INTERMITTENT DOSAGE IN THE TREATMENT OF PULMONARY TUBERCULOSIS WITH STREPTOMYCIN

A REPORT TO THE STREPTOMYCIN IN TUBERCULOSIS COMMITTEE OF THE MEDICAL RESEARCH COUNCIL

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The emergence of drug-resistant tubercle bacilli has been the major difficulty in the streptomycin treatment of pulmonary tuberculosis. In the first Medical Research Council series of cases of pulmonary tuberculosis treated in this country (Medical Research Council, 1948a) strains showing a streptomycin resistance more than 10 times that of the control were isolated from 35 out of 41 cases. The resistant organisms were usually first found within two months of beginning treatment, occasionally later. Towards the end of 1947, when the first trial was finishing, it was already obvious that any way of avoiding or delaying the emergence of resistance would be a major advance.

The quantitative studies of Pyle (1947) had shown that in pulmonary tuberculosis a minute proportion of streptomycin-resistant tubercle bacilli could be isolated from large inocula of the apparently sensitive pre-treatment strain. As streptomycin treatment continued and the sensitive organisms were gradually eliminated, the resistant minority came to occupy a larger and larger proportion of the bacterial population. Eventually the proportion was sufficient to manifest streptomycin resistance in the comparatively crude routine tests. It seemed, therefore, that even in the absence of streptomycin there was a steady but very low mutation rate to streptomycin-resistant forms. In spite of this steady mutation the proportion of resistant forms did not seem to increase unless they were put at an advantage by exposure to the drug. This failure to increase suggested that in the absence of streptomycin the resistant bacilli might be at a disadvantage, and might therefore tend to die out during intermissions in treatment.

It was known, of course, that once resistant forms were demonstrable in the crude tests it was unusual, in the individual case, to get reversion to sensitive strains. But it was unlikely that a single injection of streptomycin would eventually result in an entirely resistant bacterial population. Somewhere between these extremes the process might be reversible. It appeared possible, therefore, that by a suitable intermission of dosage the process of resistance development might be retarded, or even prevented, without loss of clinical effect.

It was accordingly decided to try out the following rhythms of dosage.

Group 1.—Alternate weeks group : 0.5 g. of streptomycin six-hourly in alternate weeks.

Group 2.—Alternate months group : 0.5 g. of streptomycin six-hourly in alternate months (the month being a four-weeks period).

Group 3.—Control group : 0.25 g. of streptomycin six-hourly without intermission.

Group 4.—Single-dose group : 1 g. of streptomycin in one dose daily without intermission.

The above regimes were to be continued over a total period of six months (168 days), at which time all cases would have had the same total dose of streptomycin. The time of emergence of streptomycin resistance, as judged by the crude routine test, was to be assessed for each case and the results in the individual groups compared. It was hoped that in at least one of the trial groups there might be a significant delay in the emergence of resistance.

Methods

The figures from the Brompton Hospital cases in the first Medical Research Council series (1948a) were used as a basis on which to judge the probable scatter of results. It was calculated that an average delay of a month in the emergence of streptomycin-resistant strains could be satisfactorily demonstrated if four cases were included in each treatment group. But it was decided that it would be wiser to aim at eight cases at least in each group, as it seemed possible that some might become sputum-negative or die before they had had six months' treatment or before resistant strains had been recovered.

As in the first Medical Research Council series the cases admitted to the trial were defined as follows : acute, progressive, bilateral pulmonary tuberculosis of presumably recent origin, unsuitable for collapse therapy ; age group 15 to 30 years. In addition, cases were admitted only if there was a reasonable presumption, on account of cavitation or a strongly positive sputum, that the sputum would continue to be positive over a number of months. Cases which seemed unlikely to survive the treatment course were excluded. The trial was carried out at Brompton and Colindale Hospitals, and the same mechanism as in the first Medical Research Council series was used for recruiting and selecting cases and for allotting them at random to the different treatment groups. Each case was observed in hospital for at least a week before treatment was started, and during this time at least two sputa were cultured. After this, sputum was usually cultured once a week and tests for streptomycin sensitivity were performed as previously described (Medical Research Council, 1948b). Formal clinical and radiological examinations were carried out once a month.

In analysing the results, any strain of tubercle bacilli showing a degree of streptomycin resistance eight times or more that of the control strain (H37Rv) is recorded as having developed some degree of streptomycin resistance, since these readings are outside the range of error of the method (Mitchison, 1949). The "mean day of resistance development" has been defined as the mean day between the day of streptomycin treatment on which the last sensitive strain was isolated and that of the isolation of the first of two successive resistant strains. The criterion of two

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successive strains was adopted because in a few cases isolated resistant cultures were followed by a series of sensitive ones before the strains became constantly resistant. It was felt that it would be misleading to time the emergence of resistance on such isolated cultures. In case it might be argued that strains of comparatively low streptomycin resistance were unimportant clinically, an analysis was also carried out on the same lines, but organisms were regarded as resistant only if they were at least 64 times more so than the control strain.

Clinical progress has been assessed on data not involving the judgment of the observer—that is, weight, pyrexia, and sedimentation rate. Radiological evidence involves judgment; to avoid personal bias the assessment was made by a radiologist (Dr. L. G. Blair) who was otherwise unconnected with the trial.

