained to the patients, who were instructed in its routine, the keeping of the diaries, and the importance of consulting their general practitioners when necessary. They were given an instruction sheet, a bottle of daily capsules, and two bottles of capsules for intermittent use. Arrangements were made for the latter to be replaced as soon as they were used up.

As in the previous trial, the following definition of "bronchitic exacerbation" was adopted: "An increase in cough with the appearance of pus in the sputum or an increase in the amount of pus over the amount usually present."

Chest physicians were asked to interview the patients once a month and to make entries on a form relating to the number of bronchitic exacerbations, pneumonic episodes, or "other respiratory" disorders developing, and the number of days on which patients were consequently unfit for work. Days spent in hospital were indicated separately. They were also asked to record symptoms attributed to the capsules, and to note any omissions of treatment together with any chemotherapy prescribed by the general practitioners. The co-operation of the latter was obtained beforehand, and practitioners remained in charge of the patients, being free to prescribe any treatment other than prophylactic antibiotics.

In his monthly assessments the chest physician could call on the following sources of evidence:

1. The ordinary methods of history-taking and examination.
2. Examination of the sputum produced that morning, which the patient was asked to bring with him.
3. The patient's diary, in which was recorded the daily colour and approximate volume of the sputum and a note

on his general condition (better, the same, worse, or much worse than usual); the 24-hour volume and colour of sputum on Sundays and all days when off sick; the dates of stopping and resuming work; and, finally, any antibiotic treatment received from the general practitioner, who was asked to make such entries whenever applicable.

4. Health visitors' reports, based on two home visits a month, the purpose of which was to report on the patient's health, sputum state, work status, toxic symptoms, and whether or not capsules were being taken, together with any relevant comment.

At the end of the trial, weekly tobacco consumption was recorded; all chest physicians' reports, diaries, and health visitors' reports were then forwarded for analysis.

Laboratory Organization

The collection of sputum specimens from patients and their delivery to the laboratory was organized by the chest physicians at each clinic. Three sputum examinations were carried out during the trial: (a) during the week preceding its commencement, (b) during a week in the middle of the trial, and (c) during the second week after the end of the trial. On each occasion three specimens of sputum from each patient were cultured, in order to reduce the sampling errors inherent in the examination of single specimens (May, 1953). The three samples were all expectorated by the patient on the same day.

The arrangements for bacteriological examination of the sputa were as follows.

1. *Clinics in the London Area.*—The sputa of patients attending 12 clinics in or near London were delivered by hand on the day of expectoration to the bacteriology laboratory of the Institute of Diseases of the Chest, where all cultures were carried out.

2. *Provincial Clinics.*—Sputum examinations were undertaken on the patients attending 24 clinics outside London. The examinations were carried out in the bacteriology laboratory normally serving each clinic. As before, the cultures were made on the day of expectoration of the sputum.

This procedure was not ideal, since there could be no absolute standardization of culture techniques. However, all bacteriologists were asked to adopt, if possible, the method used at the Institute of Diseases of the Chest (see below), and in fact 20 of the 24 did so. The results suggest that errors introduced from this source were not appreciable.

Sputum Culture Technique.—The method used for all specimens from the London clinics and for those from the majority of provincial ones was the pancreatin liquefaction technique described by Rawlins (1953). Briefly this consists in mixing the sputum with an equal volume of 1% pancreatin solution buffered to pH 7.6 and incubating in a water-bath at 37° C. until liquid. The standard primary culture medium was blood-agar, additional special media being used as appropriate for the isolation and identification of individual bacterial species. Attention was paid especially to the isolation of *H. influenzae* and pneumococci.

Sensitivity of Bacteria to Antibiotics.—In order to maintain a standard technique for sensitivity-testing, all tests were carried out in one laboratory (Institute of Diseases of the Chest), to which cultures of strains isolated in provincial laboratories were sent. Strains of *H. influenzae* only were investigated. The pneumococcus was accepted as being invariably sensitive to the drugs used in the trial (penicillin and tetracycline).

Sensitivity was estimated by titration on a solid medium (agar containing X and V factors) in Petri dishes. The organisms were "spotted" on to a series of plates containing 0.3, 0.6, 1.25, 2.5, and 5 units of penicillin per ml. respectively, and on to a second series containing 0.3, 0.6, 1.25, 2.5, and 5 μ g. of tetracycline per ml. respectively. A control plate containing no antibiotic was included in each series, and a standard test strain of *H. influenzae* was inoculated with each batch of organisms tested. By this method 16 strains could be tested simultaneously on each set of plates. The "sensitivity" of each strain was recorded as the lowest concentration of antibiotic causing complete inhibition of growth.

