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PROPHYLACTIC STREPTOMYCIN IN THORACOPLASTY OPERATIONS

A REPORT TO THE MEDICAL RESEARCH COUNCIL

The satisfactory results obtained in the treatment of pulmonary tuberculosis with streptomycin (Medical Research Council, 1948) led to the hope that the drug would also be a useful accessory in the surgical treatment of this disease, particularly in diminishing the danger and extending the scope of thoracoplasty operations. A trial of streptomycin as a routine "cover" for thoracoplasty was therefore initiated by the Streptomycin in Tuberculosis Trials Committee of the Medical Research Council, and the work was planned by a subcommittee.*

The following hospitals took part in the investigation:

Broadgreen Hospital, Liverpool; Brompton Hospital, London; Cheshire Joint Sanatorium, Salop; City Sanatorium, Yardley Green, Birmingham; Fazakerley Sanatorium, Liverpool; Harefield Hospital, Middlesex; Killingbeck Hospital, Leeds; King Edward VII Sanatorium, Midhurst, Surrey; London Chest Hospital, London and Bedfordshire; Pinderfields Emergency Hospital, Yorks; Poole Sanatorium, Yorks; Queen Elizabeth Hospital, Birmingham; Shotley Bridge Hospital, Durham; Sully Hospital, Glamorganshire; University College Hospital, London; Wordsley Hospital, Worcestershire; and Wrightington Hospital, Lancashire.

The Committee wish to express their gratitude to the specialists at these centres who made this work possible; their number is so great that individual acknowledgment is not practicable.

Dr. A. C. C. Hughes, lately of the Council's Tuberculosis Research Unit, was responsible for the clinical co-ordination of the trials, and he also prepared this report, with assistance from Dr. J. R. Bignall, also of the Unit's staff. The radiological changes were assessed by an independent panel composed of Dr. L. G. Blair and Dr. Geoffrey S. Todd.

Design of the Trial

The 17 hospitals were grouped into 10 centres. The first patient was admitted in January, 1948, and the last in September, 1948. The progress of two groups of patients was compared: one series (S group) received streptomycin treatment as a routine during the thoracoplasty stages; the other (C group) received streptomycin only when required as treatment for a tuberculous post-operative complication.

Selection of Patients.—The names of all patients who, in the ordinary course of their illness, were selected for thoracoplasty at each centre were referred (before operation) to the Tuberculosis Research Unit of the Medical Research Council. Here each case was allocated either to the S or to the C group, as determined from

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order lists previously constructed by the use of random sampling numbers, separate lists being drawn up for men and women and for each centre. Patients were not accepted for the trial if they had previously received streptomycin.

Seven hundred and twenty cases were so referred for a category to be assigned to each, 372 being placed in the S group and 348 in the C group. The slight excess of S over C cases was due merely to the play of chance in the construction of random sampling lists.

Withdrawals from the Trial after Selection.—Some patients in each series were withdrawn from the investigation after being referred to the central office.

It will be seen from Table I that the numbers involved are almost the same in the two series (47 S and 51 C). The commonest reason for withdrawal was a change in the original plan, a thoracoplasty not being performed. This occurred either because the patient became unsuitable for operation after allocation to the S or the C group, or because the findings at operation led to the substitution of some

TABLE I

THE DISTRIBUTION BETWEEN THE S AND C GROUPS OF PATIENTS WITHDRAWN FROM THE INVESTIGATION

	Number of Patients		
	Total	S	C
Number referred for category symbol	720	372	348
Plan changed: thoracoplasty not performed	45	22	23
Monaldi drainage performed	34	16	18
Treated in the wrong category (S as C: C as S) ..	16	8	8
Lost sight of less than four weeks after operation ..	2	1	1
Cavity opened at operation on C case: streptomycin given	1	0	1
Total withdrawn from the investigation	98	47	51
Number remaining in the investigation	622	325	297

other operative procedure. The numbers are almost equal (22 S and 23 C). Patients in whom a Monaldi drainage was performed have been excluded from the investigation, as it was considered that this small group might have been exposed to greater risk of post-operative complications than those having operations not involving damage to lung tissue.