Results

Material.—Altogether 45 cases were admitted to the trial, the first in December, 1947. These were allotted as follows: Group 1, alternate weeks group, 9 cases; Group 2, alternate months group, 13 cases; Group 3, control group, 12 cases; Group 4, single-dose group, 11 cases.

In Tables IA and IB a comparison is made, for the different treatment groups, of the time taken for streptomycin resistance to emerge. If the criterion of streptomycin resistance is that two successive cultures have yielded tubercle bacilli of resistance at least eight times that of the control, there is no statistically significant difference between the groups (Table IA). The same is true if the criterion is taken as two cultures of resistance at least 64 times the control (Table IB). Nor is there any striking difference in the number of cases from which no resistant strains were isolated, though here, of course, the numbers are too small for any but a gross difference to emerge. Defining the maximum degree of resistance attained in each case as the highest degree of streptomycin resistance found in two successive cultures, there is also no gross difference between the groups (Table II).

TABLE IA.—*Differences Between Treatment Groups in the "Mean Day of Emergence" of Two Consecutive Strains with Streptomycin Resistance Greater than Four Times that of H37Rv*

Treatment Group	Total Cases	Deaths	Streptomycin Resistance Remained Less than 8 Times that of H37Rv until Sputum-negative	"Mean Day of Emergence" of 2 Consecutive Strains of Resistance greater than 4 Times that of H37Rv		
				0–69	70–149	>149
Group 1 ..	9	0	0	4	4	1
Group 2 ..	13	1	2	5	5	0
Group 3 ..	12	0	2	4	4	2
Group 4 ..	11	0	1	3	5	2
All groups	45	1	5	16	18	5

The "mean day of emergence" is defined as the mean day between the day of streptomycin treatment on which the last sensitive strain was isolated and that of the isolation of the first of two successive resistant strains.

TABLE IB.—*Differences Between Treatment Groups in the "Mean Day of Emergence" of Two Consecutive Strains with Streptomycin Resistance Greater than 32 Times that of H37Rv*

Treatment Group	Total Cases	Deaths	Streptomycin Resistance Remained Less than 64 Times that of H37Rv until Sputum-negative	"Mean Day of Emergence" of 2 Consecutive Strains of Resistance greater than 32 Times that of H37Rv		
				0–69	70–149	>149
Group 1 ..	9	0	1	2	3	3
Group 2 ..	13	1	3	2	2	5
Group 3 ..	12	0	3	4	1	4
Group 4 ..	11	0	1	3	1	6
All groups	45	1	8	11	7	18

TABLE II.—*The Differences Between Treatment Groups in the Degree of Streptomycin Resistance Reached by Two Consecutive Strains in Patients whose Sputum Remained Positive Throughout 24 Weeks' Treatment*

Treatment Group	Total Cases	Deaths	Sputum-negative Before 168th Day	Degree of Resistance in Multiples of that of H37Rv			
				<8	8–32	64–512	>512
Group 1 ..	9	0	1	1	2	3	2
Group 2 ..	13	1	3	0	5	3	1
Group 3 ..	12	0	4	2	2	1	3
Group 4 ..	11	0	1	2	4	1	3
All groups	45	1	9	5	13	8	9

It is clear that the trial has been unsuccessful in its primary object. No delay of the emergence of streptomycin resistance has been attained by any of the regimes tested. But in the course of treatment other results of interest have been reported and some of these will now be examined.

Clinical Aspects

Analysis of the clinical results showed no important differences between the treatment groups, though of course the numbers were too small for any but gross differences to emerge.

Table III summarizes the extent of radiographic change after six months' observation. Analysis of the groups with regard to change in temperature, weight, and erythrocyte sedimentation rate at various stages of treatment also showed no important differences. It seems, therefore, that from the clinical point of view there is nothing to be gained by giving streptomycin in alternate weeks or months. In fact, we thought that very ill patients sometimes deteriorated in the periods off treatment, though this was not often clear-cut. The single injection a day, as opposed to six-hourly injections, is of course preferred by the patient; it seems to have no disadvantages, and is now generally adopted. In this connexion it should be added that in one case on alternate-months treatment resistant bacilli were first detected when the patient was in a rest period. A strain of resistance 32 times that of the control was isolated 20 days after the completion of the first month's streptomycin, two sensitive cultures having been previously obtained since stopping treatment.

TABLE III.—*Differences Between Treatment Groups in the Radiographic Change after 24 Weeks' Treatment*

Treatment Group	Total Cases	Radiographic Change after 24 Weeks		
		No Improvement	Slight Improvement	Considerable Improvement
Group 1 ..	9	3	1	5
Group 2 ..	12*	2	6	4
Group 3 ..	11†	2	4	5
Group 4 ..	11	1	3	7
All groups	43	8	14	21

* Excluding one patient who died before the 24th week. † Excluding one patient in whom the data were incomplete.

Other Possible Factors Affecting Streptomycin Resistance

Since there were no significant differences between the four treatment groups in the time of emergence of streptomycin resistance or in its degree, it was of interest to see whether any correlation with other factors could be found. The factors examined were:

1. Condition before treatment, as assessed by (*a*) average evening temperature in the week before starting treatment; (*b*) erythrocyte sedimentation rate before treatment; and (*c*) degree of (i) cavitation and (ii) "confluence of shadows" in the radiograph before treatment; cases were classified in one of three categories.