Results

The trial started on November 16, 1959, and ended on April 16, 1960—a total of 153 days. The reports received were on the whole clear-cut, but where information was equivocal or incomplete it was necessary to consult the diaries or health visitors' reports to supplement factual information such as the date of a patient's return to work. This procedure was not often invoked, but it was always carried out according to a set of pre-established rules. Particular care was taken to establish whether a patient was exposed to risk according to the terms of the trial. Thus, an exacerbation of bronchitis or a pneumonic episode could be regarded as relevant only if the patient was at work and taking his daily capsules at the time of onset. He could not "qualify" for a second attack until he had returned to work after the first. Days on which a patient omitted his daily capsules were counted as "out of trial," since he was not fulfilling the conditions of the experiment. This ruling led to an anomaly in the case of patients admitted to hospital, when daily capsules were often discontinued, such days also being "out of trial." Fortunately the numbers involved were small, and even if those days were included in the totals lost by each group the results are not affected. These cases are fully discussed later.

Physicians in 51 chest clinics in urban and rural areas throughout England, Wales, and Scotland took part in the trial, and the total number of patients starting the trial was 551. Of these, 10 refused to co-operate and never reported for subsequent interview; in six cases the data were inadequate or conflicting, and two cases had to be rejected because, contrary to the agreed conditions of the trial, their general practitioners treated them for prolonged periods with a daily antibiotic prescribed by themselves. A total of 18 patients have therefore been excluded from further consideration. Table I shows their distribution in the four regimens.

The number of patients available for study is therefore 551 less 18, or 533. It was a condition of the trial

that all patients should be at work; in fact, 14 were unemployed throughout, and although their experience can be taken into account when considering side-effects of treatment they clearly cannot be included in the main analysis, which is concerned with days of unfitness for work. The total number of patients available for statistical study is therefore 533 less 14, or 519, which represents 94% of those entering the trial. Table I summarizes the position.

Statistical Analysis of Results

Some lack of balance in the distribution of patients was inevitable, since not all clinics could fill their quota of suitable patients. Experience with the previous trial had shown that this was not a serious fault, as the errors introduced by an uneven distribution of the regimens among the clinics are negligible compared with the uncontrolled variations between patients. All estimates of treatment effects are based on the days off work per 100 days exposed in the trial averaged over all clinics. The corresponding standard errors include the difference between clinics as a source of variation.

Information on four variables used to check the randomization is given in Table II. It will be seen that the average ages of patients, their smoking habits, and the proportions working indoors are very similar. The

TABLE II.—Average Values of Some Characteristics of Patients in the Four Regimens

Characteristic	Inter. Pen.	Daily Tet.	Daily Pen.	Inter. Tet.
Average age (years) ..	52.6	53.9	53.0	53.4
.. days withdrawn from trial ..	10	12	11	11
.. tobacco smoked (cigs./wk.) ..	59	59	63	61
Proportion of indoor workers ..	61%	69%	60%	63%

average days withdrawn from the trial for reasons unconnected with respiratory disease are also similar. None of the differences between the treatment groups are statistically significant, and they are in fact about what would be expected from the known variations between patients. Information was also asked for on body weight, but this was very incompletely reported and has not been used for comparative purposes.

The main results of the trial are shown in Table III, which gives the average number of days off work from bronchitis per 100 days exposed for the four regimens.

TABLE III.—Mean Days Off Work Per 100 Days Exposed, From Bronchitic Exacerbations, With Standard Errors of Means and Numbers of Patients on Which They Are Based

Regimen	Mean Days Off Work per 100 Exposed to Risk	S.E. of Mean	No. of Patients
Intermittent penicillin ..	8.311	1.373	129
Daily tetracycline ..	4.039	0.911	125
.. penicillin ..	8.127	1.652	135
Intermittent tetracycline ..	9.339	1.641	130

It can be seen that the group receiving daily tetracycline had about half as many days off as those on the other three regimens. With the use of the test for the deviation of the smallest of four averages in *Biometrika Tables for Statisticians* (1958, Table 26), it was found that the effect of daily tetracycline is significant statistically ($P \leq 0.01$). The differences between the other regimens are not significant.

