THE TREATMENT OF EXACERBATIONS OF CHRONIC BRONCHITIS IN GENERAL PRACTICE

A comparison between Oxytetracycline and Oral Phenoxymethyl Penicillin

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In a large urban practice in north Liverpool, where chronic bronchitis is a major cause of ill-health, it was decided to carry out a 'double-blind' trial to compare the relative efficacy of oxytetracycline and oral phenoxymethyl penicillin in the treatment of acute exacerbations of chronic bronchitis.

Method

Chronic bronchitic patients complaining of increase in cough and dyspnoea were given the trial tablets and told to take one four times a day—one, first thing in the morning, one, last thing at night and the other two tablets to be spaced as evenly as possible between. The two types of tablet were enteric-coated and identical in appearance and the doctor treating the patient did not know which antibiotic was being given. The tablets in one set contained 125 mg. of phenoxymethyl penicillin and in the otheı 250 mg. of oxytetracycline.

Not all cases of acute exacerbation of chronic bronchitis occurring in the practice during the period of the trial were included. It was thought ethically unjustifiable to include anyone dangerously ill; other patients were regarded as unsuitable; and a few patients given trial tablets had to be excluded for various reasons. When the patient failed to improve or deteriorated the tablets were usually replaced by another antibiotic—generally chloramphenicol. Antispasmodics and other drugs were given as indicated irrespective of the trial.

Three patients who were given trial tablets were excluded because it soon became evident that the apparent exacerbation of the chronic bronchitis was due to a bronchial carcinoma. This incidental

observation underlines the importance of x-raying patients apparently suffering from exacerbations of chronic bronchitis as bronchitics are especially liable to develop carcinoma of the lung. A chest x ray is particularly indicated if the symptoms are in the least atypical, for example, including pleurisy or haemoptysis.

To facilitate analysis, cases were roughly classed as mild, moderate, or severe. Mild cases attended the surgery or could easily have done so; moderate cases did not require more than two days in bed; severe cases required more than two days in bed.

Results

Thirty patients were given phenoxymethyl penicillin: in 15 (50%) the response was unsatisfactory, in 12 (40%) satisfactory and in 3 (10%) good.

Of 29 patients given oxytetracycline 11 (38%) responded unsatisfactorily; 10 (34.5%) gave a satisfactory response and 8 (28%) a good response.

TABLE I

RESPONSE
PATIENTS GIVEN PENICILLIN

	Unsatisfactory		*Satisfactory*		*Good*		*Total*
	No.	*Per-centage*	*No.*	*Per-centage*	*No.*	*Per-centage*	*No.*
Mild ..	6	67	3	33	0	0	9
Moderate	5	38.5	7	54	1	8	13
Severe ..	4	50	2	25	2	25	8
All Patients	15	50	12	40	3	10	30

RESPONSE
PATIENTS GIVEN OXYTETRACYCLINE

	Unsatisfactory		*Satisfactory*		*Good*		*Total*
	No.	*Per-centage*	*No.*	*Per-centage*	*No.*	*Per-centage*	*No.*
Mild ..	7	47	5	33	3	20	15
Moderate	3	25	5	42	4	33	12
Severe ..	1	50	0	0	1	50	2
All Patients	11	38	10	34.5	8	28	29

These results suggest that oxytetracycline is superior to phenoxymethyl penicillin. But as can be seen from table I, the best results in both groups were observed in severe exacerbations of bronchitis and, by chance, there was a larger proportion of such cases in the penicillin treated series. If a correction is made for this the difference between the two groups becomes even greater and can be regarded as of statistical significance.

The two groups of patients were similar with regard to sex ratio, average age, and severity of the basic bronchitis.

The average number of days taken for the patient's chest to return to normal in the cases treated with oxytetracycline was 5.92 (average of 13 cases; standard deviation 1.49). The corresponding time for patients treated with penicillin was 6.52 days (average of 15 cases; standard deviation 2.8). The difference of 0.6 days in favour of oxytetracycline is not great enough to be of statistical significance as the standard error of difference is 0.8. But in any case no great difference in these figures can be expected as the patients who failed to respond to treatment did not have the time taken to return to normal recorded.

In six patients receiving penicillin, but in only four receiving oxytetracycline, the trial tablets had to be replaced by another antibiotic. The majority of these patients were given chloramphenicol; but it so happened that three patients given penicillin in the trial were changed on to terramycin SF capsules. Two of these progressed satisfactorily on the new treatment, but the other, although she was slowly improving on terramycin, was eventually given chloramphenicol as it was thought that she may have already had oxytetracycline during the trial. One of the four patients mentioned above who was on the oxytetracycline trial tablets was given terramycin SF instead because, although the chest was improving, he developed a urinary infection and it was thought that if the unknown tablets were penicillin they would not benefit this additional complaint.

