improvement was limited more by the irreversible changes of bronchitis and emphysema than by failure of the drug to eliminate particular infecting organisms.

It is significant that no serious toxic effect was recorded and that only two patients were unable to continue the trial. It may be concluded that the oxytetracycline regime used is both beneficial in severe cases of bronchiectasis and also safe. It is, however, expensive. A year's treatment on the lines indicated would cost, at the time of writing, at least £60 per patient for oxytetracycline. In regard to the overall problem, it is clear that the response obtained and expense entailed do not justify the widespread use of long-term oxytetracycline therapy in most patients with bronchiectasis. For the relatively few advanced cases it does offer a measure of relief not apparently attainable by oral penicillin in the doses used. The characteristic symptoms of bronchiectasis can be modified and the natural history of the disease influenced whilst oxytetracycline therapy is maintained, but there is no indication that such improvement as may be achieved is permanent, and relapse is almost certain after treatment is stopped.

Summary

In a controlled trial at seven centres 122 patients with bronchiectasis were allocated at random to one of three treatments—38 to penicillin, 44 to oxytetracycline, and 40 to lactose. The drugs were provided as indistinguishable 0.25-g. capsules, two of which were given four times a day on two days each week for a period of a year. Regular visits were paid to the out-patient departments throughout this period, at which measurements were made of the volume of a 24-hour sputum specimen and of the severity of cough, dyspnoea, haemoptysis, and disability since the previous visit.

The three treatment groups were similar in their age distribution, the history of previous respiratory illnesses, and the extent of involvement as determined by a recent bronchogram. During the year's observations three deaths occurred—one in each treatment group. Two patients—one on penicillin and one on oxytetracycline—could not tolerate the capsules and stopped treatment. Four patients—two on oxytetracycline and two on lactose—defaulted before six months' treatment had been completed. One patient given lactose who died subsequent to the year's observation was found to have had fibrocystic disease of the pancreas and was excluded from the analysis.

The records of the remaining 112 patients, 36 on penicillin, 40 on oxytetracycline, and 36 on lactose, were examined to compare the response to the treatments. Each group showed a reduction in sputum volume, greater for the pus than for the mucus fraction, during the year. The reduction in the oxytetracycline group was rapid, and for pus to about half the pre-treatment level. The reduction in the penicillin and lactose groups was slower, and to about 70% of the original level in each. There was some reduction in each treatment group in the severity of cough and dyspnoea and in the number of episodes of haemoptysis, with a slight advantage shown by those taking oxytetracycline. A more pronounced effect in the oxytetracycline group was observed in the reduction of disability expressed by the number of days off work, in the episodes of fever, and in the number of days confined to bed. No serious toxic effects were observed in any group. Although in general oxytetracycline was beneficial and was more effective than oral penicillin, the limited effect of long-term therapy, having regard to its cost, would not justify its widespread use in most patients with bronchiectasis.

Those taking part in the trial were: Chester: Dr. A. C. C. Hughes (clinician). Edinburgh: Professor J. W. Crofton and Dr. A. R. Somner (clinicians). Glasgow: Drs. T. Anderson, A. W. Lees, and G. Allan (clinicians); Dr. J. B. Landsman (bacteriologist). Leeds: Drs. M. Telling and G. N. Chandler (clinicians). Liverpool: Drs. W. S. Sutton and G. Penrhyn Jones (clinicians); Dr. F. Whitwell (pathologist). Newcastle: Dr. A. G. Ogilvie (clinician). Sheffield: Drs. C. S. Darke and J. E. Middleton (clinicians); Drs. E. H. Gillespie and J. E. M. Whitehead (bacteriologists).

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ADULT CHRONIC BRONCHITIS—THE INFECTIVE FACTOR AND ITS TREATMENT

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The pathogenesis of chronic bronchitis involves several factors, one of which is believed to be infection (May, 1953a, 1953b; Oswald and Medvei, 1955).

During 1955 in the City of Leeds (population 508,000) 67 persons died of pulmonary tuberculosis, 270 from carcinoma of the lung, and 463 from the effects of bronchitis. The actual incidence of bronchitis in the population is difficult to determine, but Goodman *et al.* (1953) have shown that chronic respiratory disease is an important cause of disability, and accounts for more unemployment than any other physical condition. Similarly, Stuart-Harris (1954) reported finding cough and sputum in 55% of men aged 50–60 in an industrial population, whilst Higgins *et al.* (1956) estimated that 10% of non-miners in the mining community they investigated had bronchitis. Stocks (1947) has drawn attention to the inverse relationship that exists between hours of sunshine and deaths from bronchitis.