Information was also available on the days off work due to pneumonia and other respiratory diseases. The number of patients having an attack of pneumonia was

TABLE I.—Clinical Material

	Totals	Regimen			
		Inter. Pen.	Daily Tet.	Daily Pen.	Inter. Tet.
No. entering trial, Nov. 16, 1959 ..	551	133	135	140	143
Not available for study:					
(1) Uncooperative: no data ..	10	2	2	2	4
(2) Insufficient or conflicting data ..	6	1	3	0	2
(3) Prophylactic chemotherapy from G.P. ..	2	0	2	0	0
Remainder available for study ..	533	130	128	138	137
Patients unemployed throughout ..	14	1	3	3	7
Available for statistical analysis ..	519	129	125	135	130

too small to be worth detailed consideration, but the average days lost from other respiratory disease in the four groups are given in Table IV. The very considerable excess of days off from other respiratory disease in the group receiving penicillin intermittently is highly

TABLE IV.—Mean Days Off Work Per 100 Days Exposed, From Respiratory Infections Other than Bronchitis or Pneumonia

Regimen	Mean Days Off Work per 100 Exposed to Risk	S.E. of Mean	No. of Patients
Intermittent penicillin ..	1.756	0.640	129
Daily tetracycline ..	0.710	0.270	125
.. penicillin ..	0.523	0.201	135
Intermittent tetracycline ..	0.570	0.214	130

significant statistically, and it seems probable that the other three regimens were able to produce a reduction, since it is unlikely that the penicillin was actually harmful.

In the first trial it was found that neither daily tetracycline nor daily penicillin reduced the actual number of bronchitic attacks. The differences in the average number of attacks on each regimen are not significant, though the two groups on daily medication do have rather smaller averages than the others.

It is of interest to consider the frequency with which intermittent medication was resorted to by patients in the different groups. A true prophylactic effect of intermittent medication would reduce the actual number of attacks, since the patients were supposed to take their capsules when they felt an attack coming on. However, the number of such courses taken was almost equal to the number of attacks, the proportions followed by an attack in the four groups being: intermittent penicillin, 87%; daily tetracycline, 90%; daily penicillin, 83%; and intermittent tetracycline, 82%.

Clearly there was little difference between the inert tablets and the antibiotics. A true control group having no form of medication would be required to settle the matter, but it appears from these findings that the effect of taking capsules was on the course of the attack once it had developed.

Information on the number of attacks for which the patient sought treatment from his general practitioner was recorded. The average number of these per patient in the four groups was: intermittent penicillin, 0.25; daily tetracycline, 0.10; daily penicillin, 0.10; and intermittent tetracycline, 0.13.

The relatively large number of these treatments among patients taking penicillin intermittently is significant statistically and might be of importance when it is remembered that this group also had an excess of other respiratory disease. These differences could be due either to the general inadequacy of penicillin when taken intermittently or, possibly, to the concentration of some particular type of patient in this group as a chance consequence of the randomization procedure.

Symptoms Attributed to the Capsules

Most of the side-effects attributed to the capsules occurred for a short period only at the beginning of the trial. In some instances symptoms were reported occasionally throughout the trial, and in only a small number of cases were they said to be persistent. Only 10 patients refused to take their capsules because of side-effects, which were attributed to starch in six cases, penicillin in three cases, and tetracycline in one case.

The proportions of patients affected by the individual antibiotic capsules were as follows: intermittent penicillin, 12%; daily tetracycline, 27%; daily penicillin, 27%; and intermittent tetracycline, 17%. They are effectively equal when sampling variation is taken into account. Mild gastro-intestinal symptoms were in the majority. A few patients developed skin rashes and there were a few complaints of headache and attacks of asthma. Further details are recorded in Table V.

TABLE V.—Patients Having Symptoms Attributable to Capsules

Capsules to which Symptoms Attributable	No. of Patients in Whom Symptoms were Reported			No. of Patients Refusing to take Capsules
	Total	Occasional Symptoms	Persistent	
Daily penicillin ..	27	19	8	2
.. tetracycline ..	27	19	8	1
.. starch* ..	23	17	6	3
.. starch† ..	28	21	7	3
Intermittent penicillin ..	12	7	5	1
.. tetracycline ..	17	14	3	0
Intermittent starch† ..	9	9	0	0
.. starch§ ..	14	9	5	0

* With penicillin intermittently. † With tetracycline intermittently. ‡ With penicillin daily. § With tetracycline daily.