There is clearly a possibility that the few instances of patients not being treated according to their category may have introduced bias. If patients allocated to category C were given streptomycin because they were considered to have a bad prognosis, and those allocated to category S were not given streptomycin because they were considered to have a good prognosis, the method of random sampling would be invalidated. Fortunately, the numbers wrongly treated are small and it is unlikely that their exclusion from the investigation has materially altered the results.

Six hundred and twenty-two patients remained in the investigation, 325 in the S group and 297 in the C group.

Types of Operation.—The series included some patients treated by various modifications of the standard thoracoplasty. The distribution of the standard and modified operations between the S and C groups is shown in Table II.

TABLE II

THE DISTRIBUTION OF TYPES OF OPERATION BETWEEN THE S AND C GROUPS

	Number of Patients		
	Total	S	C
Standard thoracoplasty operations	551	290	261
Modified thoracoplasty operations	71	35	36
Total	622	325	297

Treatment.—Patients in the S group received 1 g. of streptomycin daily for two days before, and 21 days after, each operation or stage. When, as was usually the case, the interval between stages was three weeks or less, administration of streptomycin was therefore continuous from two days before the first stage until 21 days after the last stage. The daily dose was given in four 6-hourly intramuscular injections of 0.25 g.

The local application of 1 g. of streptomycin to the wound at the time of operation was optional in S cases, being at the discretion of the surgeon. No rules were laid down about the administration of penicillin to S and C cases. In some centres it was given as a routine cover to all patients; in others only to those in whom there was a special indication, such as copious purulent sputum.

Patients in the C group received no streptomycin locally or intramuscularly before operation and none afterwards unless they were considered to have a tuberculous lung "spread" or a tuberculous wound infection. It was agreed that, should any such complications occur, all patients, whether originally S or C, could be treated with 1 g. of streptomycin daily for eight weeks, or for four months if considered essential.

The comparison, therefore, is between two groups of patients: the first received routine streptomycin cover as well as streptomycin treatment for any tuberculous complications; the second group did not receive routine cover, but some of them were treated with streptomycin for tuberculous post-operative complications.

RESULTS

Comparability of the Groups.—The comparability of the two series has been tested by analysis of the distribution of certain factors between them. No great differences between the groups were found in the age and sex of the patients (S group 184 males and 141 females, C group 173 males and 124 females; S group 54 aged 40 years or more and 271 under 40, C group 40 aged 40 or more and 257 under 40) or in the incidence of preceding phrenic paralysis or artificial pneumothorax on the side of operation. Patients with fever at the time of operation, or with recognizable cavitation in the contralateral lung, were approximately equally distributed between the two series.

Tuberculous Spreads.—The term "spread" denotes the appearances in the chest film of an extension of pre-existing tuberculous infiltration or the appearance of new infiltration considered to be tuberculous. To establish uniformity in the diagnosis of spread, the radiographs of all patients who had been considered to have this complication, and as many as possible of the others, were reviewed by an independent panel, who did not know the various categories of the patients. The radiographs of 556 of the 622 patients were so reviewed.

After examining the radiographs from immediately before the first stage to three months after the last stage, the panel were asked to state if there had been a spread during this period, after which stage it had occurred, and in which lung.

Table III shows the incidence of post-operative tuberculous spreads. The number of patients at risk at the beginning of the second and third stages is arrived at by deducting from the total for the preceding stage those in whom spreads were diagnosed by the panel, those in the C group who received streptomycin after a spread diagnosed at the surgical centre but not by the panel, and those without a spread in whom the operation finished at that stage. It follows that not more than one spread is recorded for any one patient.

TABLE III

THE INCIDENCE OF POST-OPERATIVE SPREADS IN THE S AND C GROUPS

Number of Spreads after Each Operation Stage					Total Incidence of Spreads			
		Operation Stage					Total	%
		1	2	3				
Number of patients at each stage of operation	S	325	272	126	Total patients	S	325	100
	C	297	232	104		C	297	100
Contralateral spreads	S	15	9	0	Contralateral spreads	S	24	7.4
	C	15	9	4		C	28	9.4
Homolateral spreads	S	5	0	0	Homolateral spreads	S	5	1.5*
	C	20	5	0		C	25	8.4

* The difference between the streptomycin and control groups in the percentage incidence of homolateral spreads is 6.9%, with a standard error of 1.7.