Six patients received both types of tablet during the trial. Five of these responded better in the exacerbation treated with oxytetracyline, whereas in the remaining patient both drugs seemed to be equally effective.

With regard to side effects, one patient on oxytetracycline complained of nausea, one had ' burning of the mouth ', and a third had cracking of the lips, a sore mouth due to glossitis, and perianal soreness. However, this last patient had been unable to swallow the tablets whole and had therefore broken them up. Of the patients given penicillin, one complained of nausea and another of precordial pain.

Discussion and Conclusions

Although in general practice we lack the more refined techniques and facilities for careful observation that are available to our hospital colleagues, we believe that the assessment of the patient's response by the overall impression of the doctor treating the patient provides a reliable test of the value of treatment in exacerbations of chronic bronchitis, provided that subjective errors are eliminated by the use of a ' double-blind ' technique.

An investigation of antibiotic treatment in chronic bronchitis in general practice is of particular value because results of hospital trials may not necessarily be applicable to patients seen by the general practitioner. The type of patient seen in hospital is clearly different; moreover, antibiotic resistance is a far more serious problem in hospital patients.

The general practitioner must decide whether or not to give antibiotics in mild flare-ups of chronic bronchitis; and if so, which drug to give. The therapeutic problem is further confused by economic considerations.

In this trial the patients receiving oxytetracycline responded better than those treated with oral phenoxymethyl penicillin. Those on oxytetracycline returned to normal quicker and had to be changed on to another antibiotic less frequently; and five of the six patients receiving both drugs fared better on oxytetracycline. All our results are consistent in suggesting that oxytetracycline is superior to oral penicillin V in the dosages employed.

Although Elmes *et al.* (1957) using a ' double-blind ' technique on 67 cases of chronic bronchitis showed that exacerbations were shortened by giving one capsule of terramycin four times daily for five days at the onset of each exacerbation, we have been tempted, on grounds of economy, to give oral penicillin V to patients with mild flare-ups of bronchitis. The results of Frances and Spicer (1960) provided some justification for this approach. Studying 226 cases of chronic bronchitis in a ' double-blind ' trial they found that continuous administration of either penicillin V 312 mg. b.d. or tetracycline 250 mg. b.d. approximately halved the number of days lost from work although neither drug reduced the number of attacks. However, had a higher dose of tetracycline been employed, this drug may have proved more effective than penicillin V. On the other hand, in our own trial a higher dose of penicillin may possibly have given better results.

Penicillin given intramuscularly is generally accepted as being much more reliable than oral penicillin. Douglas *et al.* (1957) recommended treating exacerbations of chronic bronchitis by

6-hourly injections of penicillin. Giving 1—2 mega-units of penicillin daily they found that the sputum was rendered non-purulent in 53 per cent of cases; chloramphenicol was successful in 78 per cent of penicillin failures and oxytetracycline in 39 per cent. The figures for penicillin are, of course, not comparable with those for the broad-spectrum antibiotics. The danger of blood dyscrasias with chloramphenicol has probably been over stressed; nevertheless, it must be remembered that patients with chronic bronchitis frequently need repeated courses of antibiotics. At least ten chronic bronchitics in this practice required more than one course of antibiotics for acute exacerbations during this winter alone. The additive effects from repeated courses of chloramphenicol if it were used as a routine treatment for chronic bronchitis exacerbations would probably greatly increase the risk of toxic effects.

It is usually difficult to give adequate doses of intramuscular penicillin at properly spaced intervals in general practice. However, we often give crystamycin (which contains 500,000 U. crystalline penicillin and 1G. streptomycin in each ampoule) once, twice or even three times daily to patients with acute exacerabtions of chronic bronchitis. We find this form of treatment particularly valuable when the patient is vomiting, or, when from our knowledge of the patient, we think he cannot be relied upon to take oral therapy conscientiously.

In considering the financial aspects, the cost of the extra visits by the doctor and district nurse should be assessed, in addition to the cost of the drugs, when injections are given. We hoped that in mild exacerbations oral penicillin V might be adequate but our trial has shown that even in mild cases oxytetracycline is superior.

If the sputum is non-purulent judging by macroscopic appearances we have been tempted to withhold antibiotics. But in this trial we found that there was no great difference in the results whether the sputum was purulent or not. However we frequently relied on the patient's description of his sputum for our data and this often proved misleading.

Tetracyclines may cause soreness of the tongue, nausea, vomiting, diarrhoea, proctitis, and pruritis ani. The incidence of recorded side effects on tetracycline medication varies. During long-term prophylactic therapy 60 per cent of the patients of Moyes and Kershaw (1957) complained of diarrhoea whilst about half of the patients of May and Oswald (1956) had this symptom. Moyes and Kershaw specifically warned their patients about diarrhoea and even 39 per cent of the controls who were receiving aminophylline complained of diarrhoea. May *et al.* (1956) used both tetracycline and oxytetracycline and thought that the former was less prone to

cause diarrhoea. Helm *et al.* (1954) mention looseness in about half their cases but only one out of 21 patients in the series of Buchanan *et al.* (1958) had diarrhoea. In the last two trials vitamin B was given.

