The final results up to 15 years are reported of clinical trials of the management of tuberculosis of the spine in Korea and Hong Kong. In Korea, 350 patients with active spinal tuberculosis were randomised to ambulatory chemotherapy or bed rest in hospital (in Masan) or a plaster-of-Paris jacket for nine months (in Pusan). Patients in both centres were also randomised to either PAS plus isoniazid for 18 months or to the same drugs plus streptomycin for the first three months. In Hong Kong, all 150 patients were treated with the three-drug regime and randomised to either radical excision of the spinal lesion with bone graft or open debridement.

On average, the disease was more extensive in Korea, but at 15 years (or 13 or 14 years in a proportion of the patients in Korea) the great majority of patients in both countries achieved a favourable status, no evidence of CNS involvement, no radiological evidence of disease, no sinus or clinically evident abscess, and no restriction of normal physical activity. Most patients had already achieved a favourable status much earlier.

The earlier results of these trials are confirmed by the long-term follow-up with no late relapse or late-onset paraplegia. The results of chemotherapy on an outpatient basis were not improved by bed rest or a plaster jacket and the only advantage of the radical operation was less late deformity compared with debridement.

A second series of studies has shown that short-course regimes based on isoniazid and rifampicin are as effective as the 18-month regimes: ambulatory chemotherapy with these regimes should now be the main management of uncomplicated spinal tuberculosis.
The Medical Research Council Working Party on tuberculosis of the spine has undertaken two series of controlled clinical trials to investigate different methods of treatment.

The first trials studied outpatient treatment with a then standard 18-month regime based on para-aminosalicylic acid (PAS) and isoniazid. In Korea this was shown to be effective with no therapeutic advantages from either initial bed rest in hospital or the wearing of a plaster jacket. Nor was there any advantage in simple surgical debridement as shown by a study in Rhodesia, or from an initial supplement of streptomycin.1,2

In Hong Kong, because of the high level of initial resistance to antituberculosis drugs, all patients received PAS and isoniazid with an initial streptomycin supplement; debridement of the spinal focus was compared with the radical resection of the spinal focus and repair by bone grafting. The overall results were similar in all the trials, but the radical operation in Hong Kong gave more rapid healing with complete bony fusion and less deformity.3

It was intended to continue follow-up in Korea and Hong Kong for as long as possible, aiming at 20 years, but circumstances have caused earlier termination, with follow-up to 13 to 15 years in Korea and 15 years in Hong Kong. Previous reports have given the results up to five years in all centres4,5 and to ten years in Korea and Hong Kong.1,3 We now report the final results from these centres.

The second series of studies investigated different short-course chemotherapy regimes and the results have been reported for up to three years from Korea and Hong Kong and up to five years from Madras.6-8

Organisation and conduct of the study

Full details of the methods have been given in earlier reports.9-11 The main criterion for admission to the study was clinical and radiological evidence of active tuberculosis of any vertebral body from the first thoracic to the first sacral. Patients with lesions involving only the cervical spine were not admitted, as were patients with paralysis severe enough to prevent them from walking 4 m across a room, a history of previous antituberculosis chemotherapy for 12 months or more, or any serious extraspinal disease likely to affect management or the response to treatment. In the Hong Kong study, patients with a total loss of three or more vertebral bodies were not admitted because the surgeons considered that bone grafts were essential for such severe disease.

The timing of clinical and radiological assessments has been described previously.1,3 After ten years, patients were assessed clinically once a year and radiographs were obtained at 15 years or, in Korea, at the last attendance before the study was terminated. Radiological assessments were made by independent assessors (the late Sir Herbert Seddon until 1977; thereafter Mr Geoffrey Walker); they recorded the vertebral body loss, angle of kyphosis, bony fusion, and the activity of the lesion and compared the latest radiograph with the previous film.1

Allocation to treatment

Korea. At Masan in Korea, patients were allocated at random to:
1) the inpatient series (IP), treatment in bed in hospital for the first six months; or
2) the outpatient series (OP), ambulant outpatient treatment from the start.

At Pusan in Korea, all patients were treated as outpatients and allocated at random to:
1) the plaster jacket series (J) (splintage of the trunk for the first nine months); or
2) no jacket (NoJ).

In both Masan and Pusan all the patients were also allocated at random either to:
1) the PH series, isoniazid and sodium PAS daily for 18 months; or
2) the SPH series, as above plus streptomycin daily for the first three months.

