The mortality of sea-snake bite appears to be low, but fear of them is universal and a potent source of worry. Effective treatment, including a polyspecific antivenene, would be a great boon to Asian fishing folk.

We wish to thank the State Surgeon, Kedah and Perlis, the Chief Medical Officer, Penang and Province Wellesley, the Director of Fisheries, Federation of Malaya, and many members of their departments for helpful co-operation in the survey; and Mr. C. J. Sundram for the maps.

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PROPHYLACTIC USE OF OXYTETRACYCLINE FOR EXACERBATIONS OF CHRONIC BRONCHITIS

BY

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Investigations both here (Elmes *et al.*, 1953) and elsewhere (Mulder *et al.*, 1952; Stuart-Harris *et al.*, 1952; May, 1953) have shown that exacerbations of chronic bronchitis are usually associated with proliferation in the sputum of one or more of a few species of bacteria which have become recognized as pathogens. Of these, *Haemophilus influenzae* is the organism most often found. *Streptococcus pneumoniae* is the next most frequent, while beta-haemolytic streptococci, *Staphylococcus pyogenes*, and *Klebsiella friedländeri* are occasionally found. Exacerbations are usually sequels of upper or lower respiratory infections by a virus or follow exposure to cold or to smoky fog. Subsequent bacterial invasion is thought to prolong exacerbations, to increase their severity, and to play an important part in causing permanent damage to the lungs (Reid, 1954).

Since wide-spectrum antibacterial drugs are effective against these organisms they should be able, given early enough, to prevent bacterial multiplication and its consequences. There is evidence (McVay and Sprunt, 1953; Helm *et al.*, 1956; May and Oswald, 1956; Edwards *et al.*, 1957) that the tetracycline group of drugs given continuously over long periods may control persistent bronchial infection and reduce the frequency and severity of acute exacerbations. These drugs are, however, too expensive for continuous use among the vast numbers of patients with chronic bronchitis in this country, most of whom have only one or occasionally two exacerbations each winter, between which they are able to continue at work. The trial described in this paper was to determine whether a short course of oxytetracycline given at the first sign of the onset of an exacerbation could reduce its duration, and thus provide an economic method of reducing loss of working time.

Clinical Method

The criteria for selection of patients for the trial were that they should be under the age of 65, be in regular employment, have had a productive winter cough for not less than three years, during which time they had had at least two illnesses with purulent sputum, causing loss of time from work. The patients had no other disabling disease. Twenty-one of them were attending a bronchitis clinic; other cases were referred by local general practitioners at our request. Of 125 cases so referred, 67 were selected (16 failed to attend and 42 were unsuitable in one way or another). Eighty-eight patients were therefore admitted to the trial at various times between November, 1954, and November, 1955. Special clinics were held on Saturday mornings to reduce loss of time from work. Each patient was seen at approximately monthly intervals in the winter and at two- to three-monthly intervals in the summer.

It was decided to make the trial a "double blind," by allocating oxytetracycline tablets to some patients and indistinguishable dummy tablets (containing lactose) to the others, neither doctors nor patients knowing which was which. This was achieved by allocating oxytetracycline and control tablets in equal proportions to the serial numbers 1 to 99, using Fisher and Yates's (1948) table of random numbers. The patients were each given a serial number in the order in which they entered the trial and were prescribed tablets of the same number. The key list of numbers was held by the hospital's chief pharmacist, who dispensed 28 oxytetracycline or control tablets according to the serial number of each patient. Table I shows the distribution of patients in the oxytetracycline and control groups according to age, sex, degree of respiratory disability, and amount of time lost from work during the 18 months preceding their admission to the trial. The two groups were similar except for a small preponderance of females in the control group.