Patients Admitted to Hospital

Only 15 patients were reported to have been admitted to hospital, several of these having had cardiac complications of respiratory disease. Only six of the patients are known to have continued taking daily capsules while in hospital, and three were admitted to hospital during periods when they were technically "out of trial" because of a temporary failure to fulfil the criteria of exposure to risk. In fact, two patients who died were in this latter group. For these reasons, days off work in hospital were not included in the analysis, the validity of the results being unaffected since inclusion of these patients would make virtually no difference to the average days unfit for work per 100 days' exposure, each regimen being affected about equally.

Table VI shows the numbers of patients in each regimen who were admitted to hospital together with the duration of stay. No clear advantage can be attributed to any single regimen.

TABLE VI.—Patients Admitted to Hospital

Regimen	No. of Cases	Average Days in Hospital	Deaths
Intermittent penicillin ..	5	29	1 after 46 days
Daily tetracycline ..	2	17	
.. penicillin ..	2	21	
Intermittent tetracycline ..	6	28	1 .. 6 ..

Deaths

There were six deaths among the 533 patients available for study. Two were in the intermittent tetracycline group, three were in the daily penicillin group, and one was receiving daily tetracycline. The following are brief case histories:

Regimen—Intermittent Tetracycline

1. H. W., No. 15/12, aged 51. This patient was off work continuously from two weeks preceding the beginning of the trial and is included in the "unemployed" group in Table I. He was admitted to hospital suffering from incapacitating emphysema on January 14, 1960, his sputum having dried up after the trial had started. He died in hospital on January 20 of respiratory insufficiency and his days off work were not included in the main analysis.

2. C. B., No. 43/1, aged 57. This patient died at home on December 23, 1959, before his first assessment. So far as we know, he fulfilled the conditions of the trial up till death, which was certified at necropsy as being caused by "cor pulmonale due to an acute flare of chronic bronchitis and emphysema." His days off work are included in the statistical analysis.

Regimen—Intermittent Penicillin

1. L. S., No. 35/9, aged 60. This patient died on the fifth day of the trial. He started daily capsules on November 16, 1959, and intermittent ones on November 17. He died on November 20 from "bronchitis," and his four days of exposure have been included in the analysis.

2. A. B., No. 06/1, aged 61. This patient died of cor pulmonale due to chronic bronchitis and emphysema on December 16, 1959, and his 31 days' exposure have been included in the analysis.

3. B. P., No. 32/8, aged 55. This patient was exposed to risk for 33 days, which have been included in the analysis. He stopped work because of an attack of "other respiratory" disease, and, while thus temporarily not exposed to risk, he developed bronchitis, for which he was admitted to hospital on February 24, 1960, where he died on April 11.

Regimen—Daily Tetracycline

G. B., No. 5/1, aged 47. This patient was exposed for 45 days till sudden death on December 15, 1959, certified by the general practitioner as due to cerebral haemorrhage.

The number of deaths is so small and the variation between patients so large that no useful comparisons can be made between the regimens on a mortality basis.

Bacteriological Results

The total isolation rates of *H. influenzae* differed slightly in London and the provinces. Combining all regimens and all phases of the trial, *H. influenzae* was isolated in 141 (41%) of 343 patient-examinations in London, compared with 190 (26%) of 730 patient-examinations in the provinces. This difference may represent an actual difference in the prevalence of the organism in London and the provinces, but a more likely explanation is that it results from the differences in technique used in various laboratories. For example, no *H. influenzae* was isolated from any patient at any stage of the trial in one laboratory, in which cultures were made by dipping a throat swab into the sputum and inoculating on a blood-agar plate. Since the clinic served by this laboratory was near London, close to the clinics where *H. influenzae* was isolated frequently, it seems unlikely that these patients were in fact free from this organism. Although there were a few other examples of laboratories with low isolation rates for *H. influenzae*, in the majority they were similar to those in London. The geographical distribution of the laboratories with low rates was haphazard and did not suggest that *H. influenzae* was in fact less prevalent in certain parts of the country. It seems reasonable to conclude, therefore, that the difference between the isolation rates for London and the provinces was the result of differences in the technique used for sputum culture. Therefore the total isolation rates of *H. influenzae* from all clinics combined are probably rather lower than the true prevalence of the organism.

