ADULT CHRONIC BRONCHITIS—CONTINUOUS ANTIBIOTIC THERAPY

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The use of the broad-spectrum antibiotic in the treatment of chronic bronchitis has occasioned considerable interest in the recent past (*Lancet*, 1955; *B.M.J.*, 1957). Several trials employing drugs of this kind in the management of chronic or recurrent pulmonary infection have been carried out to determine the results which immediately follow such a prolonged course of treatment (Helm *et al.*, 1954, 1956; May and Oswald, 1956; Moyes and Kershaw, 1957). We have also reported our experience in such a controlled trial employing a double-blind technique using oxytetracycline (Edwards *et al.*, 1957). The antibiotic was used alone, or in combination with other agents, in the domiciliary management of patients with chronic bronchitis, and was given continuously during six winter months in 1955–6. We here describe the further progress of these patients to show the duration of the benefit which followed such a course of treatment, and to determine the frequency with which these courses require to be repeated.

In the original oxytetracycline trial, 66 patients were allotted to various treatment schedules by random selection, and of these 53 completed the six-months course of treatment. In the oxytetracycline series of 29 patients, 21 were improved and 8 showed no improvement. In the control group of 24 patients who completed the course of treatment, 7 were improved and 17 showed no real change. This represents a significant degree of improvement in the oxytetracycline-treated group as compared with the control series. In order to assess the fate of these patients, follow-up studies for a further period of 12 months were carried out on the 29 oxytetracycline-treated patients (Series 1) and 13 selected patients of the 24 controls (Series 2).

Further Follow-up

Series 1

Of the 29 oxytetracycline-treated patients who were to be followed up, those alternately numbered on the Trial Register continued therapy with oxytetracycline with or without a sulphonamide as in the first trial. The other alternate patients were now treated with blank control material exactly similar in appearance to the active substances which they had previously received. Thus the 29 patients were divided into group A and group B. Group A consisted of 14 patients who continued with the antibacterial substances for a total of 18 months' continuous therapy. Group B consisted of 15 patients who, after the initial six months' oxytetracycline treatment, continued under observation as controls on blank material for a further 12 months. When patients relapsed they were removed from the trial so that other antibiotic therapy could be given as required. All the patients followed up were seen monthly for review and assessment in accordance with the method we have described elsewhere.

The results of the assessments at the end of each six-monthly review period are shown in Table I. Each assessment refers to the patient's condition at the end of the review period compared with that obtaining at the start of that period. No patient in group A on continuous therapy was known to have relapsed during any of the observation periods lasting through two winters and one summer from November, 1955, to April, 1957, and some patients even continued to improve during each observation period. In Group B, after six months' active therapy during the first winter followed by dummy control therapy for a further year, 7 patients relapsed during the period April to November, 1956, and another 4 relapsed in the succeeding winter. During the total period of follow-up, three patients were lost to the trial—namely, two who defaulted in the second six months of observation, although both were known to be well, and one who died from so-called "heart failure," no other information being available. These patients were all in group A, and have been shown as "exclusions." Comparison of the patients' conditions at the end of 18 months' observation with their condition at first entry into the trial in November, 1955, shows that all of the 11 remaining in group A on continuous therapy were improved, while there were no known relapses. In group B only 2 out of 15 patients were improved after 18 months' observation, but 11 had relapsed.

Series 2

From the 24 patients in the control group of the original trial who completed the first six months' observation, 13 had previously been selected for continued observation for another purpose. These 13 patients, who comprise Series 2, were treated continuously for a second period of six months from April to November, 1956, with the various agents (excluding oxytetracycline) used in the original investigation. On the anniversary of their entry into the trial, 6 of these patients chosen at random were given in addition oxytetracycline (group C), whilst the other 7 (group D) continued treatment as before. Apart from this change, groups C and D were comparable. These two groups were then observed for a further period of six months from November, 1956, to April, 1957.