TABLE I.—*Comparison between the Oxytetracycline and Control Groups before the Trial*

	Oxytetracycline	Control
Males	37	37
Females	5	9
Mean age and range	54·6 (31–65)	53·5 (28–65)
Mean dyspnoea grade and range*	2·289 (1–4)	2·283 (1–4)
Time lost in days during 18 months before trial	76·6 (0–560)	71·24 (0–547)

* Grades ranging from 1 (normal) to 5 (breathless on least movement) (Fletcher, 1952). The figure used was the grade of dyspnoea noted by the patient when he was feeling well.

On their first attendance a full clinical history was taken from the patients and the results of examination of their cardiovascular and respiratory systems were recorded. They were then given the following instructions:

"If you have a head cold, increased difficulty in breathing, increased cough and phlegm, or any other chest symptoms which you think may indicate the beginning of a chest illness, take one tablet after breakfast, dinner, tea, and supper—that is, four tablets in the day. Continue with the tablets for *at least five days at first*. If you are then quite well again, stop the tablets. If not, continue taking four daily until they are finished. If you develop looseness of the bowels or diarrhoea while you are taking the tablets take three tablespoonfuls of the medicine† daily. If diarrhoea continues stop the tablets. If, in spite of taking the tablets, your chest gets worse, consult your doctor. Please put a specimen of your phlegm into one of the containers: (*a*) before you start taking the tablets, (*b*) when you have been taking the tablets for five days, (*c*) five days after you stop the tablets. The specimens should be brought to the bacteriology department of the hospital on the same day either by yourself or a friend. Please report to the clinic as soon as you are well again."

On subsequent visits to the clinic details of the onset, symptoms, and duration of any chest illnesses were recorded, further supplies of tablets were given, and further clinical examinations were performed if necessary. Many patients

†Chalk and opium mixture (*N.F.*).

were given additional routine treatment and advice. The majority received antispasmodic drugs, usually ephedrine or choline theophyllinate by mouth, with or without a hand inhaler, using either 1% isoprenaline or the combined spray of adrenaline and atropine (*N.F.*). On a few occasions patients who continued to produce purulent sputum after a week's course of "tablets" were given a course of an antibacterial drug (usually tetracycline) to which the bacteria in their sputum were sensitive.

Bacteriological Method

The sputa were examined in most cases within six hours of expectoration. Gram-stained films were made from the purulent part of the sputum. The whole specimen (or 5 ml. when the total volume was greater than this) was then homogenized with an equal volume of saline and some glass beads for 10 minutes on a mechanical shaker. (This method was checked against multiple sampling of unhomogenized sputum by Dr. Mary Ralston and found to be efficient.) Cultures were made on whole heated blood-agar plates containing 0.2 unit of penicillin per ml. of agar, which is selective for *H. influenzae*, and on blood-agar plates having a central ditch filled with agar containing an initial concentration of 25 μg. of oxytetracycline per ml. The plates were incubated at 37° C. for 18–24 hours. The sensitivity of the organisms to tetracycline was related to the Oxford staphylococcus.

Clinical Results

During the period of observation the 88 patients had a total of 146 exacerbations. Table II gives the distribution of these exacerbations between those who took oxytetracycline and control tablets for at least five days and those who took tablets for shorter periods or not at all. The patients did not always take the tablets at the onset of each exacerbation. Sometimes the initial symptoms were unusual, some patients mislaid the tablets, some first went to see their general practitioner, who gave them some other treatment, and some had no confidence in the tablets. Side-effects were not important in deterring patients from taking tablets. Twenty-two had mild diarrhoea or loose stools, these being easily controlled by chalk and opium mixture; four of these cases were receiving control tablets. One case receiving oxytetracycline had severe diarrhoea, which prolonged his illness. Mild and brief anal pruritus was experienced by six patients taking oxytetracycline.

