ophthalmoscopic features progress throughout life, giving crude pigmentary reactions of the chorio-retinitis type and well-established optic atrophy.

In one family the mode of inheritance was clearly dominant; in the second family it was in all probability recessive. In the first family the two affected children in the third generation showed gross mental defect. In the second family only one of the four affected sibs showed a mental anomaly, and that slight.

The brain and the eyes of the older of the two children in the first family came to necropsy. The brain showed no gross macroscopic anomalies; the retina was disorganized beyond the possibility of recognizing individual layers. The brain is being subjected to a more detailed study.

It is suggested that the blindness recorded here is determined by a failure of the retina to develop into a functioning tissue—aplasia of the retina—and that this undeveloped retina subsequently undergoes secondary degenerative changes. Attention is drawn to a possible parallel with the changes in the more fully developed retina seen in retinal dystrophy—a genetically determined retinal degeneration—in some strains of mice, rats, and the Irish setter.

It is pointed out that the findings in the second family recorded here conform to those described by Alström and Olson in their study on 105 families in Sweden in whom they observed a recessively inherited congenital retinopathy, and to the cases more recently reported from Holland.

We are indebted to Dr. L. T. Hilliard, of the Fountain Hospital, Dr. A. E. P. Swinson and Dr. S. L. Pugmire, of Pewsey Hospital, Swindon, the Rev. B. G. Bartlett and Miss E. A. Cronin, of the Royal School for the Blind, Leatherhead, and Mr. R. Peppitt, of Linden Lodge School, for facilities to carry through the investigations recorded. We are obliged to Dr. D. Oppenheimer, of the Radcliffe Infirmary, Oxford, and Dr. L. Crome, of the Fountain Hospital, for pathological material and information.

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The "Recommendation on the Organization of Occupational Health Services in Places of Employment," discussed at the International Labour Conference in 1959, enumerates the functions of such services, having first stated that their role is essentially preventive. The list of functions includes surveillance within the undertaking of all factors which may affect the health of workers, and advice in this respect to management and to workers or their representatives in the undertaking; pre-employment, periodical, and special medical examinations; training of first-aid personnel and supervision and maintenance of first-aid equipment; education of works personnel in health and hygiene; compilation and periodic review of relevant statistics and research in occupational health. The United Kingdom Government and employers' and workers' delegates all voted in favour of this recommendation. A subject discussed for the first time with a view to the adoption of international regulations at the 1960 conference was protection of workers against ionizing radiation. (*International Labour Conference, 43rd Session, Geneva, 1959*, H.M.S.O., price 35s. 6d.)

CHEMOTHERAPY IN CHRONIC BRONCHITIS

INFLUENCE OF DAILY PENICILLIN AND TETRACYCLINE ON EXACERBATIONS AND THEIR COST

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

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Between June, 1955, and June, 1956, bronchitis caused the loss of 22 million working days among men in England and Wales, representing about a quarter of all male sickness incapacity (Ministry of Pensions and National Insurance).

Previous work has suggested that antibiotic treatment is of value in this condition; much of this work has been reviewed by May (1958), who considered the tetracycline group of compounds to be the most satisfactory. These compounds were used in recent investigations by Edwards *et al.* (1957), Elmes *et al.* (1957), Buchanan *et al.* (1958), and Moyes and Kalinowski (1959). Antibiotics may be given continuously throughout the winter on a prophylactic basis, or for short periods at the onset of certain respiratory symptoms, there being no clear evidence that either method is preferable. It has been suggested, however (May, 1958; Moyes and Kalinowski, 1959), that, where the expected number of attacks is small, intermittent treatment is less costly, the converse being true for more severe cases likely to have frequent attacks. The prophylactic value of 1 g. daily of potassium penicillin G and 2 g. daily of tetracycline were compared in a study by Cherniack *et al.* (1959). Penicillin was found ineffective compared with tetracycline in this trial, but 45 out of the 67 patients had demonstrable bronchiectasis, and the duration of treatment varied from 3 to 18 months, the seasonal differences being unstated. The diagnoses of patients lost from study were not stated, and on the whole the findings cannot be taken as applying to patients suffering from bronchitis.

The present trial† was undertaken first because previous trials had been based on small numbers and confirmatory evidence seemed desirable; secondly, the high cost of the tetracycline compounds suggested that the value of

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Dr. R. S. Francis and Dr. C. C. Spicer co-ordinated the work and prepared the report, which should be referred to as "British Tuberculosis Association (1959) . . . etc."