It is therefore of some importance to assess critically the value of any treatment of this common disease, particularly in relation to the control of the infective element.

Several workers in this country have already reported their experiences with the tetracycline group of drugs (Helm *et al.*, 1954, 1956; May and Oswald, 1956). In the main these trials have been conducted without adequate controls.

We report here the results of an investigation into certain bacteriological aspects of the infective factor in chronic bronchitis, and of a controlled therapeutic trial, using oxytetracycline alone or in combination with other measures.

Pre-treatment Bacteriology

Single sputum specimens from patients with chronic bronchitis attending the Leeds Chest Clinic for the first time were examined bacteriologically during the period October, 1954, to June, 1956. An early morning specimen was examined within a few hours of collection, and was classified as either purulent or mucoid. Smears of each specimen were stained by Gram and Leishman methods. The presence or absence of Gram-negative cocco-bacilli and other bacteria was noted, together with an estimate of the approximate number of pus cells and of eosinophils per oil-immersion field. Each specimen was cultured on fresh blood and heated blood (chocolate) agar. A simple inoculation technique previously described (Allison *et al.*, 1943; Allibone *et al.*, 1956) was employed. The cultures were examined after 24 and 48 hours' incubation.

Results

Sputum specimens from 320 consecutive patients were investigated, of which 61 were examined in the winter months of 1954–5, 169 during the winter of 1955–6, and 90 in the spring and summer months of the two years 1954–6. Of these sputa, 156 were purulent and 164 mucoid. Microscopical examination for pus cells mostly confirmed these findings. Mucoid specimens contained up to 10 pus cells per oil-immersion field, whilst frankly purulent sputa showed 50 or more neutrophils per field. In the whole series examined eosinophils were rarely found. Table I shows the incidence of the five commonly accepted "potential pathogens" (May, 1954) in purulent as compared with mucoid sputa.

H. influenzae and the pneumococcus were most commonly found. *H. influenzae* was most frequent in purulent sputa (60–70%). In mucoid sputa, however, the incidence was reduced to about half of that in purulent sputa. In contrast the incidence of the pneumococcus was constant in both purulent and mucoid sputa (30–40%).

In 93 of the 102 purulent sputa containing *H. influenzae*, this micro-organism was predominant or present in equal numbers with one or two of the other "potential pathogens." In these 93 sputa (59.7% of the total) *H. influenzae* was present alone in 35, whilst in 48 one other "potential pathogen" was isolated, and in 10 *H. influenzae* was found with two other "potential pathogens." In no specimens were more than three "potential pathogens" found together.

Of the 158 specimens yielding *H. influenzae* in culture, this organism was recognized microscopically in direct sputum smears in 129 (81.6%). Such Gram-stained films were of little value in forecasting the presence of pneumococci, since they cannot readily be distinguished from other Gram-positive cocci unless capsulation is present.

Therapeutic Trial

The marked predominance of *H. influenzae* and pneumococci in the sputa examined seemed sufficient reason for taking into account only these two micro-organisms when assessing bacteriologically the effect of treatment. In planning the trial the assumption was made that either *H. influenzae* or the pneumococcus or both were pathogenic in chronic bronchitis.

Zinnemann (1950) showed that a number of sulphonamides effectively inhibited *H. influenzae in vitro*, and that chloramphenicol was the most effective oral antibiotic, closely followed by oxytetracycline (Zinnemann, 1953).

The purpose of the investigation was to determine the value of an oral antibiotic in chronic bronchitis when given continuously during the six winter months of 1955–6, following a pilot trial which had been carried out during the winter of 1954–5. In view of the reported risk of marrow aplasia following prolonged chloramphenicol therapy, oxytetracycline was selected as the drug of choice in a controlled clinical trial, and we also planned to assess the value of a sulphonamide. In addition, an autogenous *H. influenzae* vaccine was used in an attempt to overcome any allergy to *H. influenzae* that might play a part in the disease. Lastly it was planned to determine whether the effect of the antibiotic could be enhanced by either one or both of these substances.