In contrast, the isolation rates for pneumococci were very similar in the two groups of clinics. In London, pneumococci were isolated from 92 (27%) of 343 patient-examinations (all phases of the trial combined), while in the provinces they were found in 213 (29%) of 730 patient-examinations. In general, the pneumo-

coccus is easier to isolate from sputum than *H. influenzae* and differences in culture technique are unlikely to be important; hence the similarity of the results in the two groups of clinics.

Tables VII and VIII show the isolation rates for *H. influenzae* and pneumococci respectively within the four regimens. At the beginning and end of the trial

TABLE VII.—Isolation Rates of *H. influenzae* From Sputum in Different Regimens. (All Clinics Combined)

	Regimen			
	Inter. Pen.	Daily Tet.	Daily Pen.	Inter. Tet.
Beginning of trial:				
No. of patients	101	98	103	103
<i>H. influenzae</i> isolated	26 (26%)	28 (29%)	31 (30%)	33 (32%)
Middle of trial:				
No. of patients	92	83	91	88
<i>H. influenzae</i> isolated	37 (40%)	13 (16%)	39 (43%)	25 (28%)
End of trial:				
No. of patients	83	75	81	79
<i>H. influenzae</i> isolated	25 (30%)	20 (27%)	28 (35%)	25 (32%)

TABLE VIII.—Isolation Rate of *Pneumococci* From Sputum in Different Regimens. (All Clinics Combined)

	Regimen			
	Inter. Pen.	Daily Tet.	Daily Pen.	Inter. Tet.
Beginning of trial:				
No. of patients	101	98	103	103
Pneumococci isolated	41 (41%)	41 (42%)	38 (37%)	46 (45%)
Middle of trial:				
No. of patients	92	83	91	88
Pneumococci isolated	20 (22%)	10 (12%)	14 (15%)	27 (31%)
End of trial:				
No. of patients	83	75	81	79
Pneumococci isolated	23 (28%)	11 (15%)	11 (14%)	23 (29%)

the isolation rate of *H. influenzae* was substantially the same among patients in all four groups, but there were some divergences in the middle of the trial. In the intermittent penicillin group and the daily penicillin group the isolation rate rose by nearly 50%; in the daily tetracycline group it fell by nearly 50%; while in the intermittent tetracycline group it remained unchanged. These differences are in fact not statistically significant at the 0.05 level, but the trends are clear. The most likely explanation is that there was a rise in the carrier rate of *H. influenzae* in the middle of the trial (February) and that this was unaffected by either of the penicillin regimens. Daily tetracycline, however, caused a reduction in the carrier rate, while intermittent tetracycline was able to prevent only the seasonal rise. At the end of the trial the isolation rates were the same as those at the beginning. This was not unexpected, since the cultures were made one to two weeks after the end of chemotherapy, by which time *H. influenzae* would have been expected to reappear in those patients in whom it had been temporarily suppressed.

The behaviour of pneumococci (Table VIII) contrasted with that of *H. influenzae*. The isolation rates were substantially the same in all regimens at the beginning of the trial, but all were reduced in the middle. This reduction was very marked in the two groups receiving daily antibiotics, being slightly greater in the patients having daily tetracycline. The carrier rate was reduced by about 50% in the group receiving intermittent penicillin, while in the intermittent tetracycline group it fell by about 33%. At the end of the trial isolation rates did not return to the pre-trial figures but remained approximately the same as those in the middle. This is in accordance with the known tendency of chemotherapy to eradicate pneumococci completely. These

organisms seldom reappear as quickly as those of *H. influenzae*.

No change in the sensitivity pattern as regards penicillin was observed in any regimen, but in the daily tetracycline group there was a slight trend towards increased tetracycline resistance at the end of the trial. This trend, however, was very small and of no significance statistically.

Full details of the bacteriological findings in this trial together with certain other aspects not given in the present report will be published elsewhere.

Discussion

The main finding of the present trial is the existence of a clearly defined superiority of the daily tetracycline regimen over the other three regimens. This is in contrast to the result of the previous experiment, in which daily penicillin and daily tetracycline appeared equally effective in halving the days lost from work compared with the control group.