Both groups had reacted in a similar fashion by the end of the first 12 months of observation. When the condition of these patients was assessed at the end of the second six-months review period and compared with the condition at the end of the original trial (Table II), 3 of the 6 in group C, and 3 of the 7 in group D, had relapsed, whilst none in either group showed any improvement. When the assessment was made at the end of the third six-months observation period and compared with the condition at the end of the previous review, 4 of the 6 patients in group C now receiving oxytetracycline were improved and 2 showed no real change. In group D, however, 3 patients had again relapsed, whilst the remaining 4 showed no real change. Comparing the situation at the end of this 18 months' observation with the condition at first entry to the trial, the relapse rate in those bronchitics not receiving oxytetracycline is considerably greater than in the treated group. In group C 4 patients were improved, whilst in group D none was improved and 4 were worse.

Time of Relapse

No patient in group A was known to have relapsed, but three patients have been excluded from further follow-up for reasons already stated. Of the 7 patients in group B who relapsed in the period April–November, 1956, one relapsed one month after stopping treatment, 4 after five months in September, and two in October, 1956, in the sixth month of the period. Of the 4 relapses in the next six months two occurred in November and one each in December and January. In group C 3 patients relapsed in the period April to November, 1956—one in August and the other two in October. Similarly, of the 3 relapses in group D, one also took place in August and two in October. Of the 3 further relapses in group D in the succeeding period,

one occurred in December and two in the following January. No patient in group C relapsed in the final six-months observation period while receiving oxytetracycline.

The time relationship of the total relapses in all of the groups is shown in Table III, where the exclusion of three patients from group A has been assumed to be due to relapses. This accounts for a loss or possible relapse rate of about 20%. In group B no relapses occurred whilst the patients were treated with oxytetracycline, but within six months of stopping the antibiotic about half of them had relapsed. Of those who remained under further observation, another 50% relapsed during the last half-yearly review period, making a total relapse rate of about 75% during the whole period of 18 months' observation. Of those patients treated without oxytetracycline (groups C and D), about one-third relapsed during the first six months' observation, whilst about a half relapsed in the second six months' review period. The group C patients were then treated with oxytetracycline, and the relapse rate was reduced to zero, whilst in group D, whose treatment continued without oxytetracycline, a relapse rate of about 50% was maintained.

Over the whole 18-months period the relapse rate in group A appeared to be nil, although it is possible it may have been in the order of 20% ; in group B it was 73% ; in group C 83%, and in group D, after 18 months' observation without antibiotic therapy, all patients had suffered one or more severe exacerbations, producing a summated relapse rate of 114%.

Discussion

It has been shown that continuous oxytetracycline therapy throughout the six winter months produces statistically significant improvement in chronic bronchitis during the period of its use (Edwards *et al.*, 1957), and when given continuously for 12 to 18 months the improvement rate apparently

TABLE I.—*The Results in Series* 1 *at End of Each Six-monthly Period as Compared with the Condition at End of Previous Period, and at End of* 18 *Months' Observation as Compared with the Start*

Series 1 Treatment Groups	No. of Patients	Assessment Gradings	Assessment at End of Each 6 Months' Observation Period as Compared with Assessment at End of Previous Period			Assessment at April, 1957, as Compared with Condition at First Entry in Nov., 1955
			First Period: Nov., 1955, to April, 1956	Second Period: April, 1956, to Nov., 1956	Third Period: Nov., 1956, to April, 1957	
Group A: 18 months' continuous oxytetracycline therapy from Nov., 1955, to April, 1957	14	Improved	11	2	5	11
		No change	3	9	6	—
		Relapsed or worse	—	—	—	—
		Exclusions	—	3	—	3
Group B: 6 months' oxytetracycline therapy (Nov., 1955–April, 1956), followed by 12 months' blank control therapy (April, 1956–April, 1957)	15	Improved	10	—	—	2
		No change	5	8	4	2
		Relapsed or worse	—	7	4	11
		Exclusions	—	—	—	—

Note: All patients marked " Exclusion " or " Relapsed or Worse " are excluded from the subsequent assessments.