Methods and Materials

The criteria for diagnosis and entry to the clinical trial were that the patients should be over 20 years of age, should have cough, sputum, shortness of breath for more than a year and some degree of disability arising therefrom, and that there should be no evidence of other causes for these symptoms. Since an autogenous *H. influenzae* vaccine was to be used, it was necessary that that organism should have been recovered from the sputum before acceptance. The nature of the trial was explained to the patients, and their agreement to take part was obtained. As a result 66 consecutive patients who fulfilled these criteria were admitted to the trial between September and November, 1955. There were 57 males and 9 females, aged from 28 to 71, who were all treated as out-patients.

The age and sex distribution of the patients admitted to the trial, and of those who completed the course and were available for analysis, are shown in Table II. More than half the

TABLE I.—*Incidence of the Five "Potential Pathogens" Found in the Sputa of 320 Consecutive Chronic Bronchitics Examined from October, 1954, to June, 1956*

Organism	Type of Sputum	Oct.–Mar. 1954–5		Oct.–Mar. 1955–6		Apr.–Sept., 1955 Apr.–June, 1956		Whole Period Oct., 1954–June, 1956	
		No.	%	No.	%	No.	%	No.	%
H. influenzae	Purulent	18/25	72	53/87	61	31/44	70·4	102/156	65·4
	Mucoid	15/36	41·6	27/82	32·9	14/46	30·4	56/164	34·1
Pneumococcus	Purulent	10/25	40	30/87	34·5	22/44	50	62/156	39·7
	Mucoid	14/36	38·9	26/82	31·7	25/46	54·3	65/164	39·6
Friedländer's bacillus	Purulent	4/25	16	11/87	12·8	3/44	6·8	18/156	11·5
	Mucoid	4/36	11·1	11/82	13·9	1/46	2·1	16/164	9·75
β-Haemolytic streptococci	Purulent	5/25	20	21/87	24·1	4/44	9	30/156	19·25
	Mucoid	9/36	25	20/82	24·4	2/46	4·2	31/164	18·9
Staph. aureus	Purulent	1/25	4	9/87	10·4	4/44	9	14/156	8·9
	Mucoid	0/36	0	1/82	1·2	1/46	2·1	2/164	1·2

Note.—The criteria used for the recognition of *H. influenzae* and the pneumococcus were:
H. influenzae: Usually poor growth on fresh blood agar, luxuriant growth on chocolate agar; characteristic (indole) odour of cultures and greyish-green colour of colonies on chocolate agar (Allison *et al.*, 1943); microscopical appearance; confirmation by X and V requirements when necessary.
Pneumococcus: Intense yellow discoloration of chocolate agar after 24 hours' incubation; α-haemolysis and typical colonial appearance on fresh blood agar; confirmation by bile-solubility test when necessary. No typing undertaken.

TABLE II.—*Age and Sex Incidence of Patients Admitted to the Trial and of Those who Completed It*

Age	Admitted		Defaulted		Died		Other Exclusions		Completed	
	M	F	M	F	M	F	M	F	M	F
21–30 ..	1	1	1	—	—	—	—	—	—	1
31–40 ..	4	3	—	—	—	—	—	—	4	3
41–50 ..	11	4	4	—	—	—	1	—	6	4
51–60 ..	22	1	1	—	1	—	1	—	19	1
61 over ..	19	—	3	—	1	—	—	—	15	—

TABLE III.—*Clinical Features of Patients Admitted to the Trial and of Those Who Completed It*

	No. of Patients Admitted to Trial		No. who Completed Trial	
	Males	Females	Males	Females
Duration of symptoms:				
Less than 5 years in adult life ..	10	1	8	1
6–10 years in adult life	13	1	10	1
11–15 ,, ,, ,, ,, ..	15	2	10	2
16–20 ,, ,, ,, ,, ..	6	1	5	1
Over 20 ,, ,, ,, ,, ..	11	—	11	—
Continued since childhood ..	2	4	—	4
Mode of onset:				
Sudden following:				
Acute bronchitis	7	3	4	3
Pneumonia	9	1	8	1
Other respiratory infections ..	4	—	4	—
Insidious	34	—	25	—
Continued from childhood ..	3	5	3	5
Degree of disability on admission:				
Severe disability	6	1	4	1
Moderate ,, ...	39	4	31	4
Mild ,, ...	12	4	9	4

patients said their symptoms had been present for longer than 10 years, but proportionately more females reported their continuous persistence from childhood into adult life (see Table III). The mode of onset of bronchitis is also shown in Table III, where it will be seen that about 36% of the patients clearly dated the start of their symptoms from an acute respiratory episode, whilst about 12% claimed that their symptoms originated from a respiratory catarrhal illness in childhood. In the remaining patients the beginning of their symptoms was indefinite and apparently insidious in origin. The degree of disability arising from the bronchitis at the time of admission to the trial is shown in Table III, and was assessed according to the severity of the symptoms, their effects on the patient's livelihood and earning capacity, and on the frequency and duration of acute exacerbations of pulmonary infection.