There are two obvious possible explanations of this discrepancy. Either the large sampling errors of the estimated effects of the regimens are responsible or there was a difference in the aetiology of bronchitic exacerbations in the two years of the trials. The corresponding results of the two experiments in terms of mean days off per 100 exposed were:

	Tetracycline	Penicillin	Difference (Tet. minus Pen.)
First trial	8.38	6.57	+1.81 $\pm$ 2.34
Second trial	4.04	8.13	-4.09 $\pm$ 2.04

The difference between the two trials in the relative effects of daily tetracycline and penicillin does not quite reach statistical significance, and it would be legitimate on this evidence alone to regard the superiority of the daily tetracycline regimen as unproved. However, the difference is large and there is good reason to believe that tetracycline, by virtue of its ability to suppress both *H. influenzae* and pneumococci, might be superior to penicillin. It is probably most reasonable to conclude that the relative value of the two antibiotics differs from year to year according to the prevalence of each organism. It is difficult to see how the true position can be made clear without repeating the trial on about the same scale over a period of several years. Experience with other bacteria shows that the prevalence of an organism may vary from one year to another, and in the present case this could be of particular importance since it is probable that the haemophilus is susceptible virtually only to tetracycline. In addition to this it is known that the incidence of bronchitic exacerbations is considerably affected by weather conditions, which may interact in a complex way with the bacterial invaders: the weather during the first trial was much more severe than that during the second.

In the present trial, ethical considerations precluded the inclusion of a group of patients having both daily and intermittent inert capsules, and for this reason the regimens adopted can be assessed only in relation to each other. It is of interest, however, that in the trial of January to March, 1959, the control group lost an average of 12 days per 100 exposed, a much higher figure than any of the groups in the present experiment.

Clinicians experienced in the use of self-administered broad-spectrum antibiotics by chronic bronchitics at the onset of their attacks may be surprised at the comparatively poor results in this trial of antibiotics

taken in this fashion. Scrutiny of the reports on individual patients showed that in fact they had not always followed the instructions concerning intermittent medication. Sometimes they had allowed attacks to become well established before taking their capsules, and in some cases had failed to take them at all. The circumstances of a centrally co-ordinated "blind" clinical trial differ considerably from those of ordinary medical practice, and in this particular instance it would not be justifiable to conclude that self-administered antibiotics taken at the start of symptoms leading to bronchitic exacerbations will in all circumstances give unsatisfactory results compared with daily administration.

Apart from the relative expense of the two antibiotics the experience of both trials suggests that daily tetracycline is the treatment of choice, since it has not been significantly worse than penicillin and it may be better. However, in view of the high cost of tetracycline further investigation is desirable to determine those conditions under which penicillin may be as good as tetracycline, so that a more economical form of prophylaxis can be worked out.

Summary

A second controlled investigation was carried out during the winter of 1959-60 in an attempt to establish the value of penicillin and tetracycline when administered to chronic bronchitics in widely scattered areas of England, Wales, and Scotland. Patients were allocated at random to one of the four regimens: (1) Tetracycline 250 mg. twice daily throughout the trial. (2) Penicillin-V potassium 312 mg. twice daily throughout the trial. (3) Tetracycline 500 mg. thrice daily for three days at the onset of symptoms followed by 250 mg. thrice daily for three days. (4) Penicillin-V potassium 624 mg. thrice daily for three days at the onset of symptoms, followed by 312 mg. thrice daily for three days.

Daily treatment with tetracycline led to a significant decrease in working days lost from bronchitis compared with the other three regimens. Probable explanations for these findings are discussed, with particular reference to the results of the previous winter's investigation, in which daily tetracycline and daily penicillin had been found equally effective.

Side-effects of the antibiotics presented no special problems.

The bacteriological aspects of the investigation showed that the prevalence of pneumococci was reduced by about 75% when either antibiotic was given daily and to a lesser degree when they were given intermittently. The carrier rate of *H. influenzae*, however, was reduced only in patients receiving daily tetracycline.

We are indebted to Mr. H. R. Simpson, of the statistics department, Rothamsted Experimental Station, for his help in the analysis of this trial on the electronic computer there, and to Miss Molly Fretton for statistical assistance. We are grateful to the North-East Metropolitan Regional Hospital Board for facilitating the participation of Dr. R. S. Francis, together with a grant for expenses; to Derrick May, Brian Gibbins, and Doreen Harmsworth for technical assistance; to Barbara Bavester and Jean Goodchild, of Edmonton Chest Clinic, for secretarial assistance; and to Mrs. Lawrie Stradling, Edna Lee, and Mrs. F. J. Fraser, of North Middlesex Hospital, and Sandra Johnson, of the Institute of Diseases of the Chest, also for secretarial assistance.