Hong Kong. In Hong Kong, patients were allocated at random either to:
1) the radical series (RAD), radical excision with autologous bone grafting (details in the earlier reports11); or
2) the debridement series (Deb), open debridement with, as far as possible, removal of all pus, caseous material, sloughs and sequestra, but not of apparently unaffected bone, and without bone grafting.

All patients were treated with the SPH regime shown above for Korea (full details are given in earlier reports8,16).

Results

Korea. A total of 350 patients was admitted, but 67 were excluded from the analysis during the first ten years for reasons already reported.1

Exclusions after ten years. Another eight patients were excluded after ten years. Two (1 IP, 1 OP: 1 SPH, 1 PH) died from non-tuberculous causes in the 12th and 13th years. One patient (J/PH) was treated for pulmonary tuberculosis in the 13th year and the other five defaulted from follow-up in the 10th (J/SPH), 12th (J/PH), and 13th (2/J/PH, 1NoJ/SPH) years. All these patients had a favourable status at their last attendance.

Four patients (3 IP, 1 OP: 2 SPH, 2 PH) died before five years from extraspinal tuberculosis (3) or cardiopulmonary failure (1) and were excluded from the analyses, but because their deaths were related to tuberculosis they are included in Table II. All four had quiescent spinal disease at the time of death.

The remaining 271 patients (78 IP, 79 OP: 51 J, 63 NoJ: 130 SPH, 141 PH) were included in the three comparisons at 13 to 15 years.
Pretreatment details. On admission (Table I) 99% of patients were aged under 15 years: 23% had a clinically evident abscess and/or sinus, 44% had mediastinal or psoas abscess shadows, and 10% had central nervous system (CNS) lesions. Most patients had thoracic (40%) or thoracolumbar lesions (23%). Many of the lesions were radiologically extensive: 24% involved four or more vertebrae, 27% had a total vertebral loss of two or more, and

| Pretreatment details. On admission (Table I) 99% of patients were aged under 15 years: 23% had a clinically evident abscess and/or sinus, 44% had mediastinal or psoas abscess shadows, and 10% had central nervous system (CNS) lesions. Most patients had thoracic (40%) or thoracolumbar lesions (23%). Many of the lesions were radiologically extensive: 24% involved four or more vertebrae, 27% had a total vertebral loss of two or more, and |
23% had an angle of kyphosis of 41° or more.

**Final assessment at 13 to 15 years** (Table II). At the final assessment, 190 (70%) of the 271 patients had a favourable status. They had no evidence of CNS involvement, no sinus or clinically evident abscess, no radiological evidence of activity and no restriction of normal physical activity. Another 46 patients had no radiograph at their last followup examination, but their status was favourable in all other respects and the penultimate radiograph had been satisfactory. Thus, 236 patients (87%) were classified as having a favourable outcome at their final assessment at 15 years (151), at 14 years (66) or at 13 years (19). The proportions with a favourable status were similar in all series, ranging from 81% to 91%. One patient (OP/SPH) had a doubtful status because the disease was not considered to be radiologically quiescent although in every other respect the status was favourable.

The remaining 34 patients had an unfavourable outcome. Six had died from causes associated with the spinal disease, five before ten years. The 6th (J/PH) died in the 13th year from the complications of bedsores, after decompression surgery had been performed privately for mild pyramidal signs, against the advice of the co-ordinating doctor at nine years; the operation had resulted in total paraplegia. Three patients (1 IP, 2 OP: 1 SPH, 2 PH) had persisting myelopathy with functional impairment at 14 years; two had weakness of both legs and moderate or severe difficulty in walking and the third had weakness in the right leg and slight difficulty in walking. One patient (NoJ/PH) had a sinus at the last attendance at seven years but defaulted subsequently.

Twenty-four patients were recorded as having an unfavourable status because they had needed additional chemotherapy with or without surgical intervention for their spinal lesion, in 22 of them before ten years. All except one (who had died in an accident at seven years) had a favourable status in all other respects at the last attendance.

**Sinuses and abscesses.** Two patients (1 J/SPH, 1 OP/PH) had sinuses at ten years; both had resolved by 13 years with additional chemotherapy for one (J/SPH). Three patients developed abscesses for the first time after ten years: in the first (OP/PH) in the 11th year the abscess was incised and resolved without further chemotherapy, in the second (NoJ/SPH) in the 13th year it resolved with additional chemotherapy in the 14th year, and in the third (P/PH) in the 15th year it was incised and resolved with additional chemotherapy.