Organization.—The proprietary preparations "terramycin-SF" capsules and "sulphatriad" tablets were used, and will subsequently be referred to as oxytetracycline and a sulphonamide respectively. The individual autogenous *H. influenzae* vaccines under test were prepared by two of us. Dummy capsules and tablets and a non-specific *E. coli* vaccine were also used. The two bacteriologists in the team, who were unaware of the clinical findings, allotted the patients to the treatment groups by random selection after balancing for age and sex. They marked the vaccine with the patient's name only, and the drugs were issued in containers labelled with a code letter, so that neither the patients nor the clinicians knew what treatment was being given. Thus all patients were receiving a brown capsule, a white tablet, and a vaccine, without any difference in appearance between the active substances or their dummy controls. There were therefore eight possible different treatment groups.

Treatment Regimes.—Each patient started treatment with 1.5 g. daily of oxytetracycline or its control, with 1.5 g. of sulphonamide or its control, given in divided doses. This dose was maintained until the sputum became mucoid, when it was reduced to 1 g. daily of each. Further dosage was adjusted on clinical grounds to complete six months' therapy. The vaccine was given at weekly out-patient attendances, starting with a dose of 100 million bacilli and increasing to a maximum of 2,000 million organisms, which was maintained for the rest of the six months' course of treatment. All the patients were taught breathing exercises and encouraged to practise them regularly.

Periodic Reviews.—Every patient was observed for a period following admission to the trial before therapy was started, in order to establish a baseline. Each patient was issued with a calibrated sputum measure and a chart on which to record each day the 24-hour volume of sputum and its colour, the onset and duration of head colds and when they went to the chest, the time lost from work by going to bed as a result of chest infections, and the number of tablets and capsules taken each day, with details of any upset due to the treatment. The patients were seen every month, when their diaries were scrutinized, their sputum was inspected for purulence, and a fresh sputum specimen was collected for bacteriological examination. In addition a record was made of the results of a series of special investigations consisting of body weight, full blood count, E.S.R., vital capacity, chest expansion, and an *x*-ray film of the chest taken synchronously by double exposure in full inspiration and full expiration.

Method of Assessment

The final assessment was made according to both the patient's monthly charts and the physicians' monthly records. The same questions were asked at each visit. Marks were accorded under the following main headings:

1. *Sputum.*—(i) Changes of 24-hour volume. (ii) Changes of purulence using the scale: 0 (clear), + (cloudy), ++ (yellow), +++ (green).

2. *Respiratory Disability.*—(i) Changes in degree of dyspnoea, according to a scale adapted from Sinclair (1955). Grade 0: Normal; capable of heavy work. Grade 1: Breathless on walking one mile or more on the flat; moderate work. Grade 2: Breathless on walking 400 yards to one mile on the flat; moderate or light work. Grade 3: Breathless on walking less than 400 yards on the flat; light or sedentary work. Grade 4: Breathless on the slightest exertion; unable to work but can potter about. (ii) Degree of wheezing, which, in the absence of any objective means of measurement, was assessed on clinical grounds and recorded as nil, slight, moderate, or severe.

3. *Physical Disability.*—(i) Change in frequency and duration of head colds. (ii) Change in frequency and severity of acute chest exacerbations. (iii) Variations in time lost from work or time spent in bed according to experience in previous years obtained at entry to the trial.

4. *General Health.*—(i) The patient's own assessment, month by month and at the end of trial, whether any benefit derived had been marked, moderate, slight, or nil, or whether there had been deterioration. (ii) The results of the special investigations carried out monthly. (iii) The clinicians' assessment of progress during and at the end of the trial. All patients at their last attendance were seen by one of us for their final assessment. Progress was recorded as marked, moderate, slight, or no improvement.