There appears to have been no significant difference in the incidence of contralateral post-operative spreads. Homolateral spreads, however, were significantly more frequent in controls than in those receiving streptomycin cover. Of the C group 8.4% had post-operative homolateral spreads compared with only 1.5% of the S group.

Post-operative Atelectasis.—The incidence of post-operative atelectasis in the S and C groups is shown in Table IV. The diagnosis of atelectasis was made in the surgical centres on clinical and radiological evidence, and it refers only to major atelectasis involving most or all of the lobe.

There is no significant difference between the groups in the incidence of transient or persistent atelectasis after operation.

TABLE IV

THE INCIDENCE OF POST-OPERATIVE ATELECTASIS IN THE S AND C GROUPS

	S		C	
	Total	%	Total	%
Number of operations*	723	100	633	100
Transient atelectasis lasting under seven days	31	4.2	27	4.2
Atelectasis lasting more than seven days	13	1.8	14	2.2

* Since it is possible for a patient to have more than one episode of atelectasis, the total number of operations performed, and not the total number of patients, is used.

Wound Infection.—Table V shows the incidence of wound infections in the two series.

TABLE V

THE INCIDENCE OF WOUND INFECTION IN THE S AND C GROUPS

	Number of Patients	
	S	C
Transient wound infection*	14	11
Healing incomplete at three months	3	18†
Healing incomplete at six months	2	14†
Total patients	325	297

* Healing complete by three months. † Includes one patient with a severe wound infection who died before the end of three months.

Transient infections (i.e., infections lasting less than three months from the time of operation) were as frequent in the S as in the C groups. On the other hand, prolonged infections causing serious delay in healing occurred with greater frequency in control cases, the differences at three and six months being statistically significant.

Sputum Examination.—The results of sputum examination three months after operation are shown in Table VI.

TABLE VI

THE RESULT OF SPUTUM EXAMINATION THREE MONTHS AFTER OPERATION IN THE S AND C GROUPS

	S	%	C	%
Smear negative, culture negative*	141	45.0	117	41.8
Smear negative, not cultured	90	28.8	67	23.9
Smear or culture positive	82	26.2	96	34.3
Number of patients with known sputum results	313	100	280	100
Results not known	12		17	
Total	325		297	

* The sputum is recorded as negative to smear or culture at three months if no positive result was obtained in the preceding four weeks.

Taking the most stringent criterion of sputum-conversion three months after the end of operation, 45.0% of the S group had a negative smear and culture, compared with 41.8% of the C group. This difference is not statistically significant.

A comparison was also made of the results at six months, but, owing to the irregularity and incompleteness of the sputum examinations in the later months of observation, the results are not tabulated. The differences between the incidences of negative cultures in the S and C groups were of the same slight degree as at three months.

Mortality.—The difference in mortality of the two groups during the period of the investigation is small and not statistically significant. During the first three months five died in the S group and eight in the C group. By the end of six months another patient in the S group had died, making the total deaths, up to six months after operation, six in the S group and eight in the C group.

Differences Between the Sexes.—Certain differences were noted in the incidence of post-operative spreads and wound infections in men and in women (Table VII).

TABLE VII

THE DIFFERENCES IN POST-OPERATIVE SPREADS AND WOUND INFECTION IN MEN AND WOMEN

	S		C	
	Men (%)	Women (%)	Men (%)	Women (%)
Number of patients	184 (100.0)	141 (100.0)	173 (100.0)	124 (100.0)
Contralateral spreads	11 (6.0)	13 (9.2)	16 (9.2)	12 (9.7)
Homolateral spreads	3 (1.6)	2 (1.4)	20 (11.6)	5 (4.0)
Infected wound unhealed after 3 months	2 (1.1)	1 (0.7)	15 (8.7)	3 (2.4)

Little difference is apparent in contralateral spreads in either treatment group, or in the incidence of homolateral spreads in the S group. In the C group 11.6% of the men, but only 4.0% of the women, were diagnosed as having homolateral spreads. This difference is significant.