We wish also to record our appreciation to Messrs. Eli Lilly for supplies of penicillin-V potassium ("V Cil K"), and to Messrs. Lederle for supplies of tetracycline ("achromycin"), and to both firms for a grant towards the expenses of the trial. To Messrs. Eli Lilly we express our thanks for their invaluable assistance in the preparation, bottling, and distribution of the capsules in code numbers to the participating chest clinics. It is a particular pleasure to thank all the chest physicians, their staffs and health visitors, the bacteriologists, and general practitioners for their tireless co-operation.

The names of the participating chest physicians are given below, together with the clinics and hospitals at which the investigation was carried out.

Ashford: Dr. P. Baldry, Dr. D. B. Rook. Barrow: Dr. J. R. Edge, Dr. J. C. P. Weber. Birmingham: Yardley Green Hospital, Dr. H. J. Ross. Bournemouth: Dr. W. H. Tattershall, Dr. A. T. Hendry. Bristol: Tower Hill, Dr. A. T. M. Roberts, Burton-on-Trent: Outwoods Hospital, Dr. M. B. Paul. Camberwell: Dr. K. Marsh. Camborne: Dr. B. A. Gwynne Jenkins, Dr. E. W. Hughes, Dr. R. L. Ray. Cambridge: Dr. M. J. Greenberg, Dr. R. Bruce. Cardiff: Dr. S. H. Graham, Dr. H. A. Evans. Croydon: Dr. R. H. J. Fanthorpe, Dr. J. F. Heffernan. Doncaster: Dr. F. N. C. Holden. Dudley: Dr. M. Sheldon. Dundee: Dr. R. N. Johnston, Dr. R. T. Ritchie. Ealing: Dr. H. Climie. Edmonton: Dr. R. S. Francis. Epping: Dr. V. U. Lutwyche. Epsom: Dr. S. A. C. Hunter. Farnworth: Dr. J. L. Armour, Dr. F. R. Glover. Finchley: Dr. B. Butterworth. Glasgow: Belvidere Hospital, Dr. R. S. Kennedy; Knightswood Hospital, Dr. G. Johnston; Southern General Hospital, Dr. R. J. Cuthbert. Hammersmith: Dr. Peter Stradling, Dr. D. G. Massey. Ipswich: Dr. Charles Stewart, Dr. P. Embleton, Dr. D. van Zwanenberg. Islington: Dr. J. Wallace Craig. Kingston, Surrey: Dr. S. R. Wilson, Dr. C. O. Edwards. Lewisham: Dr. Mary Farquharson. Leicester: Regent Road, Dr. C. M. Connolly; London Road, Dr. M. C. Brough. Liverpool: N. Liverpool, Dr. W. D. Gray; S. Liverpool, Dr. F. E. Crawley. Mansfield: Ransome Hospital, Dr. D. Davies, Dr. J. J. Glowinski. Merton and Morden: Dr. E. Sanders. Newcastle upon Tyne: Dr. P. O. Leggat, Dr. L. W. Carstairs. Nottingham: Dr. J. V. Whittaker. Oxford: Dr. F. Ridehalgh, Dr. N. J. England, Dr. J. M. Black, Dr. W. S. Hamilton, Dr. D. O. Lewis. Paddington: Dr. J. A. Keeping, Dr. Z. M. Hall. Reading: Dr. A. J. Karlish. Sheffield: Dr. D. H. Anderson, Dr. R. H. Townsend. Southend: Dr. E. G. Sita Lumsden, Dr. J. D. Stevens. Sunderland: Dr. A. B. White, Dr. G. H. N. Bates. Sutton: Dr. H. F. Harwood. Swansea: Dr. T. W. Davies, Dr. G. L. Lewis. Tonbridge: Dr. S. J. Sutton, Dr. R. G. May. Uxbridge: Dr. J. Nicol Roe. Warrington: General Hospital, Dr. R. M. White. Walthamstow: Dr. Hugh Ramsay. Willesden: Dr. C. H. Toussaint, Dr. J. R. Mikhail. Wimbledon: Dr. F. J. H. Walters. Wrexham: Dr. E. Clifford Jones, Dr. J. E. Wilson, Dr. J. F. Durrans, Dr. M. K. Dhole.