5. *Bacteriology.*—Rough estimates of the number of viable organisms present in the sputum were made according to whether growth of *H. influenzae* and/or pneumococci was predominant, moderate, sparse, or nil. The bacteriological results were then assessed by comparing the monthly alteration with the pre-treatment level in the sputum of (*a*) the presence of *H. influenzae* alone, (*b*) the presence of both *H. influenzae* and the pneumococcus.

Any change in these factors was then recorded using a simple marking system, one point being awarded for one degree of change, two points for two degrees, etc. These marks were entered as plus or minus according to whether improvement or deterioration had taken place. In this way an objective method of summing up all the different factors was achieved.

Results of Treatment

Of the 66 patients who entered the trial, two died—one from congestive heart failure in the second month and one from coronary thrombosis after two months' treatment. Three patients failed to attend after their first visit, three others defaulted after the first review, two after the second,

and one in the fourth month. One patient did not start treatment until late in the winter, and so did not complete the six-months course in time with the other patients. These patients were all excluded from the final assessment. Another patient's monthly sputum cultures were persistently overgrown with *Proteus vulgaris*, thus preventing full bacteriological analysis, and, although the clinical assessment had been made, he also has been excluded from the final results. The results of the trial, therefore, are based on the remaining 53 patients who completed the full course of treatment. Amongst these 53 it was found that the eight treatment groups were reasonably well balanced for age, sex, duration of symptoms, purulence and volume of sputum, and degree of disability.

In the regime used by us most patients taking active drugs were maintained after the first month's treatment on 0.5 g. or less of oxytetracycline and/or sulphonamide twice daily. Toxic effects from this dosage were not a serious problem, and it was not necessary to withdraw any patients from the trial for this reason.

The special investigations carried out monthly did not seem to show any significant alterations, nor did they appear to be related to the progress or deterioration of the patient; they have accordingly been ignored in the final assessment.

Clinical and bacteriological assessments were carried out on the marking system under the main headings as already described, and the final figures expressed as percentages of the total marks possible. From a scattergraph the median percentage level of improvement of all 53 patients was obtained and found to be 37%. Only those patients with marks in excess of this median level were regarded as clinically improved. Table IV shows the number of patients improved clinically when one common drug factor in treatment is considered. Similarly Table V shows the number of patients clinically improved in each of the eight different treatment regimes. From these tables it appears that the results following oxytetracycline therapy are better than those achieved with a sulphonamide, whilst the autogenous vaccine has little, if any, clinical effect.

TABLE IV.—*Number of Patients Clinically Improved According to Common Factor in Treatment*

Common Treatment Factor	Improved	No Real Change	Mean Percentage Improvement
Patients on oxytetracycline ..	21	8	46·4
,, not on ,, ..	7	17	24·5
Patients on sulphonamide ..	17	9	42·6
,, not on ,, ..	11	16	30·6
Patients on autogenous vaccine..	12	16	35·2
,, not on ,, ,,	16	9	38·0

Note.—All patients with marks above the median percentage level of improvement of the whole series (37%) are shown as "improved."

TABLE V.—*Number of Patients Clinically Improved on Each Treatment Regime*

Group	Treatment Regime	Improved	No Real Change
1	Oxytetracycline, sulphonamide, and vaccine	7	1
2	,, and sulphonamide ..	5	2
3	,, and vaccine	4	4
4	,, alone	5	1
5	Sulphonamide and vaccine	1	5
6	,, alone	4	1
7	Vaccine alone	0	6
8	No treatment	2	5

Note.—All patients with marks above the median percentage level of improvement of the whole series (37%) are shown as "improved."

Statistical Analysis

The method of marking used by us permitted the results to be analysed statistically. The mean percentage improvement of the patients receiving any of the three therapeutic substances was determined and compared with the mean percentage improvement of their respective control groups. Thus, all patients receiving one substance were compared with those not receiving it, and these comparisons are shown in Table IV. The value of t was calculated and the probability determined. This is shown in Table VI, which confirms beyond doubt the clinical value of oxytetracycline in the treatment of chronic bronchitis and suggests that a sulphonamide is not without effect, whilst, if additional proof is required, an autogenous *H. influenzae* vaccine is ineffective. Further, it will be seen that there is no correlation between the bacteriological and clinical assessments. Moreover, with one exception, the difference between the mean percentage bacteriological improvement due to the common treatment factors and their controls is negligible.