In the C group 8.7% of the men, but only 2.4% of the women, had operation wounds unhealed after three months. This difference is also significant.

DISCUSSION

The two groups of patients investigated appear to have been of comparable composition, and the observed differences after operation may fairly be attributed to the effect of the streptomycin administration. The prophylactic use of 1 g. of streptomycin daily from two days before to 21 days after operation led to a significant reduction in the frequency of homolateral spreads and of persistent wound infections. On the other hand, the incidence of contralateral spreads was little altered.

This difference in the behaviour of spreads on the two sides could be explained if there were differences in the pathology of the lesions themselves. The radiological diagnosis of a " spread " may cover such lesions as aspiration tuberculous pneumonia, exacerbation of pre-existing disease, and non-tuberculous lesions wrongly considered to be tuberculous. The majority of spreads in the contralateral lung were in the

upper part of the lung and many were in the zones already showing tuberculous lesions, whereas in the homolateral lung the spreads were mainly in the lower parts, where there was probably less old tuberculous disease. Moreover, on the side of operation the physical condition, especially the distortion of the bronchial tree, may well have favoured bronchial spread of the disease. These considerations suggest that the spreads in the homolateral lung were mainly tuberculous aspiration pneumonias, and that those in the contralateral lung were predominantly exacerbations of old disease. If streptomycin were more effective in preventing fresh tuberculous bronchopneumonia than exacerbations of existing disease, more protection against homolateral than contralateral spreads would be expected. The suggestion cannot be further tested with the data available in the present investigation. It is interesting, however, to note that during a similar study in America (Murphy, 1948) it was found that the majority of the " spreads " in the group receiving streptomycin were reactivations of old disease.

The prophylactic administration of streptomycin did not materially alter the proportion of patients with negative sputum cultures three months after the operation. Nor was there any significant reduction in mortality during the period of observation.

A satisfactory explanation for the apparent differences in the incidence of homolateral spreads between men and women has not been found. The fact that this difference only shows to a significant extent in the C cases may merely be due to the small total number of homolateral spreads in the S cases. The higher incidence of serious wound infection in men than in women seems to be in accordance with previous surgical experience, though the reason for it also is not clear.

Since this investigation took place it has been found that the concurrent use of P.A.S. and streptomycin greatly reduces the risk of the emergence of streptomycin-resistant tubercle bacilli (Medical Research Council, 1950). Yet this danger cannot be said to be entirely removed; and when this risk, in addition to the occasional toxic effects, is considered in conjunction with the small advantages shown by the present investigation, it is doubtful whether the routine use, even of both drugs, prophylactically in thoracoplasty operations (as opposed to therapeutically for such complications as occur) should be advocated. A similar conclusion was reached in the United States as a result of a controlled investigation organized by the Streptomycin Committee of the Veterans' Administration (Report to Council on Pharmacy and Chemistry, 1948). These conclusions do not, of course, conflict with the view that longer pre-operative chemotherapy may be beneficial in selected cases.

Summary

A controlled trial into the effect of streptomycin cover at the time of thoracoplasty operations is described.

Patients were divided by random selection into S and C groups. The former received 1 g. daily of streptomycin for two days before and 21 days after each operation or stage. C cases (controls) received streptomycin only if required for a post-operative tuberculous spread or wound infection. There were 325 patients in the S and 297 in the C group.

The occurrence of a post-operative spread was determined, on radiographic evidence alone, by the inspection of the radiographs by an independent panel.

The incidence of contralateral spreads did not differ significantly between the S and C groups, but there was a significantly greater number of homolateral spreads in the controls than in the S cases.

The incidence of serious wound infections was significantly greater in the controls.

Sputum examination three months after operation did not show any statistically significant difference between the S and C groups.

Certain differences between the results in men and women have been discussed.

The routine use of streptomycin prophylactically in thoracoplasty operations is not advocated. The drug is best reserved for treating complications as they arise.

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