TABLE II.—*Results in Series* 2 *at End of Each Six-monthly Period as Compared with Condition at End of Previous Period, and at End of* 18 *Months' Observation as Compared with the Start*

Series 2 Treatment Groups	No. of Patients	Assessment Gradings	Assessment at End of Each 6 Months' Observation Period as Compared to Assessment at End of Previous Period			Assessment at April, 1957, as Compared with Condition at First Entry in Nov., 1955
			First Period: Nov., 1955, to April, 1956	Second Period: April, 1956, to Nov., 1956	Third Period: Nov., 1956, to April, 1957	
Group C: 12 months' continuous control therapy (Nov., 1955–Nov., 1956) followed by 6 months oxytetracycline (Nov., 1956, to April, 1957)	6	Improved	1	—	4	4
		No change	3	3	2	2
		Relapsed or worse	2	3	—	—
		Exclusions	—	—	—	—
Group D: 18 months' continuous control therapy without oxytetracycline from Nov., 1955, to April, 1957	7	Improved	2	—	—	—
		No change	3	4	4	3
		Relapsed or worse	2	3	3	4
		Exclusions	—	—	—	—

TABLE III.—*Showing Frequency and Periodicity of Bronchitis Relapses in Series* 1 *and* 2

Observation Period	Series 1. Group A				Series 1. Group B				Series 2. Group C				Series 2. Group D			
	Nos. at Risk	Drug Regime	Nos. Relapsed	%	Nos. at Risk	Drug Regime	Nos. Relapsed	%	Nos. at Risk	Drug Regime	Nos. Relapsed	%	Nos. at Risk	Drug Regime	Nos. Relapsed	%
Nov., '55–April, '56 ..	14	T	Nil	0%	15	T	Nil	0%	6	C	2	33%	7	C	2	29%
May, '56	14	T	2*	—	15	C	1	—	6	C	Nil	—	7	C	Nil	—
Aug., '56	12	T	Nil	—	14	C	—	—	6	C	1	—	7	C	1	—
Sept., '56	12	T	1*	—	14	C	4	—	6	C	Nil	—	7	C	Nil	—
Oct., '56	11	T	Nil	—	10	C	2	—	6	C	2	—	7	C	2	—
April, '56–Nov., '56 ..	14	T	3*	21%	15	C	7	47%	6	C	3	50%	7	C	3	43%
Nov., '56	11	T	Nil	—	8	C	2	—	6	T	Nil	—	7	C	Nil	—
Dec., '56	11	T	Nil	—	6	C	1	—	6	T	Nil	—	7	C	1	—
Jan., '57	11	T	Nil	—	5	C	1	—	6	T	Nil	—	7	C	2	—
April, '57	11	T	Nil	—	4	C	Nil	—	6	T	Nil	—	7	C	Nil	—
Nov., '56–April, '57 ..	11	T	Nil	0%	8	C	4	50%	6	T	Nil	0%	7	C	3	43%
April, '56–April, '57 ..	14	T	3*	21%	15	C	11	73%	6	C & T	3	50%	7	C	6	86%
Nov., '55–April, '57 ..	14	T	3*	21%	15	T & C	11	73%	6	C & T	5	83%	7	C	8	114%

*=Exclusions. T=Treatment with oxytetracycline. C=Treatment excluding oxytetracycline.

increases. Conversely, continuous drug therapy prevents relapse in bronchitis, and the longer the duration of therapy the more effective the preventive measure against relapse appears to be. It would seem that relapse in chronic bronchitis during the summer and autumn months is considerably reduced, if not entirely prevented, by continuous antibiotic therapy. Without such continued treatment about half of the bronchitics during a six-monthly review period may be expected to relapse, and this seems to occur irrespective of whether antibiotics were used continuously in the previous season or not. Once a severe exacerbation occurs, many bronchitics are often appreciably disabled for a long period unless the relapse is intensively treated with antibiotics. These appear to be adequately suppressive in controlling the effects of bronchial infection.