All patients receiving autogenous vaccines can therefore be included in the corresponding treatment groups without further regard to this factor. In this way three treatment groups can be derived from Table V by combining groups 1 with 2, 3 with 4, and 5 with 6, while groups 7 and 8 can be regarded as one untreated control group. By so doing a sufficiently large number of patients can be obtained for a further similar analysis by comparing the effects of oxytetracycline alone, of a sulphonamide alone, and of these two drugs combined, with the untreated control group, and with each other. The results of this analysis are shown in Table VII, where the clinical efficacy of oxytetracycline is again confirmed. However, no significant difference between the results following sulphonamide therapy and those of the control group is now evident. The discrepancy between the P value for sulphonamide in Table VII and that in Table VI may be due to the inclusion within the sulphonamide series of Table VI of some patients also receiving oxytetracycline.

TABLE VI.—*Statistical Significance of Mean Percentage Improvement According to Common Treatment Factor*

Common Treatment Factor	Clinical Assessment			Bacteriological Assessment					
				H. influenzae			*H. influenzae* and Pneumococcus		
	Mean Percentage Improvement	Difference from Control Mean	P	Mean Percentage Improvement	Difference from Control Mean	P	Mean Percentage Improvement	Difference from Control Mean	P
Oxytetracycline	46·4	21·9 (±4·9)	<0·001	53·5	−12·2	—	44·6	21·3 (±14·4)	—
Sulphonamide	42·6	12·0 (±4·8)	>0·01<0·02	59·5	1·5	—	38·2	4·9 (±12·6)	—
Autogenous vaccine ..	35·2	−2·8	—	57·5	−2·5	—	33·6	0·9	—

TABLE VII.—*Statistical Significance of Mean Percentage Clinical Improvement of Patients on Various Treatment Regimes*

Groups (Derived from Table V)	Treatment Regime	Mean Percentage Improvement	Difference from Control Mean (19·2) (Groups 7 and 8 of Table V)	P	Difference from Sulphonamide Mean (30·9)	P	Difference from Oxytetracycline Mean (41·3)	P
1 and 2	Oxytetracycline and sulphonamide	51·2	32·0 (±5·5)	<0·001	20·3 (±7·9)	0·01	9·9 (±6·6)	—
3 ,, 4	Oxytetracycline ..	41·3	22·1 (±6·4)	<0·001	10·4 (±8·5)	—		
5 ,, 6	Sulphonamide ..	30·9	11·7 (±7·7)	—				

Table VII shows a trend suggesting that a sulphonamide has some effect in chronic bronchitis, that oxytetracycline is more effective, and that the combination of these two drugs is more effective still than either alone.

Discussion

It is generally accepted that infection plays a part in the pathogenesis of chronic bronchitis (*Lancet*, 1954) and is associated with relapse or exacerbation (*Lancet*, 1955). It has also been assumed that purulent sputum is indicative of infection within the bronchial tree, although May (1954) has reported that in some the "purulence" of the sputum is due to eosinophils. The two most commonly implicated organisms in chronic bronchitis are *H. influenzae* and the pneumococcus (Mulder *et al.*, 1952; May, 1953a, 1953b, 1954; Stuart-Harris *et al.*, 1953; Elmes *et al.*, 1953; Knox *et al.*, 1955; Helm *et al.*, 1954, 1956). Both Mulder (1938, 1956) and May (1954) report predominance of *H. influenzae* in about 80–90% of their cases with purulent sputum, whilst in bronchitis with mucoid sputum May (1954) has reported finding 13% with *H. influenzae* and about the same number with pneumococci in first sputum specimens. Helm *et al.* (1954) go further and state: "The fact that the presence or absence of pathogenic bacteria, especially *H. influenzae*, closely paralleled the purulence of the sputum is strong evidence that these are indeed the pathogens in the infections studied."

Although it is confirmed by us that in untreated bronchitic patients the incidence of *H. influenzae* varies considerably with the purulence of the sputum, we observed an incidence of 60–70% in purulent and 30–40% in mucoid specimens. On the other hand, that of the pneumococcus was constant irrespective of the degree of purulence. These results are based on cultural studies, but it is possible to detect *H. influenzae* microscopically in Gram-stained films in about 80% of specimens yielding the organism on culture. This examination should, in our view, be regarded as no more than complementary to cultural methods.