TABLE II.—*Number of Exacerbations and Number for which Tablets were Taken in Oxytetracycline and Control Groups*

	Oxytetracycline	Control
No. of patients	42	46
,, with exacerbations	26	33
,, without exacerbations	16	13
Total exacerbations	71	75
Tablets taken at least 5 days	57	56
,, ,, less than 5 days or not at all	14	19

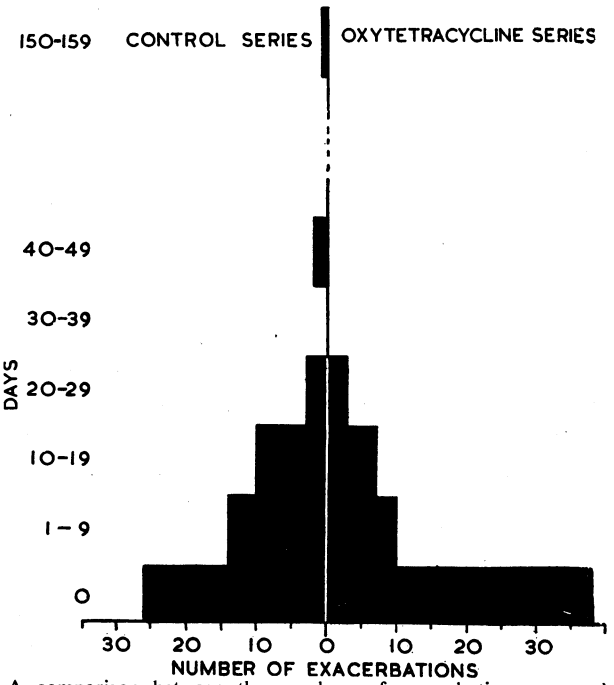
TABLE III.—*Severity of Exacerbations*

	Oxytetracycline		Control		Tablets Not Taken or For Less than 5 Days	
	Days Ill (a)	Days Off Work (b)	Days Ill (c)	Days Off Work (d)	Days Ill (e)	Days Off Work (f)
Total duration	666	242	944	528	853	752
Mean per exacerbation	11·68	4·25	16·86	9·43	25·848	22·79
Range	3–48	0–29	2–163	0–155	4–136	0–136
Variance of mean	1·38	0·94	9·66	8·80	20·8	22·3

Significance of differences between means (t test):

Comparison	P	Comparison	P
(a) v. (c) unlogged	0·2–0·1	(a) v. (e)	0·01–0·001
(a) v. (c) logged	0·3–0·2	(b) v. (f)	<0·001
(b) v. (d) unlogged	0·1	(c) v. (e)	0·2–0·1
(b) v. (d) logged	0·1–0·05	(d) v. (f)	0·02–0·01

The severity of the exacerbations was assessed by the number of days off work and by the number of days during which the patient had respiratory symptoms, especially cough and sputum, of greater severity than usual. The severity of the exacerbations for which oxytetracycline, control, or no tablets were taken is shown in Table III. The patients who took oxytetracycline tablets were on the average ill for two-thirds as long as those who took control tablets and had half the number of days off work. However, individual exacerbations varied considerably in length, so that this difference may have occurred by chance. As is seen from the histogram, there are outlying cases in the control group which have an undue influence on the mean. The chief difference between the groups is the higher proportion of exacerbations with no loss of time from work in the group given oxytetracycline. The effect of the outlying cases can be partially eliminated by using a logarithmic time scale, but this makes no material difference to the statistical results. None of the differences between control and treated groups are significant at a level of 1 in 20.



A comparison between the numbers of exacerbations grouped according to the length of time off in days.

As the general practitioners were free to give any treatment they thought fit to those whose illnesses were not responding to our tablets, they might have shortened the illnesses with antibacterial drugs; in fact, we ourselves sometimes gave tetracycline to such patients. Some supplementary treatment was given for 4 out of the 57 exacerbations treated with oxytetracycline and to 9 out of 56 receiving control tablets. One would expect patients on control tablets to require supplementary treatment more frequently, but this difference is not significant ($P=0.2$ to 0.1 on χ^2 test). When the exacerbations for which supplementary treatment was given are omitted there is still no significant difference between the length of the exacerbations in the oxytetracycline and control groups ($P=0.2$ to 0.1).