†The investigation was carried out at the following centres: Cambridge chest clinic (Dr. M. J. Greenberg and Dr. R. Bruce). Chertsey chest clinic (Dr. N. V. Birrell). Croydon chest clinic (Dr. R. J. H. Fanthorpe and Dr. J. F. Heffernan). Dudley chest clinic (Dr. M. Sheldon). Dundee chest clinic (Dr. R. N. Johnston). Edmonton chest clinic (Dr. R. S. Francis). Finchley chest clinic (Dr. B. A. Butterworth). Ipswich chest clinic (Dr. P. Embleton and Dr. D. van Zwanenberg). Islington chest clinic (Dr. J. Wallace Craig). Mansfield chest clinic (Dr. D. Davis). Preston chest clinic (Dr. M. R. Geake and Dr. R. S. Nicholson). Reading chest clinic (Dr. A. J. Karlish). St. Albans chest clinic (Dr. T. A. Watkin Edwards). Tunbridge Wells chest clinic (Dr. R. May). Walthamstow chest clinic (Dr. H. Ramsay). Willesden chest clinic (Dr. C. H. C. Toussaint and Dr. J. Mikhail).

penicillin should be tested as a possible alternative, since Douglas *et al.* (1957) reported favourably on this drug in infective exacerbations of chronic bronchitis with purulent sputum. Finally, a special study seemed to be required, relating the cost of treatment to the money lost by incapacity.

Material and Methods

Central Organization

The principle of daily prophylactic treatment was adopted. Sixteen chest-clinic physicians co-operated in a double-blind controlled trial, contributing 252 patients who were allotted at random to three groups receiving: (1) tetracycline, 250 mg. b.d. in capsules; (2) penicillin V (as potassium salt), 312 mg. b.d. in capsules—equivalent to 1 million units daily; (3) inert (starch) capsules b.d.

All capsules were identical in appearance, and it was arranged that all patients should start treatment on January 5, and cease on April 30, 1959. Information was to be recorded as to the number and duration of "bronchitic exacerbations and pneumonic episodes" in each group of cases, the average number of working days lost as a result, and the money lost to the patient through time off work and to the State from sickness benefit. The term "pneumonic episode" was not specifically defined, but in order to concentrate on the type of attack most likely to be improved by antibiotics 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."

By special arrangement the following data were obtained from the Ministry of Pensions and National Insurance concerning each patient's claims for sickness benefit in consequence of "bronchitis" or pneumonia of any kind: (1) the number of years during the past decade in which such a claim was made; and (2) the total number of spells, and their duration, for which such claims were made, since January, 1955.

The purpose of this and certain other information was to check the randomization procedure. Later, as a final check on the results of the trial, details of all the patients' claims for respiratory disease, other than tuberculosis and neoplasm during the period of the trial, were obtained from the Ministry.

A full survey of sputum bacteriology was not considered practicable, but nasal swabs, taken before and after the trial, were cultured at local laboratories and coagulase-positive staphylococci were forwarded to Dr. Robert May at Brompton Hospital, for sensitivity tests (see Appendix II).

Chest Clinic Organization

Each clinic physician recruited up to 20 patients fulfilling the following criteria (see Elmes *et al.*, 1957): They must be wage-earning males aged 30–65 who have suffered from winter cough with sputum for the past three years, during which time they must have been off work twice because of bronchitis with purulent sputum. They must be reasonably intelligent and be prepared to co-operate even if treatment appears unhelpful. Patients were not accepted if their main symptom was wheezing, if their history included heart failure or penicillin sensitivity, if there were radiographic changes other than those of bronchitis and emphysema, or if they were already taking part in a trial of chemotherapy or vaccine to reduce the incidence of bronchitis.

The co-operation of the general practitioners was sought, and they remained in sole clinical charge of the patients during any episodes of ill-health, being free to prescribe whatever treatment they wished. They were asked, however, not to give any other prophylactic chemotherapy, and to inform the chest clinic of drug reactions, pneumonic episodes, and any chemotherapy prescribed as a result of illness. They were also asked not to advise patients to omit the capsules supplied from the clinic, unless toxic symptoms occurred.

Within each clinic, chest physician, health visitors, and almoner worked as a team. At the pre-trial interview each patient was carefully instructed. He was given a graduated sputum flask and a diary in which to make the following records:

1. 24-hour sputum volume once weekly, and daily when off sick with bronchitis or pneumonia.
2. Daily sputum colour, and whether the same, more, or less sputum than usual (approximately).
3. A daily record of his general condition as follows (Lawther, 1958): (*a*) condition better than usual, (*b*) condition the same as usual, (*c*) condition worse than usual, and (*d*) condition much worse than usual.

Arrangements were also made for health visitors to make two visits per month to each patient to inspect sputum and report progress. Finally, at the same pre-trial interview, the almoner calculated average daily earnings based on the number of working days per week; nasal swabs were taken and patients were given one month's supply of capsules with written instructions. Further supplies were issued each month.