We are in general agreement with most other workers that epidemiologically *H. influenzae* and the pneumococcus are the commonest organisms found in chronic bronchitis. However, during the course of the investigation and at the end of the trial no significant change in the bacterial flora was noted in spite of changes in the clinical picture. It would appear that although the infection with *H. influenzae* or the pneumococcus was not eradicated, clinical improvement with loss of purulence in the sputum was obtained by the use of antibacterial agents. The persistence of *H. influenzae* in the sputum, in spite of more or less marked clinical improvement during treatment with one of the tetracyclines, is also evident in the reports of Elmes *et al.* (1953) and Helm *et al.* (1956).

It therefore remains to consider this discrepancy. It may be that the value of the antibacterial drugs lies in the prevention of superinfection of the bronchial tree from an infected upper respiratory tract, rather than by direct action upon the established bacterial flora of the bronchi. That this may be so can be inferred from the effect of oxytetracycline on the incidence of *H. influenzae* together with the pneumococcus, as shown in Table VI, where the difference in the mean percentage improvement from the mean of the control is far greater than any of the other differences in the bacteriological assessment. It may also be that the dosages employed were too small to effect complete elimination of the "potentially pathogenic" bacteria from the bronchial tree. If, however, much larger doses had been given, the side-effects would probably have interfered seriously with the working capacity of out-patients. Furthermore, a monthly bacteriological examination of the sputum of bronchitic patients is not necessarily representative of its usual day-to-day flora.

The assumption that the maintenance of the symptom complex of chronic bronchitis is due to *H. influenzae* or the pneumoccoccus has not, therefore, been confirmed or disproved under the conditions of this trial. Of the treatment regimes tested, oxytetracycline stood out as an effective single therapeutic agent, and it appeared that its clinical action was enhanced by the addition of sulphonamide. The latter by itself was not entirely without effect, whereas the autogenous *H. influenzae* vaccine was apparently quite valueless.

It has been remarked how on occasion it is difficult to demonstrate the findings in a clinical trial so that the factual presentation of the overall results reflects the dramatic improvement brought about in some patients (May and Oswald, 1956). We have devised a simple system of assessment, adding or subtracting marks for improvement or deterioration, as compared with the patient's pre-treatment condition, and the figures obtained can be analysed statistically. By this method we have shown that our results following treatment with oxytetracycline are highly significant.

One of the main criticisms levelled at long-term therapy with the tetracycline group of drugs is that of expense. We are in general agreement with May and Oswald (1956) that the cost to the National Health Service of about £45 for six months' treatment—or 23s. a week per patient in our regime reported here—can be an economy if it will reduce the drain on national resources in other directions. Such a drain may derive from the payment of National Insurance benefit or from the use of a hospital bed for two weeks or more each winter. Additionally, loss of productivity to the community and of earning capacity to the patient himself may well be prevented. The second criticism is that drug-resistant organisms may be produced and spread. In the few observations on the development of resistance to oxytetracycline of *H. influenzae* that it was possible to make at the beginning and the end of this trial, either no increase in resistance to oxytetracycline or, at most, only a four-fold increase was found. Similarly, the emergence of oxytetracycline-resistant coagulase-positive staphylococci in the sputum did not constitute a major problem.

Summary

A controlled trial employing a double blind technique with continuous therapy for six months in 53 patients with chronic bronchitis using oxytetracycline, a sulphonamide, and an autogenous *H. influenzae* vaccine is reported.

Continuous administration of oxytetracycline is shown to be an effective measure in the treatment of chronic bronchitis. The improvement arising therefrom is considerable, and the results are enhanced by the addition of a sulphonamide.

The use of a sulphonamide alone is of little clinical value, whilst an autogenous *H. influenzae* vaccine as employed by us is apparently valueless and has no place in the management of chronic bronchitis.

A method of assessment is described for factual demonstration of the degree of clinical improvement found in therapeutic trials where objective methods of measurement are few or difficult to achieve.

In pre-treatment sputum specimens *H. influenzae* is present, with pneumococci, as the predominant "potential pathogen" in chronic bronchitis. The incidence of *H. influenzae* is twice as great in purulent as in mucoid sputa, whilst that of the pneumococcus is unrelated to sputum purulence. No significant change could be detected in the "potentially pathogenic" flora of bronchitic sputa, following clinically effective antibacterial drug treatment.

Some possible reasons for this discrepancy are discussed.