We were surprised to find that exacerbations treated by either kind of tablet were shorter than those for which no tablets were taken (Table III). The exacerbations for which oxytetracycline was taken were significantly shorter and also caused less time off work than those which were untreated. Exacerbations treated with control tablets were of intermediate duration, and the difference between them and the untreated was also significant on the basis of days off work.

We thought that a possible explanation might be that the untreated exacerbations had a more serious pathogenesis, with an onset unassociated with obvious respiratory symptoms, so that the patients did not take the tablets promptly. The untreated exacerbations were therefore divided into those for which no tablets were taken because the onset was unusual (14) and those with a typical onset but for which tablets were not taken for some irrelevant reason such as their being mislaid or the patient being away from home at the time (19). The mean duration of illness in these two groups did not differ significantly, being respectively 33.7 and 29.35 days ill and 21 and 17 days off work. The type of onset did not therefore explain the difference in length of treated and untreated illnesses.

We sought evidence that the mere fact of attending the clinic and being given tablets and other treatment had affected our patients' loss of time from work.

We compared the loss of time from work during the winter of 1953–4 with the loss during the winter of 1955–6 in the group of patients who were under continuous observation and treatment during the second winter. This group is relatively small (40 patients), because only those making regular claims for sick benefit were included, and some of our patients were self-employed or received full pay for short periods of absence from work. Comparison between the sickness absences during 1953–4 which the patient reported when first interviewed, and the absences recorded in our notes during observation and treatment in 1955–6 (Table IV) shows that although there are the same number of illnesses in each winter the illnesses are half as long. This is a statistically significant difference which might have been attributed to treatment.

Because of the possibility that the patients had exaggerated their past sickness absences we obtained figures for sickness absence for which these patients had received benefit from the Ministry of Pensions and National Insurance. These figures differ from ours in two respects (Table IV).

TABLE IV —*Comparison Between Time Lost from Work in the Winter Before the Trial with that Lost During the Second Winter of the Trial by Patients Making Regular Claims for Sickness Benefit*

		Sept., 1953, to April, 1954	Sept., 1955, to April, 1956
Our figures	No. of illnesses	41	41
	Total days off	1,786	807
	Mean length of illness (days)	43·56	19·8*
M. of P. and N.I. figures	No. of illnesses	48	44
	Total days off	1,580	1,125
	Mean length of illness (days)	32·92	25·56†

* P=0·05 to 0·02 (t test). † P=0·5 to 0·4.

Firstly, the patients slightly overestimated their past loss of time from work, but attributed it to fewer illnesses. Secondly, during the period of observation they admitted to less absence from work than they claimed from the Ministry. These differences are statistically significant and not entirely accounted for by the inclusion in the Ministry's figures of respiratory illnesses which we had not considered due to exacerbations of bronchitis. The Ministry's figures show a shortening of the illnesses during the winter of observation by 22%, which is not statistically significant.

We cannot use the Ministry's figures for a comparison between treated and control groups because it happens that the control patients for whom figures were available had a much higher past sickness rate.

Bacteriological Results

Most of the sputa produced by patients on entering the trial were mucoid in appearance, but nevertheless a high proportion yielded *H. influenzae* (63%) (Table V). May (1954) found that 13% of mucoid and 80% of purulent sputa yielded *H. influenzae* in bronchitis. In addition 13% of the initial sputa in our series yielded *Str. pneumoniae*. No other pathogens were found.

Although a slightly higher proportion of the initial specimens from the patients who were to receive oxytetracycline yielded *H. influenzae*, the proportion in specimens obtained at the onset of the exacerbations (" pre-treatment specimens ") is identical in the two groups (74%). Treatment with oxytetracycline reduced by two-thirds the proportion of specimens yielding *H. influenzae*, and this effect was still apparent five days after the treatment ended. This change is statisfically significant, whereas the less marked changes in the specimens from the control group are not.