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2. Progress in the first two months and the first four months of treatment as assessed by weight change, temperature, sedimentation rate, and radiographic appearance.

Although a significant correlation could be demonstrated only between degree of confluence of radiographic shadows and time of emergence of resistance (Table IV), all the factors examined showed a slight trend in the same direction. There was a slight tendency for highly resistant strains to be found in patients who, by the above criteria, were most ill before treatment started, and for strains of low resistance to be found in those least ill. In the most-ill patients streptomycin-resistant strains were often isolated early; in the least-ill patients they tended to be isolated later. There was a tendency for highly resistant bacilli to be isolated from the patients who had responded least satisfactorily to streptomycin, the tendency being apparent after both two months' and four months' treatment.

TABLE IV.—*The Relationship Between the Degree of Confluence of the Shadows in the Pre-treatment Radiograph of 39 Cases and the "Mean Day of Emergence" of Two Consecutive Strains of Streptomycin Resistance Greater than Four Times that of H37Rv. Six Cases are Excluded—One Died and Five became Sputum-negative before Producing Resistant Strains*

Degree of Confluence of Shadows in Pre-treatment Radiograph	Total Cases	"Mean Day of Emergence" of 2 Consecutive Strains of Streptomycin Resistance Greater than 4 Times that of H37Rv	
		0–69	>70
Slight	12	2	10
Moderate	19	9	10
Gross	8	5	3
Total ..	39	16	23

Analysis of these figures for trend towards delay of resistance emergence with diminishing confluence gives $\chi^2_1 = 4{\cdot}17$, $P < 0{\cdot}05$.

Strains of relatively low resistance were more likely to be isolated from patients who had responded well to the drug. Here, again, strains of high resistance often emerged relatively early and those of low resistance relatively late. As an example of these slight trends, Fig. 1 indicates the relation between pre-treatment erythrocyte sedimentation rate and the time of emergence of streptomycin resistance. The correlation was no more impressive for the other factors mentioned, and there were often gross deviations from the slight general trend, especially in the middle range.

As might be expected from the above analysis, there was a statistically significant correlation (Table V, Fig. 2) between the maximum degree of streptomycin resistance in the bacilli of a given case and the time at which resistant strains were first detected. This result might have been due to strains of low resistance emerging late and not having time to develop high degrees of resistance before the end of six months. But in a number of cases with low-resistance strains treatment was intentionally continued for eight months and no important further rise in resistance occurred.

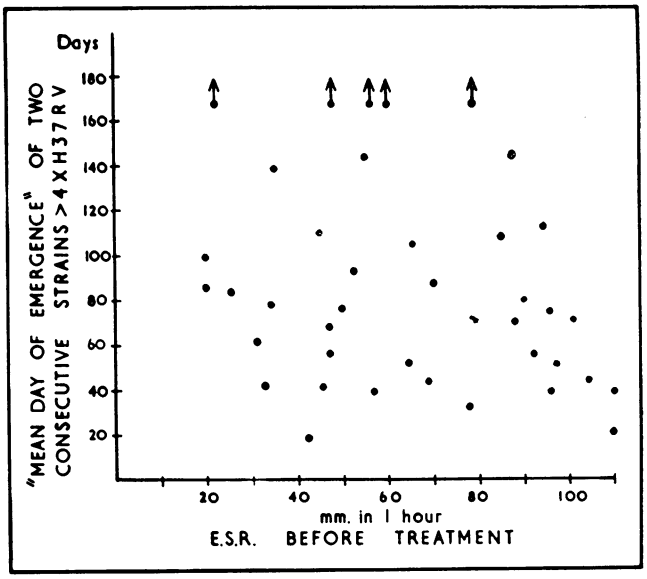

FIG. 1.—The relation of pre-treatment erythrocyte sedimentation rate to the "mean day of emergence" of two successive strains of streptomycin resistance greater than four times that of H37Rv. The arrows indicate the cases from which no streptomycin-resistant tubercle bacilli had been isolated at the end of 24 weeks' observation. The only apparent relation is in the highest and lowest ranges of sedimentation rate.

TABLE V.—*The Relationship of the "Mean Day of Emergence" of Two Consecutive Strains of Streptomycin Resistance Greater than Four Times that of H37Rv and the Degree of Resistance Reached by Two Consecutive Strains in Patients whose Sputum Remained Positive Throughout 24 Weeks of Treatment*

"Mean Day of Emergence" of 2 Consecutive Strains of Resistance Greater than 4 Times that of H37Rv	Total Cases	Degree of Resistance in Multiples of that of H37Rv		
		0–8	16–512	>512
0–69 days	15	3	5	7
>69 days	20	14	4	2
Total	35	17	9	9

$\chi^2_2 = 9{\cdot}47$, $P < 0{\cdot}01$.