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THROMBOSIS OF INTERNAL CAROTID ARTERY TREATED BY ARTERIAL SURGERY

BY

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Occlusion of the internal carotid artery is now recognized as one of the more common causes of cerebrovascular disease (Adams and Vander Eecken, 1953; Fisher, 1954). The occlusion is almost invariably due to atherosclerosis, and the arterial lesion is similar to atherosclerotic occlusions in other major arteries of the body. Many such occlusions of the aorta and peripheral arteries have been effectively treated by surgical operations designed to restore a normal blood flow. This paper describes the application of these surgical procedures to atherosclerotic occlusions involving the cervical portions of the carotid arteries. Particular attention is paid to the technical feasibility, operative risk, and early postoperative course of carotid surgery. A detailed clinical evaluation of the long-term prognosis after surgery will be the subject of a later article.

Pathogenesis

Occlusion of the internal carotid artery usually begins with the formation of an atheromatous plaque just distal to the bifurcation of the common carotid artery. As the plaque enlarges, the arterial lumen is narrowed and the blood flow is reduced. This narrowing of the lumen may be increased by haemorrhage under the plaque or by the formation of a mural thrombus. Fragments of clot may break away and form cerebral emboli, or the thrombus may extend and completely occlude the vessel. The end-result of these various processes is to decrease or abolish the blood flow through the affected vessel. This deficit in flow causes symptoms of cerebral ischaemia if (1) the cerebral collateral circulation is inadequate, (2) there is a fall in systemic blood pressure, or (3) the patient becomes anaemic or anoxic. Whether some of these processes also interfere with the cerebral circulation by producing intracerebral vasospasm has been a matter of dispute for many years.

Three points are worth emphasizing. First, the collateral circulation is of paramount importance in determining the clinical effect of any carotid occlusion. Second, a partial occlusion can produce symptoms indistinguishable from a complete occlusion if the collateral circulation is inadequate. Third, the unpredictable nature of these pathological processes leads to great variation in the clinical course of the disease.

Clinical Features

Like atherosclerotic occlusions of other vessels, occlusions of the internal carotid artery usually occur in patients over 40 years of age and are much more common in men than in women. The commonest symptom is unilateral muscle weakness, usually associated with a disturbance of speech if the dominant hemisphere is affected. Other frequent complaints are headache and unilateral sensory disorders, particularly hypaesthesia. Transient blindness of the eye on the side of the occlusion is a characteristic sign when present, and homonymous hemianopsia is occasionally seen. Mental or emotional disorders are not uncommon.

There is considerable variation in the clinical picture, and particularly in the mode of onset. Symptoms may be mild and intermittent in character, or they may be slowly progressive to complete hemiplegia. Occasionally they may be sudden, severe, and catastrophic in onset. Some of the patients may be entirely asymptomatic, depending on the state of the collateral circulation.

There are no pathognomonic physical findings, although a decreased retinal blood pressure on the side of the occlusion is most suggestive. This can be measured directly (Thomas and Petrohelos, 1953) or indirectly by noting the ease of retinal blanching on digital pressure (Denny-Brown, 1951, 1952). Palpation of the carotid pulsation is an unreliable physical sign.

Carotid angiography is an extremely useful diagnostic procedure which yields specific information about the patency of the carotid arterial system. In many cases it is the only way in which the diagnosis can be made with assurance. Although others have emphasized its risk, there has been only one mild exacerbation of symptoms in this series after arteriography. No other investigative procedures have proved of specific value, except by excluding other disease.

For a more detailed exposition of the clinical features of initial carotid occlusions the reader is referred elsewhere (Hunt, 1914; Johnson and Walker, 1951; Behrman, 1954; Shapiro and Peyton, 1954; Millikan and Siekert, 1955).

Risks of Carotid Arterial Surgery

In discussing the treatment of internal carotid thrombosis some authors have emphasized the potential dangers associated with direct surgery on the carotid arteries. The chief fear has always been that clamping the carotid arteries for several minutes might cause ischaemic cerebral necrosis, particularly if the cortex had a poor blood supply prior to the operation. In the case of a complete internal carotid occlusion, clamping the common carotid artery temporarily deprives the cortex of the collateral circulation carried by the external carotid artery, and in the case of a partial occlusion there is the additional loss of whatever flow was passing through the internal carotid artery. In addition, the resulting vascular stasis is a theoretical opportunity for thrombosis to occur. Another potential cause of cerebral ischaemia is hypotension due to anaesthetic agents or to haemorrhage during the surgical procedure itself. A further possible complication is the production of an embolus from the operative site, and a final theoretical danger is the production of intracerebral vasospasm secondary to the operative trauma.