At the end of each month of the trial progress was assessed by the chest physician, who recorded the number of attacks, their duration, and the working days lost in consequence. His assessments were made on the basis of patients' personal histories, their diaries, and the health visitors' fortnightly reports. The almoner recorded money-equivalents of working days lost and sums received from National Insurance, National Assistance, and other sources. At the end of the trial period, weekly tobacco consumption was recorded and further nasal swabs were taken. All diaries, chest physicians', health visitors', and almoners' reports were then forwarded for analysis.

Statistical Methods

The randomization of treatments was carried out regardless of the clinic to which the patient belonged, and no attempt was made to equalize the proportions in the treatment groups for each clinic. This step was taken deliberately, as it was felt that the clinical assessment of the patient's condition was highly subjective and that the chance of a clinician or health visitor guessing the treatment should be made as small as possible. For this reason also the capsules issued were not divided up into three distinct groups but allotted code numbers, which differed for every bottle of capsules. Randomization was carried out centrally and a supply of bottles sent out monthly to the clinics, each bottle being already labelled with the patient's name.

The lack of balance among the treatments which resulted from the randomization procedure was aggravated in some clinics by the withdrawal of some patients from the trial (see below). A detailed comparison of various characteristics of the patients, such as age, average earnings, whether indoor or outdoor workers, smoking habits, and previous claims for

TABLE I.—*Comparison of Various Characteristics of Control and Treatment Groups. There are No Statistically Significant Differences Between the Three Groups in Any of These Characters*

	Penicillin	Tetracycline	Control
Average age (years) ..	53	51	54
indoor employment ..	62	62	52
Average days lost in previous years	85	89	76
Averages wages per day ..	38 -	38 -	41 -
Cigarettes per week ..	54·1	54·7	55·3

sickness benefit, is summarized in Table I. There are no significant differences in any of these between the three groups. The excess of outdoor workers among the controls, and their smaller previous loss of time from bronchitis, are in any case such as to lessen any apparent benefit derived from treatment.

It is felt that systematic bias in favour of one or other type of treatment has been effectively removed, and that any errors of assessment and execution probably affected each group equally.

The technical details of the statistical analysis are given in Appendix I, as they are only of specialist interest.

Four measures of the effect of treatment were examined: these were (*a*) number of attacks, (*b*) duration of attacks, (*c*) days off work, and (*d*) money lost while off sick.

The number of attacks was found to be unaffected by the treatments, and the measure finally chosen for expressing the results was the total days off work due to attacks conforming to the definition during the period of the trial. Though closely correlated with the total duration of attacks, this is the more objective measure and showed less variation from clinic to clinic. Moreover it was checked later against Ministry of National Insurance records. It has also a direct meaning in economic and personal terms, but a possible disadvantage is that it is a rather stringent criterion of incapacity, and a proportion of the patients who in fact benefited from the treatment may have recorded no days off work.

It would have been possible to use the money lost through sickness as a measure of effect, but this, though related to days off work, is affected by the differences in average earnings among the patients, which are irrelevant to the main study.

Results

Of the 252 patients enrolled in the trial, 26 were excluded from statistical analysis, 14 because they were unemployed throughout and could provide no information on days lost from work, and 12 because no adequate records were available on their progress. Most of the latter were classified by their clinicians as uncooperative and they withdrew at an early stage. The 226 cases remaining fell into two categories: 185 were continuously under observation and at risk during the trial, and 41 were only intermittently at risk because they entered the trial late owing to previous illness or were admitted to hospital from various causes, or had spells of unemployment. The method used to include the experience of these 41 cases was to express the results in terms of man days off work per man days at risk.

Days Off Work

Analysis of the 226 cases in employment showed that both penicillin and tetracycline are beneficial in reducing the days off work due to bronchitic exacerbations or pneumonic episodes (Table II). The average days off work per man-day under observation in the three treatment groups were: 0.066 ± 0.014, penicillin; 0.084 ±0.019, tetracycline; 0.171 ± 0.025, control. It appears, therefore, that both the antibiotics approximately halved the time off work, but did not differ significantly from each other.

Serious respiratory infection occurred in six of the cases included in this analysis, leading to admission to hospital, death, or subsequent failure to continue in the trial. In the analysis these cases were counted as exposed for the whole period over which their history was known and the days off work related to this period. Two of them were on tetracycline and the remaining four were controls. The two on tetracycline both became very ill within a few days of entering the trial and can hardly be considered to have had effective prophylactic treatment at all. Of the four controls one died and the others were rather severe cases, and, taken as a whole, the inclusion of this group probably exaggerated the effects of antibiotic treatment.