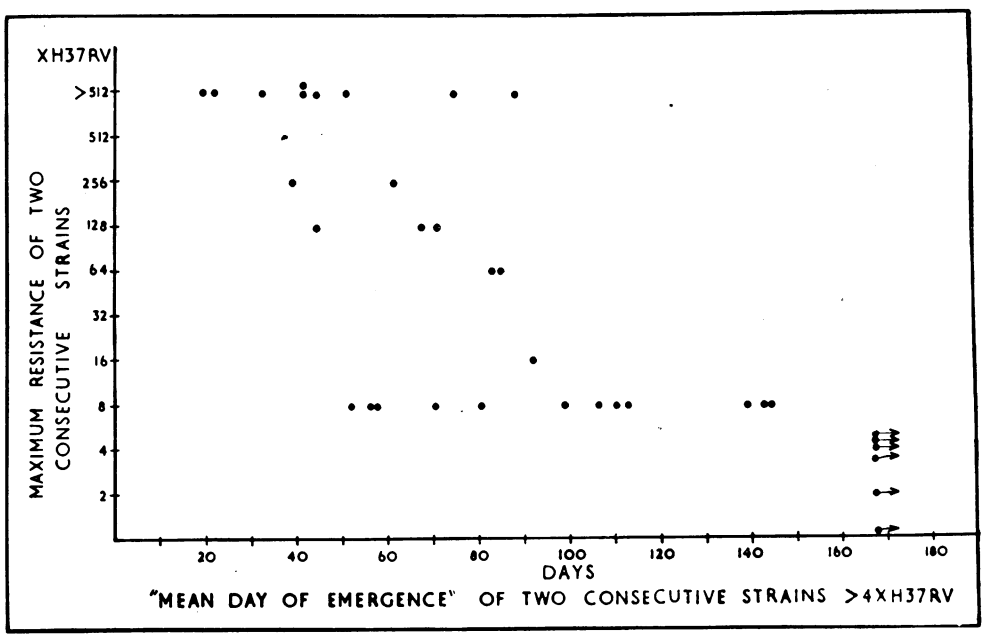

FIG. 2.—The relation, in individual cases, between the maximum degree of streptomycin resistance attained by two successive strains and the "mean day of emergence" of two consecutive strains of resistance greater than four times that of H37Rv.

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Sputum Examinations and Streptomycin Resistance

An attempt was made to see whether routine examination of the sputum could give any information about the progress of the case and the development of streptomycin resistance—apart, of course, from the obvious implications of consistent sputum conversion. The degree of positivity of each specimen for tubercle bacilli was graded as (1) direct smear strongly positive, (2) direct smear weakly positive, (3) direct smear negative, positive on culture only, or (4) negative on culture. Specimens were usually examined once a week.

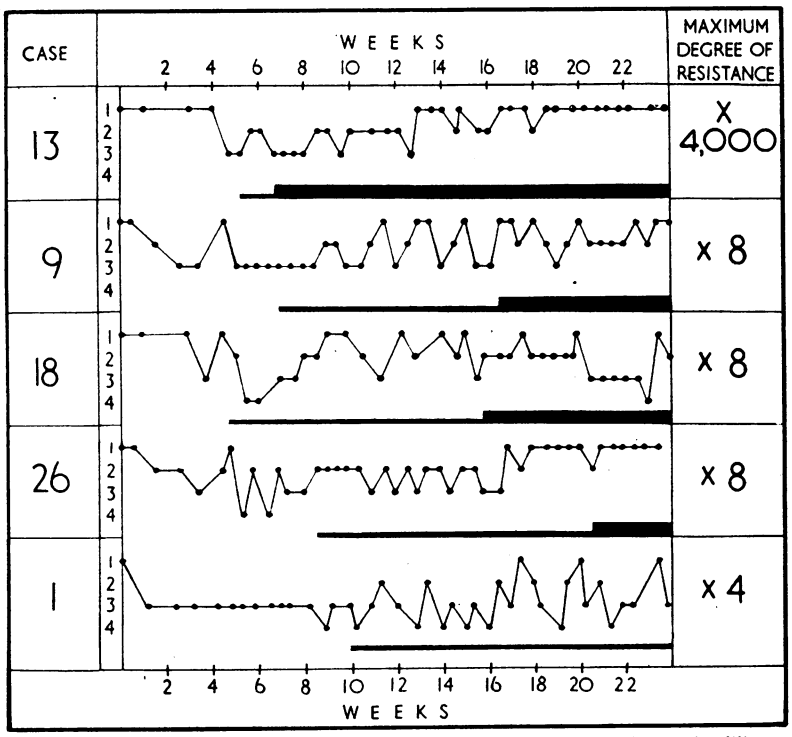

FIG. 3.—Relation of the emergence of streptomycin-resistant tubercle bacilli to the degree of positivity of the sputum. The vertical scale on the left indicates the degree of sputum positivity: (1) direct smear strongly positive; (2) direct smear weakly positive; (3) direct smear negative, positive on culture only; (4) negative on culture. The blocks indicate the time at which strains of tubercle bacilli emerged which were four times (lower blocks) or at least eight times (higher blocks) more resistant to streptomycin than the control strain (H37Rv).

In most cases (Fig. 3) there was a fall in the sputum positivity in the early stages of streptomycin treatment. When this fall was absent or minimal there was a strong tendency to develop a high degree of streptomycin resistance. There were 11 cases in which the direct smear was never found negative on three successive occasions. From all except one of these cases were isolated strains of resistance at least 128 times that of the control. In the exception (Fig. 3, Case 26) there appeared to be a fall in positivity, though in fact three successive negative smears were not obtained. But the reverse did not hold: three successive negative smears were obtained from six other cases from which were isolated strains of resistance at least 128 times that of the control.