We did not look for side effects but only recorded those mentioned spontaneously by the patient. Doubtless, if we had enquired more closely we would have found more patients with loose motions.

The incidence of side effects can be reduced by limiting the dose of tetracycline to 1G. daily, by encouraging the patient to take the tablets with milk, and by the simultaneous administration of vitamin B. The bronchitic probably already has antispasmodic tablets, a spray, and a cough mixture besides an antibiotic, so the incorporation of vitamin B in capsules containing a broad-spectrum antibiotic (as in terramycin SF) has considerable value in domiciliary practice.

Fulminating staphylococcal enteritis is rare in domiciliary practice and the possibility of it arising does not justify the avoidance of tetracyclines in the treatment of bronchitis exacerbations. We have never seen a patient with staphylococcal enteritis due to treatment with broad-spectrum antibiotics but we have seen many patients die of chronic bronchitis.

Apart from humanitarian considerations, we believe it is wrong to consider the cost of antibiotic therapy in isolation. Account must also be taken of the probable economic advantages of antibiotic treatment resulting from a contingent reduction of lost working time and of hospital admissions. These aspects have been dealt with elsewhere (Simpson; Buchanan *et al.* 1958; Edwards *et al.* 1957).

However, a consideration which appears to be generally overlooked in studying this problem is that chronic bronchitis is a progressive disease and that by effective treatment of each exacerbation the patient derives not only the obvious benefit of more rapid recovery from each acute episode, but also, over a period of years the result may be that deterioration in the patient's respiratory condition may be slowed down to such a degree that the day of premature retirement or death may be postponed for a few more winters.

Prompt treatment of every flare-up of bronchitis, however slight, is much less costly than continuous antibiotic therapy. We believe that tetracycline or oxytetracycline 250 mg. q.i.d. should be given to patients with exacerbations of chronic bronchitis in general practice —even if the attack is mild. If this fails the patient should be given a penicillin-streptomycin combination by injection of chloramphenicol.

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REFERENCES

Buchanan, J.; Buchanan, W. W.; Melrose, A. G.; McGuiness, J. B.; Price, A.V. (1958) *Lancet*, **2**, 719.
Douglas, A. C.; Summer, A. R.; Marks, B. L.; Grant, W. B. (1957) *Lancet*, **2**, 215.
Edwards, G.; Buckley, A. R.; Fear, E. C.; Williamson, G. M.; Zinnemann, K. (1957) *Brit. med. J.* **2**, 259.
Elmes, P. C.; Fletcher, C. M.; Dutton, A. A. C. *Brit. med. J.* (1957), **2**, 1272.
Francis, R. S. and Spicer, C. C. (1960) *Brit. med. J.* **1**, 297.
Helm, W. H.; May, J. R.; Livingstone, J. L. (1954) *Lancet*, **2**, 630.
May, J. R. and Oswald, N. C. (1956) *Lancet*, **2**, 814.
Moyes, E. N. and Kershaw, R. A. (1957) *Lancet*, **2**, 1187.
Simpson, W. A. (1958) Special Issue of North-west England Faculty Journal, The College of General Practitioners, p. 23.

The Host

" For host, or *cough*, and lung disease; take swails apple, and brimstone, and frankinscense, of all equally much, mingle with wax, lay on a hot stone, let *the man* swallow the reek through a horn, and afterwards eat three pieces of old lard or of butter, and sip *this* with cream. For lung disease; take betony, and marrubium, agrimony, wormwood, fel terrae *or centaury*, rue, oak rind, sweet gale; boil them in water, boil off a third part of the water, remove the worts; let *the man* drink in the morning of *this* warm a cup full, let him eat therewith three pieces of the brewit that is here afterwards mentioned.

" 2. Work *thus* a brewit for lung disease; take betony, and marrubium, wormwood, hind heal, the lower part of wen wort, lupin, helenium, radish, everthroat, fieldmore; pound all thoroughly well, and boil in butter, and wring through a cloth; shed on the decoction barley meal, shake it in a dish without fire till it be as thick as brewit; let him eat three pieces, with the drink of the warm *liquor*.

" 3. Again, boil in honey alone, marrubium, add a little barley meal, let *the man* eat at night fasting; and when thou givest him drink or brewit, give it him hot; and make the man rest after an hour, by day, on the right side, and have the arm extended."

Cocakyne's *Leechdoms, Wortcunning and Starcraft of Early England.*