The bacteriologists who carried out the sputum examinations are listed below, together with the names of the peripheral laboratories concerned (see text).

Dr. Elizabeth L. Batchelor, Southern General Hospital, Glasgow. Dr. H. R. Cayton, Public Health Laboratory, Bristol. Dr. P. B. Crone, Public Health Laboratory, Sunderland. Dr. J. M. S. Dixon, Public Health Laboratory, Ipswich. Dr. E. H. Gillespie, Public Health Laboratory, Sheffield. Dr. E. G. Gordon, Wordsley Hospital, Worcester. Dr. D. M. Green, Bacteriology Department, University of St. Andrews. Dr. G. J. G. King, Public Health Laboratory, Boscombe. Dr. W. Kwantes, Public Health Laboratory, Swansea. Dr. H. Lederer, Royal Infirmary, Glasgow. Dr. H. Loewenthal, Chase Farm Hospital, Enfield. Dr. N. S. Mair, Public Health Laboratory, Leicester. Dr. G. B. Manning, Royal Infirmary, Bolton. Dr. T. D. M. Martin, Royal Berkshire Hospital, Reading. Dr. A. J. Oliver, Fazakerley Hospital, Liverpool. Dr. R. A. M. Oliver, Mayday Hospital, Thornton Heath. Dr. E. W. Price, Yardley Green Hospital, Birmingham. Dr. H. C. Purdie, Knightswood Hospital, Glasgow. Professor D. T. Robinson, Public Health Laboratory, Liverpool. Dr. J. A. Rycroft, Westcliff Hospital, Southend-on-Sea. Dr. B. J. Stephens, St. David's Hospital, Cardiff. Dr. J. M. Talbot, Kingston Hospital, Kingston-upon-Thames. Dr. M. Thomas, Public Health Laboratory, Edmonton. Dr. J. E. Tinne, Royal Infirmary, Glasgow. Dr. R. L. Vollum, Public Health Laboratory, Oxford. Dr. A. E. Wright, Public Health Laboratory, Newcastle upon Tyne.

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A TRIAL OF PHENETHICILLIN IN CHRONIC BRONCHITIS

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Phenethicillin is the potassium salt of 6-(α -phenoxypropionamido)penicillanic acid. Knudsen and Rolinson (1959) have shown that when given by mouth the serum concentrations are at least twice those obtained with equivalent doses of potassium salt of penicillin V (phenoxymethylpenicillin) and at least equal to those obtained from the intramuscular injection of approximately equivalent weights of the sodium salt of crystalline penicillin G. Garrod (1960) has emphasized that the antibacterial action of these newer penicillins is not identical with that of penicillin G and considers their place to be doubtful apart from staphylococcal infections. The British Tuberculosis Association (1960) report on chemotherapy in chronic bronchitis indicated that penicillin V, 312 mg. twice daily, was as effective as tetracycline, 250 mg. twice daily, in reducing absence from work.

The Investigation

We record here a double blind controlled trial in a group of 40 patients who were selected on standards similar to those used in the British Tuberculosis Association (1960) report. Patients were wage-earning males between the ages of 30 and 65, working at the time, but with a history of bronchitis over the past three years and at least two certified absences from work due to this complaint. The patients selected were considered to be co-operative and likely to persevere with treatment. Excluded from the trial were those with predominant wheezing, those with any pulmonary lesion other than emphysema, and those with a history of heart failure or any other condition likely to affect their working capacity.

Patients were allotted at random to group A, receiving phenethicillin, or group B, receiving a similar placebo tablet containing dicalcium phosphate and sucrose. In addition to clinical assessment, preliminary examination included a postero-anterior radiograph of the chest, a 24-hour collection of sputum in a graduated flask, two morning sputum specimens for laboratory examination, an estimation of the peak flow rate (mean of three readings) using the Wright peak flow meter (Wright and McKerrrow, 1959), and the resting and exercise ventilations, using the Wright respirometer. The exercise test was measured when ten steps had been climbed four times at a standard rate of 116 a minute, controlled by a metronome. ("Normal" values for the last three procedures were obtained by carrying out these tests under identical conditions on twenty men of similar age whose chest radiographs were normal and who had no history of previous bronchitis or present respiratory symptoms.) Patients were given a diary in which to record their general condition as "better," "no change," or "worse," and also the colour of the sputum. Each Sunday a