**Myelopathy.** Six patients had evidence of myelopathy at between ten and 15 years, and three had residual myelopathy with functional impairment at their last assessment as described above. The fourth patient (IP/SPH) had myelopathy with no functional impairment at 15 years; weakness and difficulty in walking at 10 years had resolved by 12 years. The fifth patient (OP/PH) had myelopathy with no functional impairment at ten years; this resolved by 14 years. As already reported the sixth patient (J/PH) died in the 13th year with total paraplegia after decompression surgery undertaken elsewhere against advice in the 9th year.

**Radiological assessment.** Of the 214 patients who had radiographs assessed at their last attendance, 213 showed no change from those at ten years. One patient (OP/SPH) was considered to have disease still not quiescent radiologically although in all other respects his status was favourable.

On admission to the trial, the mean vertebral loss of the 165 patients assessed was 1.32 bodies and the mean increase at 15 years was 0.42 bodies (Table III). Most of this increase was early, with very little change after 18 months. For 84 patients with thoracic or thoracolumbar lesions, the mean angle of kyphosis on admission was 35°. The mean increase in angle at 15 years was 25° but most of this had occurred in the first 18 months. The findings in the four series were similar (data available) for both vertebral loss and the angle of kyphosis. Most of the patients had little or no change in vertebral loss (defined as a mean loss or gain of less than 0.25 bodies) between ten and 15 years; five patients (1 IP, 2 OP: 1 J, 1 NoJ: 1 SPH, 4 PH) lost more than 0.25 and only one (1 P/SPH) gained more than 0.25. Similarly, only four patients had a mean increase of 21° or more in kyphosis (1 IP, 2 OP: 1 J: 1 SPH, 3 PH).

**Table III.** Changes in vertebral loss and angle of kyphosis in patients fully assessed at entry, 18 months and at 3, 5, 10 and 15 years

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Mean on admission</th>
<th>Mean increase over period in months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 to 18</td>
</tr>
<tr>
<td>Vertebral loss (bodies)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korea, all series</td>
<td>165</td>
<td>1.32</td>
<td>0.42</td>
</tr>
<tr>
<td>Hong Kong</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rad</td>
<td>46</td>
<td>0.76</td>
<td>-0.17</td>
</tr>
<tr>
<td>Deb</td>
<td>51</td>
<td>0.77</td>
<td>0.22</td>
</tr>
<tr>
<td>Angle of kyphosis (degrees)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korea, all series</td>
<td>84</td>
<td>35</td>
<td>19</td>
</tr>
<tr>
<td>Hong Kong</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rad</td>
<td>18</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Deb</td>
<td>19</td>
<td>25</td>
<td>10</td>
</tr>
</tbody>
</table>

* thoracic and thoracolumbar lesions only
At ten years 187 of the 256 patients (73%) assessed had complete bony fusion (Table IV) and a further 21 (8%) had partial bony fusion. At 15 years the corresponding figures for the 203 assessed were 146 (72%) and 26 (13%); the remaining 31 patients had no evidence of bony fusion. Although these numbers were small, there was a suggestion that the proportion without bony fusion was higher in the PH series; 14 of 71 compared with 5 of 58 in the SPH series in Masan, and 7 of 38 compared with 5 of 36 in Pusan.

**Hong Kong.** A total of 150 patients (75 Rad, 75 Deb) had been admitted to the study, of whom 31 were excluded before ten years. Another 13 patients (6 Rad, 7 Deb) were excluded after ten years; two (both Deb) had died in the 13th year of non-tuberculous causes, one (Deb) had further chemotherapy for pulmonary tuberculosis in the 12th year and ten (6 Rad, 4 Deb) were lost to follow-up (after attending at 10 years (2 Rad), 12 years (2 Rad, 4 Deb) and 13 years (2 Rad, one of whom had emigrated)). All 13 patients had clinically favourable results at their last review and had radiologically quiescent disease at ten years.

Over half (52%) of the patients were aged 15 years or more on admission (Table I); 16% had a sinus and/or a clinically evident abscess and 60% had mediastinal or psoas abscess shadows. No patient had a CNS abnormality. The lesions were much less extensive than in Korea; 66% involved two vertebrae and over half (53%) were lumbar or lumbosacral lesions, 62% had a vertebral body loss of less than 1 body and only 30% had an angle of kyphosis of 21° or more.