TABLE II.—*Average Days Lost From Work Per Day Under Observation in the Three Treatment Groups for Each Clinic Taking Part in the Trial. Figures in Brackets are Numbers of Patients in Each Group*

	Penicillin	Tetracycline	Control
Cambridge	0·0681 (6)	0·1627 (6)	0·1543 (4)
Chertsey	0 (1)	0 (0)	0·0638 (3)
Croydon	0·0626 (5)	0·1680 (6)	0·2615 (6)
Dudley	0·0188 (6)	0·0907 (7)	0·0783 (7)
Dundee	0·0109 (4)	0·0203 (3)	0·0122 (5)
Edmonton	0 (1)	0·1203 (12)	0·0770 (6)
Finchley	0·0435 (4)	0·0058 (3)	0·8889 (1)
Ipswich	0·0017 (5)	0·1174 (4)	0·1725 (10)
Islington	0·1648 (2)	0 (5)	0·0087 (5)
Mansfield	0·1868 (5)	0·0029 (3)	0·5553 (7)
Preston	0·1551 (6)	0·0725 (3)	0·0250 (4)
Reading	0·0490 (11)	0·0671 (7)	0 (1)
St. Albans	0·0435 (2)	0·1101 (6)	0·1261 (2)
Tunbridge Wells ..	0·0435 (7)	0·0435 (4)	0·8348 (1)
Walthamstow	0·0580 (6)	0·0739 (4)	0·0609 (7)
Willesden	0 (2)	0·0304 (6)	0·2135 (5)
	0·0657 (73)	0·0838 (79)	0·1713 (74)

Penicillin, 0·0657 ± 0·0140. Tetracycline, 0·0838 ± 0·0187. Control, 0·1713 ± 0·0246. Differences (control − penicillin) = 0·1056 ± 0·0282. Differences (control − tetracycline) = 0·0875 ± 0·0309.

A separate analysis was also made of the 185 cases under observation continuously throughout the trial. Though this group may not be fully representative of the patients as a whole, it was felt that the analysis of the whole series might have given undue weight to the experience of those with very short exposures, and a more thorough statistical treatment is possible of the records concerning patients exposed throughout the trial. The benefits of antibiotic treatment are equally evident in this group, but the apparent superiority of penicillin over tetracycline disappears, being mainly due to the inclusion of one or two particularly unfavourable cases. The mean days lost per days at risk are as follows: penicillin, 0.06; tetracycline, 0.06; control, 0.12. The average days off and the average duration of attack per patient were:

Regimen	Days Off Work	Duration of Attack in Days
Penicillin	6·8	9·0
Tetracycline ..	7·5	11·5
Control	14·2	21·3

As in the main analysis, both antibiotic treatments led to halving of time off work compared with the control group.

Though the general benefit of treatment has been established its numerical value is not very accurately estimated. The variability of the days lost from work by patients in the same clinic and on the same treatment is very large; this is an important feature of the results, since it implies that they are only applicable on the average for large numbers of patients.

The approximate equal efficacy of penicillin and tetracycline is an unexpected finding, since the former is considered to have little effect on organisms of the *Haemophilus* group. From a statistical point of view the variability in response is so high that the true value of the difference between the two antibiotics is very inaccurately estimated, the errors of estimation being such that the observed difference is compatible with either drug having a saving of some four working days over the other.

Number of Attacks

The second interesting feature of the trial is that the treatments appear to have no effect in reducing the number of attacks per patient. For those patients who were under observation through the whole period of the trial the average numbers of attacks were as follows: penicillin, 0.92; tetracycline, 1.07; control, 1.04. The small differences are quite insignificant statistically.

Loss of Money

The loss of money due to the disease is of course highly correlated with the time off work and is made up of wages not earned, national assistance, and insurance payments from the State or private clubs and societies, the latter being a comparatively minor source in the present study. The average monetary losses per patient in the three groups were: penicillin, £14; tetracycline, £18; control, £40; and, as with the time off work, the effect of treatment was to halve the losses, penicillin and tetracycline being approximately equivalent.

The two drugs differ considerably in price, and the costs of treatment (calculated from retail prices in the *Prescribers' List of Proprietary Medical Products*, 1959) for the four-months period were about £32 for tetracycline and £16 for penicillin. The net costs for the three groups of patients during the four months of the trial were therefore as follows:

	Penicillin	Tetracycline	Control
Average money losses ..	£14	£18	£40
Cost of drugs	£16	£32	—
Net costs	£30	£50	£40

Compared with the control group there was an average net gain per patient of £10 (£40 down to £30) in the penicillin group; whereas in the case of the tetracycline-treated group there was a net less of £10. These considerations are apart from any question of the benefit of treatment to the patients.