After the initial fall in the positivity of the sputum there was usually a later rise (Fig. 3) unless permanent sputum conversion had been achieved. It could in general be said that when a persistent rise in sputum positivity occurred after the initial fall streptomycin-resistant strains would be detected on the routine test. This might be of some use to the clinician, as at present the routine test takes eight weeks. But there is an important proviso: this rise might occur whether the degree of streptomycin resistance was very high or relatively low.

There was often a rise in the sputum positivity after the consistent isolation of strains of a low degree of streptomycin resistance; even as low as four times that of the control, which is just within the limits of experimental error (Fig. 3, Cases 1, 9, 18, and 26). This strongly suggests that slight increases are of some clinical importance. But it seems that such slight increases are less important than great increases. In nine cases, none of which had had collapse therapy, the sputum culture remained negative for at least four weeks. In five of those no increase in resistance was detected; in one the maximum degree of resistance was four times the control, and in the remaining three eight times: this in spite of the fact that in seven out of the nine cases positive cultures were obtained more than 100 days after starting treatment, so that there had been plenty of time for highly resistant forms to emerge. It seems, therefore, that sputum conversion is more likely in cases in which bacilli show only a low degree of streptomycin resistance.

Comparison with the First M.R.C. Series

One of the surprising results of the present trial is the smaller proportion of cases which developed high degrees of streptomycin resistance as compared with the first Medical Research Council series, in which the cases were treated with 0.5 g. of streptomycin six-hourly. The criteria for selection of cases were almost the same in each series. A comparison between the results from the present series and from the 24 cases of the first series treated at Brompton and Colindale Hospitals is given in Table VI. As in the cases of the first series streptomycin was usually stopped at four months, the comparison is made at 120 days after starting treatment. It will be seen that the differences between the two series are statistically significant. Whether this difference is due to the different dosage in the present series or to some other factor is uncertain.

TABLE VI.—*Comparison of the Maximum Degree of Streptomycin Resistance of a Single Strain Isolated During the First 120 Days of Treatment from the Group Treated at Brompton and Colindale Hospitals During the First M.R.C. Investigation and from the Intermittent Dosage Series. Those in whom the Sputum became Negative Before the 120th Day have been Excluded*

Degree of Resistance in Multiples of that of H37Rv	Total Cases	First M.R.C. Series	Intermittent Dosage Series
<32	27	4	23
>16	36	17	19
Total ..	63	21	42

$\chi^2_1 = 6{\cdot}05$, $P < 0{\cdot}02$.

Tables VII and VIII compare the condition before treatment in the two series. There is little difference except that the average pre-treatment temperature was a little higher in the first series. At two months and four months after starting streptomycin the cases in the present series fared significantly better as regards weight gain, pyrexia, and sedimentation rate (Tables IX, X, and XI). There are possible explanations for some of these findings. Cases in

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TABLE VII.—*Temperature and Sedimentation Rate Before Treatment in the Group Treated at Brompton and Colindale Hospitals During the First M.R.C. Investigation and the Four Treatment Groups of the Intermittent Dosage Series. The "Mean Temperature" is the Mean Evening Temperature During the Week before Streptomycin Treatment was Begun*

Treatment Group	Total Cases	Condition Before Treatment	
		Mean Temperature °F.	Mean E.S.R. mm. in 1 Hour
		S.E.	S.E.
First M.R.C. series: 0·5 g. 6-hourly continuously	24	100·03 ± 0·28	57·75 ± 5·51
Group 1	9	99·94 ± 0·45	58·33 ± 9·00
Group 2	13	99·64 ± 0·30	71·54 ± 7·49
Group 3	12	99·50 ± 0·22	63·92 ± 7·79
Group 4	11	99·24 ± 0·26	61·91 ± 8·14

S.E. = Standard error.

TABLE VIII.—*The Radiographic Appearances Before Treatment in the Groups Treated at Brompton and Colindale Hospitals and the Four Treatment Groups of the Intermittent Dosage Series*

Treatment Group	Total Cases	Radiographic Appearances					
		Cavitation			Confluence of Shadows		
		Slight	Moderate	Gross	Slight	Moderate	Gross
First M.R.C. series: 0·5 g. 6-hourly continuously ..	24	10	8	6	7	9	8
Group 1	9	5	1	3	4	3	2
Group 2	13	4	7	2	2	9	2
Group 3	12	2	5	5	5	3	4
Group 4	11	4	6	1	4	5	2
Total ..	69	25	27	17	22	29	18

the present series on 2 g. of streptomycin a day tended to gain weight more slowly than those on lower dosage, so that the higher dosage in the first series might have resulted in less gain.

The less satisfactory progress of the first series at four months, as regards weight gain, pyrexia, and sedimentation rate, might of course have been due to more cases having developed organisms with high degrees of streptomycin resistance. This argument is less applicable at two months, when in many cases resistant organisms had not yet emerged. We cannot say whether the first series did less well in these respects, because at two months the proportion of highly resistant tubercle bacilli was already increasing, or whether the highly resistant forms emerged because the patients had done less well. It is possible that neither is correct and that the differences in weight gain, pyrexia, and sedimentation rate were merely due to the more toxic effect of the higher dosage of streptomycin. It will be noted that as regards radiographic improvement the first series did rather better (Tables XII and XIII).