**Status at 15 years** (Table II). At 15 years 45 (87%) of the 52 Rad and 47 (87%) of the 54 Deb patients had a favourable status. All but two had radiographs available for assessment. The remaining 14 patients (7 in each series) had needed additional surgery and/or chemotherapy for their spinal disease, all before five years; their status was favourable in all other respects at 15 years. No patient developed sinuses, clinically evident abscesses or myelopathy between ten and 15 years.

**Radiological assessment.** Of the 104 patients who had radiographs assessed at 15 years, all were reported to show no major changes from those at ten years. For one patient with disease assessed as still not quiescent radiologically at ten years, the lesion had healed at 15 years.

Changes in vertebral loss over the 15 years (Table II) were different in the two series, although in both the mean loss had been very similar on admission. Up to five years the Rad series had shown a mean reduction in loss of just under a fifth of a vertebra but by 10 years and 15 years this had decreased to show little change from the pretreatment mean. By contrast, the Deb series had shown a further mean increase in loss of about one quarter of a vertebra which persisted up to 15 years. The numbers in whom changes in kyphosis were assessed were small but the findings were consistent with the changes in vertebral loss; there was a mean increase in the Deb series of about 10° and virtually no change in the Rad series.

There was complete bony fusion in 56 of the 58 Rad patients and 55 of the 61 Deb patients at ten years (Table IV). At 15 years 47 of 50 Rad and 49 of 52 Deb patients had complete bony fusion and a further 3 and 1, respectively, had partial fusion.

**Discussion**

The two most important points from this report, based on the high follow-up at both centres, are first, the similarity of the results at 13 to 15 years to those at ten years and earlier, indicating persistence of good outcomes, and secondly, the excellent results of chemotherapy on an outpatient basis without bed rest, splintage or surgery, in terms of healing of spinal disease and bony fusion. Bed rest, splintage, operative treatment or the addition of streptomycin to the combination of PAS and isoniazid did not give any significant improvement in the results. In Hong Kong, where the initial disease was less extensive, the radical operation performed by the team which had devised and developed the method led to earlier bony fusion and less residual kyphosis, but gave no other benefits at 15 years.

The findings continue to be important, despite the development of more potent drugs for the treatment of pulmonary disease. Short courses of treatment, for six or nine months based on isoniazid, rifampicin and pyrazinamide, were shown to be highly effective in patients with pulmonary tuberculosis with positive sputum on direct smear and bacterial populations which were much larger than those in

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**Table IV.** Cumulative occurrence of bony fusion in both series at 5, 10 and 13 to 15 years

<table>
<thead>
<tr>
<th></th>
<th>5-year report</th>
<th>10-year report</th>
<th>Present report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 to 5 years</td>
<td>0 to 10 years</td>
</tr>
<tr>
<td><strong>Korea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients assessed*</td>
<td>299</td>
<td>256</td>
<td>203</td>
</tr>
<tr>
<td>Complete bony fusion (%)</td>
<td>45 (15)</td>
<td>139 (46)</td>
<td>134 (52)</td>
</tr>
<tr>
<td><strong>Hong Kong</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients assessed</td>
<td>60 Rad, 64 Deb</td>
<td>58 Rad, 61 Deb</td>
<td>50 Rad, 52 Deb</td>
</tr>
<tr>
<td>Complete bony fusion (%)</td>
<td>51 (85)</td>
<td>55 (92)</td>
<td>52 (90)</td>
</tr>
<tr>
<td>Rad</td>
<td>33 (52)</td>
<td>54 (84)</td>
<td>51 (84)</td>
</tr>
<tr>
<td>Deb</td>
<td></td>
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</tr>
</tbody>
</table>

* marginal differences between regimes  
† two deb still not fused at 15 years
spinal abscesses. A second series of studies confirmed that regimes based on isoniazid and rifampicin were also highly effective in spinal disease.6-8

A total of 350 patients was recruited in Korea and 150 in Hong Kong. Although 75 of the Korean patients (21%) were excluded from the final analysis for reasons ranging from death due to non-tuberculous causes to non-compliance with chemotherapy, only 14 (4%) of these had been lost to follow-up in the first ten years: there were two losses in the first three years, one between three and five years and 11 between five and ten years. After ten years, the additional five defaulters all had a favourable status at latest examination. The fact that 93% were followed up at 13 years in the mobile population of South Korea is of great credit to the follow-up team.