The suppressive action of oxytetracycline is apparently effective only during the period of its administration, and does not seem to prevent or even delay the appearance of relapse following its withdrawal. The relapse rates during six winter months from November to April in patients treated without antibiotics are but little different from those occurring in the months from April to November. However, 80% of all relapses observed in the four treatment groups appeared between September and February. This may well be related to the climatic and atmospheric changes associated with the onset of autumn, particularly in highly industrialized communities.

It would thus seem reasonable to initiate a six-months course of continuous broad-spectrum antibiotic therapy when the first significant relapse occurs. Since most of these relapses occur in the autumn and winter, such a course of treatment may well overcome the relapse itself and also prevent further deterioration during the winter months, when most bronchitics are mainly at risk. Also it may be anticipated that no further continuous antibiotic therapy may be required for about six months after completing this course of treatment. It would therefore seem that only one period of continuous prolonged treatment with oxytetracycline in a dosage of 0.5–1 g. daily for about six months—the actual duration depending on the time of starting the treatment—may be required to prevent incapacitating exacerbations and maintain many bronchitics in effective and useful employment throughout the whole year.

Comment has already been made concerning the expense of prolonged therapy with the tetracycline group of drugs for a period of six months. If a course of antibiotic treatment is started at the time of the first major relapse and continued for six to seven months, as may be required, the total cost to the National Health Service would be about £45–£55, and would be occasioned but once in each year. The arguments already adduced for suggesting that such a course of treatment with a seemingly expensive drug may in fact be an economy when other aspects of national expenditure—such as National Insurance benefit, the cost of a hospital bed, etc.—are considered, now have added significance.

No untoward difficulties or complications occurred in those patients on prolonged antibiotics; toxicity was minimal, significant drug resistance was not observed, and the development of bronchial or intestinal oxytetracycline-resistant coagulase-positive staphylococci and of monilia did not materially differ in any of the treated or control groups.

Summary

The results of an 18-months follow-up of 42 patients with chronic bronchitis, when treated with or without oxytetracycline for periods of varying duration, are presented.

Continuous and prolonged antibiotic therapy for one year or more not only prevents relapse in chronic bronchitis but increases the rate of improvement the longer the therapy is maintained.

Acute exacerbations of chronic bronchitis assume major proportions during the autumn and winter, particularly between September and February, when 80% of relapses tend to occur.

It is suggested that continuous therapy with oxytetracycline for one period of about six months in each year, to include the period of maximum relapse, may prevent exacerbations and maintain most bronchitics in effective and useful employment.

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CARBON DIOXIDE POISONING

REPORT OF EIGHT CASES, WITH TWO DEATHS

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Although rarely reported, carbon dioxide poisoning is probably not so infrequent an occurrence. McNally (1937) states that it is one of the most commonly occurring of all gases, and is often the cause of death of persons entering caves, wells, and other low-lying or confined spaces. Smith and Cook (1948), on the other hand, state that death from carbon dioxide poisoning is very rare, and that cases so reported are nearly always due to other gases, such as carbon disulphide.

Deaths due to carbon dioxide poisoning are included in the rubric E894 of the *International Classification of Diseases, Injuries, and Causes of Death*, "Accidental Poisoning by Other Specified Gases and Vapours," and in 1955 17 males and one female died from this cause in England and Wales. These figures include deaths due to gases other than carbon dioxide, and it is not known how many of them were caused by carbon dioxide poisoning.

The following cases are reported to illustrate the occurrence of carbon dioxide poisoning as a hazard in the handling of ships' cargoes.

Early in March, 1956, a liner arrived at Penang with a cargo of onions. The particular hold had been loaded six days previously, and contained 5,000 bags of onions and a quantity of "jaggery" (a crude brown sugar obtained from the sap of palm trees). It was full to within 9 ft. (2.7 m.) of the deck. At about 1 p.m. the ship was boarded by labourers, who removed the hatch covers and opened the hatch. One entered the hold and collapsed as he was standing on the onions. Another went in to help him and also collapsed. Then the ship's doctor was sent for; he went