Treatment by General Practitioners

Practitioners were asked to inform chest physicians whenever they prescribed chemotherapy, and the latter were asked to report such treatment each month. The numbers of treatments in 185 patients exposed to risk for the whole period were as follows:

	Treatments by General Practitioners		
	Total	< 1 Week	> 1 Week
Penicillin group	7	5	2
Tetracycline ,, ...	13	10	3
Control ,, ...	9	8	1

Side-effects of Treatment.—During the trial all patients were repeatedly asked by health visitors and chest physicians if they thought the treatments were causing side-effects. Thirty-five positive answers were received, the symptoms being mostly mild and transitory and occurring nearly always very early in the trial. Only six patients withdrew from the trial on this account, four of these being "control" cases. In none of the men taking antibiotics were side-effects of a serious nature. Gastro-intestinal symptoms consisted in the main of loose motions for a few days; other symptoms were mainly transient rashes and headaches. The information on side-effects is summarized in Table III.

TABLE III.—*Numbers of Patients Complaining of Toxic Symptoms in the Three Treatment Groups*

	Penicillin		Tetracycline		Control	
	W	NW	W	NW	W	NW
Gastro-intestinal	0	5	0	8	2	7
Other	2	4	0	5	2	0
Total	11		13		11	

W = Withdrawn from trial. NW = Not withdrawn from trial.

Deaths: Three deaths occurred among the 252 patients. Two were in the tetracycline group, both being due to pneumonia and cardiac failure. One patient in the control group died of acute-on-chronic bronchitis with emphysema and hypertensive heart disease. A further patient who started treatment with tetracycline died of carcinoma of the lung. The first three deaths occurred within two weeks of the start of the trial and the death from carcinoma took place on February 6, 1959.

Discussion

The benefits of the treatment given are largely confirmatory of previous work. Two findings are unexpected: first, that the improvement was in the duration rather than the number of exacerbations, and, secondly, the apparently equal efficacy of penicillin and tetracycline in the doses used.

The first of these could have arisen because the antibiotics acted as therapeutic rather than prophylactic agents, ensuring prompt treatment of the attacks without preventing them. It is also possible that their effect was to control secondary infection, the attacks themselves being precipitated by some other cause, such as a virus infection or some meteorological factor.

The main factors taken into account in choosing the doses of the antibiotics used in this trial were the nature of the pathogenic organisms likely to be important and the cost of the drugs. The most important pathogenic bacteria in chronic bronchitis are known to be *Haemophilus influenzae* and the pneumococcus. Pneumococci are always highly

sensitive to penicillin, but *H. influenzae* is seldom inhibited *in vitro* by concentrations lower than 1.25 u./ml., and bronchial infections caused by it respond to intramuscular penicillin G only in doses of 8 mega-units or more per day (Goslings and Hers, 1953) or to "estopen" in doses of 2 mega-units a day (May, 1955). Oral penicillin V, therefore, at a dosage level equivalent to 1 mega-unit daily, as prescribed in the trial, could only be expected to combat infections caused by pneumococci. As regards tetracycline sensitivity, the disparity between the two organisms is not so great, though the pneumococcus is still the more sensitive. The dose usually required to suppress *H. influenzae* in patients with bronchitis is 0.5 g. b.d. or higher (Helm *et al.*, 1954; May and Oswald, 1956), but, owing to the high cost of this drug, and to reports of encouraging results with chlortetracycline using a dose of 0.25 g. b.d. (McVay and Sprunt, 1953), the lower dose was chosen. It was hoped that both drugs would, in the doses used, suppress pneumococci, and that tetracycline might in addition suppress a reasonable proportion of *H. influenzae* strains.

Bacteriological examination of the sputum of patients in this trial was considered impracticable and was not carried out; interpretation of the results, therefore, can only be speculative. The most probable explanation, however, of the apparently equal efficacy of penicillin and tetracycline in shortening exacerbations is that only pneumococci were suppressed, the dose of tetracycline being inadequate to inhibit more than an occasional strain of *H. influenzae*. If this were so, exacerbations caused by the latter organism would remain uncontrolled in all treatment groups. Another possible explanation is that exacerbations caused by pneumococci were exceptionally prevalent during the months of the trial, but no reports to this effect have been received. In any case, even if this were so, tetracycline would still be expected to be the more effective drug if the dose were sufficient to suppress *H. influenzae* as well.

It seems probable, therefore, that this trial has in fact measured the value, both clinical and financial, of prophylaxis with particular doses of penicillin or tetracycline against pneumococcal exacerbations of bronchitis, and clearly, if this is the correct bacteriological interpretation of the results, the high cost of tetracycline makes its routine use *in the manner and dosage used in this trial* unjustifiable; but it cannot be assumed that the use of tetracycline in higher doses would not produce a better result than penicillin. Attempts are being made, in a second trial of prophylactic chemotherapy in chronic bronchitis, to carry out a bacteriological survey in order to facilitate interpretation of clinical results.