At four months the cases in the first series had had twice as much streptomycin as those in the present series. But if the figures for the present series are taken at six months there is still a big difference in the incidence of highly resistant organisms. At six months bacilli of resistance less than 32 times that of the control strain were grown from 14 out of 35 cases of the present series, compared with 4 out of 21 of the first series taken at four months. (These differences, though suggestive, are not statistically significant : $\chi^2 = 1.78$, P = 0.2—0.1). Again, daily dosage

TABLE IX.—*The Differences in the Temperature Change During the First Eight Weeks and the Second Eight Weeks Between the Group Treated at Brompton and Colindale Hospitals During the First M.R.C. Investigation and the Four Treatment Groups of the Intermittent Dosage Series. The Figure for Temperature is Based on the Mean Evening Temperature for the Preceding Week. The Figures in Heavy Type are Significantly Different from the Corresponding Figures for the Other Groups*

Treatment Group	Temperature Change Degrees F.							
	After 8 Weeks				From 8 to 16 Weeks			
	Total Cases	Mean Change	Mean Pre-treatment Temperature	Mean Change Allowing for Pre-treatment Differences	Total Cases	Mean Change	Mean Temperature at 8 Weeks	Mean Change Allowing for Differences at 8 Weeks
				S.E.				S.E.
First M.R.C. series: 0·5 g. 6-hourly continuously ..	24	−0·87	100·03	**−0·66 ± 0·13**	24	−0·13	99·16	**−0·02 ± 0·10**
Group 1	9	−1·33	99·94	−1·18 ± 0·22	9	−0·14	98·61	−0·21 ± 0·16
Group 2	12*	−0·95	99·52	−1·07 ± 0·19	12*	−0·21	98·58	−0·29 ± 0·14
Group 3	12	−0·98	99·50	−1·11 ± 0·19	12	−0·27	98·52	−0·37 ± 0·14
Group 4	11	−0·40	99·24	−0·71 ± 0·20	11	−0·45	98·84	−0·44 ± 0·14

* Excludes one patient who died after four weeks' treatment.

Note.—The second column shows, for each group, the mean temperature change between 0 and 2 months after treatment. Since this change is correlated with the pre-treatment temperature (the largest fall being expected when the pre-treatment temperature is highest), it is desirable to know whether any differences there may be between the groups in mean change could be due merely to initial differences in pre-treatment temperature. The mean values of the pre-treatment temperature are shown in the third column. The fourth column shows the mean changes which would have been expected had there been no differences between the groups in mean pre-treatment temperature. The significance of differences between these corrected means has been assessed by the analysis of co-variance.

TABLE X.—*The Differences in the Change in E.S.R. During the First Eight Weeks and the Second Eight Weeks Between the Group Treated at Brompton and Colindale Hospitals During the First M.R.C. Investigation and the Four Treatment Groups of the Intermittent Dosage Series. The Figures in Heavy Type are Significantly Different from the Corresponding Figures for the Other Groups, Analysed as in Table IX*

Treatment Group	Change in E.S.R. mm. in 1 Hour							
	After 8 Weeks				From 8 to 16 Weeks			
	Total Cases	Mean Change	Mean Pre-treatment E.S.R.	Mean Change Allowing for Pre-treatment Differences	Total Cases	Mean Change	Mean E.S.R. at 8 Weeks	Mean Change Allowing for Differences at 8 Weeks
				S.E.				S.E.
First M.R.C. series: 0·5 g. 6-hourly continuously ..	24	−2·21	57·75	**−3·54 ± 4·71**	23†	−12·09	54·91	−10·51 ± 4·03
Group 1	9	−10·67	58·33	−11·81 ± 7·67	9	−18·67	47·67	−19·54 ± 6·41
Group 2	12*	−14·92	70·00	−12·16 ± 6·69	12*	−16·58	55·08	−14·95 ± 5·55
Group 3	12	−17·85	63·92	−17·03 ± 6·64	12	−17·00	46·08	−18·41 ± 5·55
Group 4	11	−20·00	61·91	−19·95 ± 6·93	11	−13·00	41·91	−15·83 ± 5·79

* Excluding one patient who died after four weeks. † Excluding one patient in whom the data were incomplete.

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TABLE XI.—*The Difference in Weight Change During the First Eight Weeks and the Second Eight Weeks Between the Groups Treated at Brompton and Colindale Hospitals During the First M.R.C. Investigation and the Four Treatment Groups of the Intermittent Dosage Series*

Treatment Group	Weight Change (lb.)			
	After 8 Weeks		From 8 to 16 Weeks	
	Cases	Mean Change	Cases	Mean Change
First M.R.C. series: 0·5 g. 6-hourly continuously ..	20*	+1·40±1·16	19‡	+0·63±1·08
Group 1	9	+4·00±1·73	9	+5·11±1·57
Group 2	12†	+4·16±1·50	12†	+3·41±1·36
Group 3	12	+6·58±1·50	12	+5·83±1·36
Group 4	11	+6·45±1·57	11	+6·55±1·42

* Excluding 4 patients in whom the data were incomplete; in 3 because they were too ill to weigh. † Excluding one patient who died after 4 weeks. ‡ Excluding 5 patients in whom the data were incomplete; in 4 because they were too ill to weigh.

alone cannot explain the discrepancy, for of those positive at four months 10 out of 20 cases in the present series receiving 2 g. a day by intermittent dosage showed strains of resistance under 32 times that of the control, compared with 4 out of 21 in the first series. (The differences are almost, but not quite, statistically significant : $\chi^2 = 3.15$, $P = 0.1—0.05$.)