The expected increase in *Str. pneumoniae* with exacerbations was found. The figures for the control group are compatible with the way in which this organism tends to disappear spontaneously from the sputum. More specimens from the oxytetracycline group yielded *Str. pneumoniae* at the onset of exacerbations (48%)—nevertheless this organism was not isolated from any specimen during treatment and was infrequently isolated five days after treatment.

No tetracycline-resistant strains of *H. influenzae* or *Str. pneumoniae* emerged; coliform type bacilli were isolated from a few specimens but had no clinical effect. No coagulase-positive staphylococci resistant to oxytetracycline were isolated from any specimen even after several courses of this drug. It made no difference to the length or frequency

TABLE VI.—*Length of Exacerbations (in Days Ill) Related to the Bacteria Grown from the " Initial " and " Pre-treatment " Sputa*

Specimen	Organism	Treatment	No. of Patients	No. of Exacerbations	Mean Length	Variance
Initial	*H. influenzae* present	Oxytetracycline	23	40	12·34	3·18
		Control	21	31	14·26	6·09
	H. influenzae absent	Oxytetracycline	4	9	10·55	8·89
		Control	12	29	14·69	6·61
Pre-treatment	*H. influenzae* present	Oxytetracycline	—	26	11·42	2·66
		Control	—	32	20·26	26·5
	Str. pneumoniae present	Oxytetracycline	—	18	11·67	1·82
		Control	—	13	30·0*	137·4

* Including one exacerbation lasting 163 days.

TABLE V.—*Bacteriological Findings Before, During, and After Exacerbations*

Specimen	Total No. of Specimens	No. of Specimens Producing Moderate or Heavy Growth of:				No Pathogen (Not Even a " Scanty " Growth)
		H. influenzae	*Str. pneumoniae*	Other* Pathogens	Coliform Species	
Initial sputum:						
Control	33	19 (58%) } 63%	5 (15%) } 13%	0	0	12
Oxytetracycline	27	19 (70%) }	3 (11%) }	0	0	4
Before treatment:						
Control	38	28 (74%)	12 (32%)	1	0	5
Oxytetracycline	31	23 (74%)	15 (48%)	1	0	2
During treatment:						
Control	35	18 (51%)	5 (14%)	1	0	10
Oxytetracycline	27	7 (26%)	0	0	4	11
5th day after treatment:						
Control	27	17 (63%)	6 (22%)	2	1	6
Oxytetracycline	27	6 (22%)	3 (11%)	0	3	6

* *Staph. pyogenes*, 3; *Klebsiella friedländeri*, 1; beta-haemolytic streptococci, 1.

of the exacerbations whether *H. influenzae* was or was not present in the initial specimen of sputum (Table VI), and in either case oxytetracycline was no more effective than dummy tablets. Moreover, it was immaterial to the length of the illness whether the predominating pathogen at the onset was *H. influenzae* or *Str. pneumoniae*. Although oxytetracycline-treated exacerbations were shorter, whichever the pathogen, the differences were not significant.

Discussion and Conclusions

The results of our trial were unexpected and illustrate the difficulties of this sort of investigation. Not only are exacerbations of chronic bronchitis ill-defined entities of variable aetiology, but they are also variable in severity, duration, and incidence. There is no precise method of estimating their length and severity symptomatically, and the criterion of loss of time from work is manifestly dependent on many factors, such as the weather and the nature of the work, in addition to the severity of symptoms. Even our patients' account of their loss of time from work while under observation was unreliable.

Had we chosen as a basis for comparison either the length of time lost in exacerbations treated with oxytetracycline against those for which no tablets were taken, or treated exacerbations during the period of observation compared with the patients' own accounts of a previous winter's experience, our results would have been different. On this basis our figures would have appeared to show a definite benefit from taking oxytetracycline tablets. But when comparison is made with the effect of dummy tablets, the placebo effect of these reduces the significance of our results below the conventional probability limit of 1 in 20. A preliminary analysis after the first six months of the trial revealed a mean reduction in days lost from work of 2.8 days per exacerbation, but because of the variance this could have occurred by chance once in three times. After 18 months the probability of the observed difference occurring by chance had fallen to between 1 in 10 and 1 in 20. It is likely that had we been able to continue the trial for another winter we might have obtained figures with a chance probability of less than 1 in 20.