A comparison of the Ministry of Pensions and National Insurance records of the patients during and before the trial period shows that the period under review was not exceptional, and as the trial was carried out in a variety of places all over the country in both rural and industrial areas, it seems fair to conclude that the results are likely to have general application.

The conclusions arrived at on the financial aspects of treatment depend to some extent on how far the patients in the trial are a representative sample of all bronchitics. The patients were selected according to certain criteria in the first place, and there was further elimination of patients unemployed during the course of the trial. Similar savings can be expected only in similarly chosen patients, and the financial benefit of treatment might be greatly reduced by the inclusion of patients whose condition was not in fact improved by antibiotics.

It should be emphasized that the results can only be expected to apply on the average to a similar group of patients. In any individual case or small group of patients the effect of treatment may be disappointing. It has not been possible to single out any particularly suitable type of patient; two important objects of future study would be to define more closely the type of patient to whom these conclusions apply and to investigate the effects of other techniques of administering antibiotics.

It might also be objected that treatment affects only exacerbations of bronchitis, as defined here, and pneumonic episodes, and that alleviation of these may be compensated by a corresponding increase of other respiratory disability. In fact, time lost from work due to respiratory illness as a whole, recorded by the Ministry of Pensions during the period of the trial, was very close to the losses as recorded by the chest physicians:

	Average Loss per Patient in Days		
	Penicillin	Tetracycline	Control
All respiratory causes ..	7·8	8·4	14·9
Causes as defined in trial	6·8	7·5	14·2

Clearly, in this type of patient the greater part of respiratory disability is accounted for by exacerbations as defined in this trial.

Summary

A controlled trial has been carried out to estimate the usefulness of penicillin and tetracycline as long-term prophylactics in chronic bronchitis.

Information was specially collected to determine the monetary losses from the disease in relation to the cost of treatment.

It was found that 312 mg. of penicillin V twice daily or 250 mg. of tetracycline twice daily approximately halved the days lost from work as compared with a control group receiving an inert treatment. Tetracycline did not differ significantly in its effect from penicillin, but the cost of treatment was much greater.

Neither drug significantly reduced the number of attacks of bronchitis. The validity of the results is discussed, and it is concluded that the method of study used was reliable.

The committee wishes to acknowledge with thanks the co-operation and help of: Mr. E. A. G. Cook, of Eli Lilly & Co., Ltd., who supplied the penicillin V and encapsulated and bottled all the materials used in the trial; Mr. J. R. Wilson, F.R.C.S., of Lederle Laboratories, who supplied the tetracycline; the Ministry of Pensions and National Insurance for their co-operation in supplying information relevant to the patients participating in the trial; the chest-clinic physicians, their medical staff, health visitors, and almoners; the numerous general practitioners who co-operated in the trial; the bacteriologists who cultured nasal swabs; Doreen Harmsworth for technical

assistance in carrying out sensitivity tests; and finally, to Jean Goodchild and Jean Corton for secretarial assistance.

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APPENDIX I (Statistical)

A preliminary study of the results showed at once that there was little difference between the groups in the numbers of attacks per patient. There were considerable differences between the treated and controls in duration of attack, days off work, and money lost. However, an analysis of the former on the lines indicated below showed a considerable variation between clinics in the assessment of duration, and the days off work were finally chosen as the best index of treatment.

The distribution of days off work per patient is J-shaped with a maximum at 0 and a long tail extending up to 100. In addition there was a correlation between variance and mean, the untreated with a larger mean being much more variable. A plot of the probits of the cumulative frequencies against log time, however, was approximately linear, the two treated groups having probit lines parallel to the untreated but with smaller means. It seems from this that the treatment affects the whole population and not just a group of particularly sick patients.

The presentation of the results in the main text ignores the differences between clinics and simply gives the mean days off work per days of exposure and their standard errors, from which the significance of the differences between means can be assessed. This is justifiable since it is shown below, in an analysis of the patients oberved throughout, that the differences between clinics were negligible.

The analysis of the results for those at risk all through the trial presents itself most naturally as an analysis of variance with unequal numbers in each subclass. This is appreciably more laborious to carry out than in the ordinary case when the numbers are equal, but presents no difficulties of principle or calculation. The methods used are well described by Snedecor (1946, Chapter 11).

The analysis was carried out after transforming the days off (x) to a variable y such that $y=\log_{10}(1+x)$. This considerably reduced the correlation between variance and mean but could not affect the essential skewness of the distribution.