To sum up : it is unlikely to be fortuitous that a smaller proportion of the present series developed high degrees of streptomycin resistance as compared with the first Medical Research Council series. The reason for this we have been unable to determine. It may be that there were important differences which we were unable to detect in the composition of the two series. It may be the fact that, over two or four months, the present series received only half the quantity of streptomycin, or that the dosage was differently spaced. The apparent differences in the response to treatment may provide a clue. Or there may have been some other factor which we failed to assess.

TABLE XII.—*The Difference in Radiographic Change after Eight Weeks Between the Group Treated at Brompton and Colindale Hospitals During the First M.R.C. Investigation and the Intermittent Dosage Series*

Treatment Group	Total Cases	Radiographic Change	
		Improved	Not Improved
Group 1	9	3	6
Group 2	11*	3	8
Group 3	12	5	7
Group 4	11	3	8
Groups 1–4	43	14	29
First M.R.C. series: 0·5 g. 6-hourly continuously	24	11	13

* Excluding two patients in whom the data were not available.
Comparing the two series, $\chi^2_1 = 1·16$, $P = 0·2–0·3$: this difference is not significant.

TABLE XIII.—*The Differences in Radiographic Change after 16 Weeks' Treatment Between the Group Treated at Brompton and Colindale Hospitals During the First M.R.C. Investigation and the Intermittent Dosage Series*

Treatment Group	Total Cases	Radiographic Change	
		Improved	Not Improved
Group 1	9	8	1
Group 2	12*	9	3
Group 3	12	9	3
Group 4	11	10	1
Groups 1–4	44	36	8
First M.R.C. series: 0·5 g. 6-hourly continuously	23†	17	6

* Excluding one patient who died after four weeks. † Excluding one patient in whom the data were incomplete.
Comparing the two series, $\chi^2_1 = 0·57$, $P = 0·3–0·5$: this difference is not significant.

Discussion

It is disappointing that intermittent dosage as used in this trial has been quite ineffective in avoiding or delaying the emergence of drug-resistant strains of tubercle bacilli. This suggests that the process of replacement of a streptomycin-sensitive bacterial population by streptomycin-resistant forms continues, at least to some extent, during intermissions in treatment. This conclusion is supported by the findings in one case on alternate-months treatment, in which a resistant culture was first obtained in a rest period 20 days after completing the first month's treatment.

Jensen's (1949) experiments and some unpublished investigations by one of us (J. W. Clegg) suggest that small quantities of streptomycin may persist in the body for a number of weeks after stopping treatment. The tubercle bacilli may therefore continue for some time to be exposed to low concentrations of the drug. Possibly some other scheme of intermittent treatment, such as giving doses of streptomycin every third day (Tucker, 1949), might be more effective, but the success of combined streptomycin and para-aminosalicylic acid therapy in reducing the incidence of streptomycin-resistant strains (Medical Research Council, 1949) makes it improbable that any scheme which employs streptomycin alone will now be tried. Our impression that some cases deteriorated during rest periods is an additional argument against the intermittent treatment. The clinical results in the trial, so far as one can generalize from such small numbers, suggest that a single injection of 1 g. of streptomycin a day is as effective as 0.25 g. six-hourly, and is preferred by the patient.

It will be recalled that we found some slight relation between, on the one hand, the time of resistance emergence and its degree, and, on the other, the condition of the patient before treatment and his response to streptomycin. It seems possible that such relation as has been observed is merely due to the temperature, radiographic appearance, and so on, being indirect reflections of the factors directly concerned. These factors might be such things as the size of the total population of tubercle bacilli in the lungs, the size of local concentrations of bacilli, the physical condition in the lung, or the patient's capacity to resist the disease.

The analysis of the results of routine sputum examination suggests that these may be of some use to the clinician in the management of the case, as the eight-weeks delay makes the routine streptomycin sensitivity tests of little day-to-day use. Quantitative studies have been made of the streptomycin sensitivity of the population of tubercle bacilli in the sputum of a number of our cases. These studies are being published elsewhere (Mitchison, 1950). Suffice it to say here that the results are in general accord with those obtained by routine methods.

Summary

An attempt has been made to avoid or delay the emergence of streptomycin-resistant tubercle bacilli by schemes of intermittent dosage. Forty-five cases of acute progressive bilateral tuberculosis in young people were allotted at random to one of four dosage groups: (1) 0.5 g. of streptomycin six-hourly in alternate weeks; (2) 0.5 g. of streptomycin six-hourly in alternate months; (3) 0.25 g. of streptomycin six-hourly without intermission; and (4) 1 g. of streptomycin in a single daily dose without intermission. There was no evidence that any of the four dosage schemes delayed or avoided the emergence of streptomycin-resistant tubercle bacilli. Nor was there any

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difference between the groups in the degree of streptomycin resistance shown by the bacilli.

It is concluded that 1 g. of streptomycin a day in a single injection, without intermission of treatment, is the most satisfactory way of giving the drug in pulmonary tuberculosis.