Although our figures do not show a "significant difference" by conventional statistical standards, there are other reasons for believing that the difference between the treated and control groups was due to the oxytetracycline. There is a strong clinical impression that this drug is effective in many exacerbations of bronchitis, and it caused a significant fall in the number of both *H. influenzae* and *Str. pneumoniae* —organisms which have been shown to be important pathogens in bronchitis—in the sputum of our cases. It is probable that many exacerbations in both groups may have been simple coryzas with little bacterial invasion of the bronchial tree: these would be unaffected by oxytetracycline, and they may have masked a real benefit from treatment of the remainder.

The treated group lost on the average 5.2 fewer days from work per exacerbation compared with the control group and 18.5 fewer days compared with the group receiving no tablets. Each course of treatment cost 42s., which works out at 8s. per working day saved, compared with the control tablets, and 2s. 4d. per day saved, compared with no tablets. If this saving was due to oxytetracycline then this compares favourably with the figures of 29s. per day achieved by May and Oswald (1956), using continuous treatment throughout the winter. Furthermore, none of our patients developed tetracycline-resistant staphylococci in the sputum as the result of the treatment.

Between June, 1953, and June, 1954, male insured workers in Great Britain lost nearly 15 million days' work owing to sickness diagnosed as "bronchitis" (Ministry of Pensions and National Insurance, 1953–4). The average weekly wage that year was £10, so that with sickness benefit the cost to the community may be estimated at about £30 million. The simple measures which we adopted might greatly reduce this figure. We would only advocate our procedure of giving a supply of the drug to take without consultation for those patients who are intelligent enough to understand the instructions.

Summary

Eighty-eight patients with established chronic bronchitis, in regular employment, were observed during two winters. Half were given oxytetracycline, 1 g. daily, to take for a week at the onset of exacerbations of their bronchitis, the rest were given indistinguishable control tablets to take in the same way. The oxytetracycline-treated group lost half as much time from work with each exacerbation as the control group, but, since this difference could have occurred by chance once in ten times, it cannot be regarded as certainly due to the oxytetracycline.

The exacerbations for which any treatment (oxytetracycline or control tablets) was taken were significantly shorter than untreated exacerbations. According to the patients' own reports they lost significantly less time from work during the winter they were observed than during a previous winter, but examination of sickness benefit records showed this to have been largely due to misreporting.

Only two pathogenic organisms were isolated from the sputum either at the beginning of the trial or at the onset of the exacerbations—*Str. pneumoniae* and *H. influenzae* —and their presence or absence did not affect the length of the exacerbations. Oxytetracycline banished *Str. pneumoniae* from the sputum in every case and *H. influenzae* in two-thirds of the cases. No resistant strain of either pathogen emerged, nor did any resistant *Staph. pyogenes* appear even after several courses of oxytetracycline.

It is suggested that regular medical supervision of cases of chronic bronchitis, perhaps including prompt treatment of exacerbations with antibacterial drugs, might lessen the present enormous economic loss and human suffering caused by chronic bronchitis in Great Britain.

We thank the general practitioners of this area and the consulting staff of the hospital for referring cases, Messrs. Pfizer Ltd. for supplying the oxytetracycline and dummy tablets, and the staff of the Ministry of Pensions and National Insurance for giving us details of our patients' sickness benefit records. We are indebted to Dr. P. Armitage, of the Statistical Research Unit of the London School of Hygiene and Tropical Medicine, for assistance with the design of the trial and the analysis of the results. We acknowledge the willing co-operation of the staff of the various departments of the hospital which enabled us to investigate and follow up the patients during and after the usual clinic hours, and in particular of the pharmacists who issued the tablets according to the master list.

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