The analysis of the transformed variates was done in two parts: first, constants were fitted for clinics and treatments and an estimate was made of the interaction term. This was found to be quite insignificant compared with the variance of patients on the same treatment at the same clinic, the analysis of variance table being as follows:

	S.S.	D.F.	M.S.
Constants (clinics + treatments)	10·5378	16	0·659
Interaction	11·4800	28	0·410
Within subclasses	51·161	140	0·365

The effect of fitting constants is significant at the 5% level and the interaction is not. The separate effects of treatments and clinics were tested by a weighted analysis of variance summarized in the following table:

	S.S.	D.F.	M.S.
Clinics	5·1723	14	0·369
Treatments	2·3850	2	1·193
Within subclasses	51·161	140	0·365

The mean square for clinics is almost exactly the same as the error term and not statistically significant, but the effect of treatment is significant at the 5% point.

APPENDIX II

THE INFLUENCE OF CONTINUOUS CHEMOTHERAPY ON THE CARRIAGE OF ANTIBIOTIC-RESISTANT STAPHYLOCOCCI IN THE ANTERIOR NARES

Though coagulase-positive staphylococci play only a very minor part in chronic bronchial infections, an increase in the nasal carrier rate of antibiotic-resistant strains in bronchitics receiving continuous chemotherapy would be important inasmuch as it would add to the general reservoir of resistant staphylococci in the population as a whole.

Collection of Specimens

The anterior nares of each patient were swabbed by chest physicians at the beginning and end of the trial. Swabs were soaked in nutrient broth before use and forwarded as soon as possible to the local bacteriologist for culture. Any coagulase-positive staphylococci isolated were sent to the Bacteriology Department, Institute of Diseases of the Chest, for sensitivity testing.

Sensitivity Testing

Sensitivity to penicillin and tetracycline was estimated by titration in nutrient broth. In order to minimize experimental error the following precautions were taken: (*a*) All tests were performed by one person. (*b*) The staphylococci were tested in batches, dilutions of the antibiotics being prepared in bulk and then distributed into the appropriate number of sets of test-tubes for the individual organisms. (*c*) A control titration using a standard organism (the Oxford staphylococcus) was performed with each batch of tests. (*d*) All staphylococci isolated at the beginning of the trial were preserved on agar slopes, and those derived from patients from whom staphylococci were subsequently isolated at the end of the trial were retested in parallel with the latter.

Sensitivity to tetracycline was tested over the range 10 to 0.3 μg./ml. in doubling dilutions. That to penicillin was tested initially from 0.5 to 0.01 u./ml., and any organism resistant to this range was retested over the range 10 to 0.3 u./ml.

Definition of "Sensitive" and "Resistant."—The selection of a sensitivity level above or below which a given organism might be classed as "sensitive" or "resistant" must necessarily be somewhat arbitrary. In fact, however, the sensitivities fell very clearly into two groups for each antibiotic: (*a*) Penicillin, resistant to 10 u./ml. or sensitive to 0.5 u./ml. or less; (*b*) tetracycline, resistant to 10 μg./ml. or sensitive to 1.25 μg./ml. or less. These concentrations were accordingly selected to distinguish between "sensitive" and "resistant" strains for the purposes of the present report.

Results.—Results have been compiled only in relation to those patients who completed the trial (see main report). Further, some clinics failed to take nasal swabs both at the beginning and at the end of the trial, and the patients attending these clinics have therefore had to be excluded from parts of the analysis.

The basic results obtained at the beginning of the trial are shown in Table A. They represent the current situation as regards nasal carriage of staphylococci in chronic bronchitics in the country as a whole and are in no way remarkable. The results obtained at the end of the trial (10 clinics only) are shown for comparison. They reveal little change in the carrier rate, but there is a slight relative increase in the rates of antibiotic-resistant organisms,

TABLE A.—*Nasal Staphylococcal Carrier Rates at the Beginning and End of the Trial*

	No. of Clinics	No. of Patients	Coagulase-positive Staphylococci		
			No. Isolated	No. Resistant to:	
				Penicillin	Tetracycline
Before trial	15	180	38 (21%)	4 (2%)	3 (2%)
After ,,	10	134	25 (19%)	6 (5%)	10 (8%)

especially those resistant to tetracycline. Little significance can be attached to these results, however, since they take no account of the treatment to which each patient had been exposed.

Results in Different Treatment Groups

More detailed analysis of the results in relation to treatment groups is given in Table B. It is unfortunate that the distribution of staphylococcal carriers at the beginning of the trial was not uniform between the three treatment groups, but the trends within the groups are clear. While the control group showed a slight rise in the carrier rate, there was a corresponding fall in each of the treatment groups. In both the latter, however, the *relative* number of staphylococci resistant to the particular antibiotic rose. This rise was significant in the case of tetracycline, but not significant in the penicillin group.