In Hong Kong, there was only one patient lost to follow-up in the first three years, one between three and five years, and six (three known to have emigrated) between five and ten years, giving 95% reviewed at ten years. The ten patients lost after the tenth year all had a favourable status at their last follow-up at 10 to 15 years. The 88% follow-up for 15 years is remarkable in the special circumstances of Hong Kong and much credit is due to the many people involved.

The criteria for a favourable status were strict: no symptoms, full physical activity at work or at school, no evidence of CNS involvement, no remaining sinus or abscess detectable clinically or radiologically, together with radiological evidence of healing of the spinal lesion.

The radiological assessment sometimes caused difficulties, being made by an independent surgeon with no information on the clinical state or the allocated regimen. Any doubt about radiological evidence of activity was recorded as 'not yet favourable'. The assessors gave different opinions in a few difficult cases, but these differences were usually resolved when the patient had progressed to unequivocal healing. In addition, the quality of the radiography varied appreciably in one Korean clinic and a few patients were then classified solely on clinical grounds.

The most important assessment of clinical benefit is the speed of return to normal activity. There was concern that lesions with no evidence of bony fusion and healing by fibrous union would be likely to break down with activity. The MRC Working Party studies have shown that this is not the case, and that it is wrong to interpret spinal radiographs as showing active disease in patients who returned to normal physical activity in months or one year, and subsequently have had no clinical problems for ten to 15 years. This error was also made by pulmonary physicians who considered that residual cavities or other radiological lesions needed prolonged chemotherapy and many years of follow-up.

The final analysis shows that a favourable status was reached in Korean patients in 196 of 312 (63%) at the end of the 18-month period of chemotherapy, in 258 of 303 (85%) at the end of 3 years, 262 of 295 (89%) after 5 years, 246 of 279 (88%) after 10 years and 236 of 271 (87%) after 13 to 15 years. The percentages remained much the same after three years and only one death was indirectly attributable to spinal tuberculosis after ten years. None of the adjuvant methods of treatment produced a significant improvement compared with outpatient chemotherapy. In Korea, these results were obtained using only PAS and isoniazid for 18 months. In Hong Kong, all patients had an initial streptomycin supplement because of a high level of initial resistance to isoniazid and had less extensive disease.

In these circumstances there were clear differences between the results of the two operations but both produced a favourable status in similar proportions which were much the same as those in Korea. Radiological evidence of bony fusion has long been regarded as the ultimate proof of local healing, but sound healing can and does occur in many patients with only partial bony fusion or fibrous union. The cessation of bony destruction, although more difficult to measure, is a no less valuable guide to healing. In Korea, the mean bony loss on admission in the 165 patients followed up to 15 years was estimated to be 1.32 vertebral bodies. This increased by 0.42 during the period of chemotherapy, but then remained much the same at 36 months and subsequently. In a similar fashion, most of the changes in the angle of kyphosis were during the first 18 months (mean 19°) with little or no subsequent change. In Hong Kong, where the initial disease was much less extensive, there were differences between the two surgical groups in the changes in bone loss and angle of kyphosis. The Deb group showed a further increase in mean vertebral body loss and kyphosis almost entirely in the first 18 months whereas the Rad series showed a mean reduction in loss at 18 months and up to five years but an increase between five and ten years; at 10 and 15 years the mean loss was virtually the same as on admission, as compared with a mean loss of about one-third of a body in the Deb series.

Conclusions. The earlier reports are confirmed by this extended follow-up. Chemotherapy on an outpatient basis produces results that are not improved in terms of healing by any supplementary interventions. The excellent results at ten years are sustained to 15 years, with no late relapse or late-onset paraplegia. The advantages of radical operation over debridement in terms of deformity persist, but the overall clinical outcome was equally good.

The second series of studies, considered with these results, confirm that outpatient chemotherapy with the standard short-course regimes based on isoniazid, rifampicin and pyrazinamide should be the main management of uncomplicated spinal tuberculosis.

The study in Korea was undertaken under the auspices of the Save the Children Fund and the Working Party are particularly grateful to Lt-Col J. V. Hawkins and Major J. P. Fonseca in London and Mr S. R. Dawson in Hong Kong.

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References