The relation of the emergence of streptomycin-resistant tubercle bacilli to the positivity of the sputum, and to various other factors, has been examined.

We are grateful to Dr. J. O. Irwin for assistance in the design of this trial; to Dr. L. G. Blair, who kindly made the radiographic assessments; and to the nursing staff of Brompton and Colindale Hospitals, who cheerfully undertook the added burden of work.

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BORNHOLM DISEASE

BY

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Bornholm disease, "epidemic myalgia," or "epidemic pleurodynia," has been recognized as a commonly occurring disease in the Scandinavian countries for about the last twenty years. It probably occurs equally often in this country, but, apart from the pioneering work of Pickles (1933, 1939), has been curiously neglected, though at an earlier stage outbreaks of what was described as epidemic pleurisy were recorded as having attacked nurses and patients in two children's hospitals in London (Williamson, 1924; Lloyd, 1924). It is not included in the teaching of many hospital medical schools, and it figures briefly, if at all, in textbooks.

It is recognized when it occurs in epidemics, but the single sporadic case, and the first one or two in an epidemic, are usually not diagnosed. The milder cases are often referred to as fibrositis, strained muscle, indigestion, or pleurodynia; the severer ones as pleurisy, atypical pneumonia, coronary thrombosis, mesenteric adenitis, appendicitis, or poliomyelitis—according to the presenting symptoms and the predilection of the physician. The lack of familiarity with the disease is such that, as Hamburger and McNeil (1947) have suggested, it was still possible in 1944 for an epidemic to be reported as a "new syndrome."

Clinical descriptions of the disease show considerable variations between case and case, and also between epidemic and epidemic. If one sums up what is common to the various descriptions one gets the following picture. Bornholm disease is a benign illness occurring both in epidemics and sporadically. It is usually febrile, and is characterized by pain—usually of a muscular type (frequently described "as though a muscle were strained") and of very variable intensity—felt typically on deep respiration, coughing, laughing, or movement, somewhere around the thorax or abdomen. In children the pain is usually entirely abdominal. As a rule there is at least some abdominal tenderness, and this is particularly likely to be situated just below the costal margin and the xiphisternum. There are no true signs of affection of the viscera, though such may be simulated. A coarse pleural rub may occur. The disease shows extreme variability in severity and presentation, so that while a mild case may have only some malaise and pain on deep respiration, others may present with a crippling pain of sudden onset; there may be a high fever, and possibly abdominal rigidity; rapid grunting respirations are described; headache may be prominent, and vomiting at the onset sometimes occurs.

The cause is almost certainly a virus infection. Observations which suggest that Bornholm disease may be related to infection with the Coxsackie group of viruses are described in the communication by Findlay and Howard in this issue of the *Journal*.

The morbid anatomy has not been finally elucidated. It was thought originally by Sylvest (1932, 1934) to be an inflammatory condition of the muscular system. However, Locke and Farnsworth (1936) point out that "a very important quality of the pain is its direct relationship to sneezing, coughing, laughing, deep breathing, and especially exercise—that is, anything that causes movement of the diaphragm." They go on to point out that the areas in which the muscular pains are felt are those in which Capps (1932) has shown that pain is felt when referred from the diaphragm; and they suggest that the inflammation is at least primarily in the diaphragm. Further observation is required concerning whether only the diaphragm is attacked (the other muscles suffering from reflex irritation and spasm) or whether the other muscles themselves are involved in the inflammatory process.

Scadding (1946), on the other hand, on the basis of one in three of his cases having had a pleural rub, regarded the lesion as primarily a pleurisy, suggesting that possibly his cases were of a disease differing from but related to Bornholm disease; he named it "acute benign dry pleurisy," thus returning to the nomenclature of Williamson (1924) and Lloyd (1924). There does not seem sufficient justification for this in view of the fact that pleurisy is known to occur as a complication of Bornholm disease, and that Locke and Farnsworth found a pleural rub in one in seven of their cases. (It does seem that in certain epidemics a pleural rub occurs more often than in others.)

The common occurrence of tenderness just below the costal margin and xiphisternum (where the diaphragm is partly inserted into the aponeurosis of the abdominal muscles) and of pain in the shoulder-tip suggests that Locke and Farnsworth's view is probably correct, and that pleurisy, when it occurs, is a complication, due to extension of the inflammatory process to the adjacent pleura.

It should be noted that abdominal tenderness may occur in one of two distinct areas: (1) just below the costal margin, due to tenderness of the underlying diaphragmatic insertion; and (2) as referred pain, anywhere in the area supplied by the roots of D6–D12.

The epidemiology is somewhat similar to poliomyelitis, with maximum incidence in the late summer and autumn.

Illustrative Cases

The first seven cases described below occurred in one house consisting of two flats, every one of the occupants contracting the illness. They illustrate the diversity of presentation of illness, the children in general complaining of abdominal pain, the adults of pain on breathing. The dates of occurrence suggest an incubation period of not more than from four to eight days in these cases. Thus the first patient became ill on October 12, 1949, and the next two on October 16. Two further cases occurred on October 22, another on the 23rd, and the last on October 24. The interval between the first infection and the next two cases was therefore not more than four days. The next interval was six days. This is shorter than is usually reported.

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