TABLE B.—*Results in Different Treatment Groups*

Treatment	No. of Patients	Beginning of Trial			End of Trial		
		No. of Staphs.	R. to P.	R. to T.	No. of Staphs.	R. to P.	R. to T.
Penicillin	42	13 (31%)	2 (5%)	1 (2%)	9 (21%)	3 (7%)	1 (2%)
Tetracycline	49	12 (24%)	1 (2%)	0 (0%)	8 (16%)	2 (4%)	8 (16%)
Control	43	4 (9%)	0 (0%)	0 (0%)	8 (19%)	1 (2%)	1 (2%)
Total ..	134	29 (22%)	3 (2%)	1 (1%)	25 (19%)	6 (4%)	10 (7%)

All percentages referable to number of patients in relevant treatment group. R. to P.=Resistant to penicillin. R. to T.=Resistant to tetracycline.

Changes in the Carrier State of Individual Patients

Coagulase-positive staphylococci were isolated from the anterior nares, both at the beginning and at the end of the trial, of 14 patients. Of these, nine were treated with penicillin, four with tetracycline, and one was a control. The sensitivity patterns remained unchanged after the trial in the single control patient and in eight out of the nine penicillin-treated patients. The staphylococcus isolated after the trial from the remaining penicillin-treated patient was resistant to penicillin and sensitive to tetracycline, whereas that found before the trial had been sensitive to both antibiotics. In contrast, each of the four staphylococci isolated from the tetracycline-treated patients after the trial was resistant to tetracycline (but sensitive to penicillin), whereas before the trial fully sensitive strains had been isolated in each case.

Though these figures are small there was clearly a greater tendency for sensitive strains to be replaced by resistant ones in the tetracycline-treated group than in the group receiving penicillin.

In a further 11 patients staphylococci were found after the trial but not before it. Four of these patients were treated with tetracycline, and each corresponding staphylococcus was resistant to this antibiotic; two were also resistant to penicillin. No patients receiving penicillin fell into this group, but of the seven staphylococci isolated from controls five were sensitive to both antibiotics, one was resistant to tetracycline and sensitive to penicillin, and one was resistant to penicillin and sensitive to tetracycline.

Conclusions

The development of antibiotic-resistant staphylococci in the anterior nares was not a serious problem in this trial, but when it did occur it was almost exclusively in response to tetracycline. Sixteen per cent. of the patients treated with tetracycline were nasal carriers at the end of the trial and in each case the staphylococcus was resistant to this antibiotic. At the beginning of the trial there were no carriers of tetracycline-resistant staphylococci in this group.

In contrast, the penicillin-treated group showed an increase of from 5% to 7% in the carrier rate of penicillin-resistant staphylococci—an increase similar to that in the controls.

Development of tetracycline-resistance in patients treated with penicillin was never observed. But in two patients treated with tetracycline staphylococci resistant to both drugs were found at the end of the trial.

COLD INJURY IN THE NEWBORN

A STUDY OF 70 CASES

BY

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Though the clinical picture of cold injury in the newborn had been described as early as 1889 by Henoch, and has been recognized by individual paediatricians in this country for some years (Braithwaite, 1955; Smallpeice, 1955; Everley Jones, 1955; Williamson, 1955), it was Mann who first gave a full description of the syndrome and made recommendations for its prevention (Mann, 1955; Mann and Elliott, 1957).

The condition is still not as widely recognized as it should be and it is not described in current paediatric textbooks. Though preventable, it still occurs and is often undiagnosed; this survey of all newborn babies with cold injury admitted to the Children's Hospital, Birmingham, in the years 1946–56 has therefore been made. We describe the clinical features, the aetiological factors, and the results of a follow-up investigation of those who survived.

Material

Though the diagnosis of chilling as the cause of illness in newborn babies was not often made in this hospital before 1951, we included in our initial survey all babies admitted during the years 1946–56 whose rectal temperatures were less than 96° F. (35.6° C.) at some time during the first 24 hours after admission. In this way we hoped to discover not only the incidence of hypothermia due to chilling but also the frequency of hypothermia in other diseases of the newborn. Thermometers registering temperatures below 95° F. (35° C.) were not in use before 1951, so that in the early years even the temperatures of severely chilled babies were recorded as "95" or "below 95."

The total number of such patients was 183. The diagnoses are shown in Table I; in nearly all cases they were unequivocal and in only seven did we feel sufficient doubt about the diagnosis to regard the case as unclassifiable. When hypothermia is not primarily due to external chilling or to prematurity the illness is severe and diagnosis of the primary disease is not difficult. Moreover, post-mortem confirmation of the