

Short-course chemotherapy for tuberculosis of the spine

A COMPARISON BETWEEN AMBULANT TREATMENT AND RADICAL SURGERY - TEN-YEAR REPORT

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We performed a randomised, controlled clinical trial to compare ambulant short-course chemotherapy with anterior spinal fusion plus short-course chemotherapy for spinal tuberculosis without paraplegia. Patients with active disease of vertebral bodies were randomly allocated to one of three regimens: a) radical anterior resection with bone grafting plus six months of daily isoniazid plus rifampicin (Rad6); b) ambulant chemotherapy for six months with daily isoniazid plus rifampicin (Amb6); or c) similar to b) but with chemotherapy for nine months (Amb9).

Ten years from the onset of treatment, 90% of 78 Rad6, 94% of 78 Amb6 and 99% of 79 Amb9 patients had a favourable status.

Ambulant chemotherapy for a period of six months with daily isoniazid plus rifampicin (Amb6) was an effective treatment for spinal tuberculosis except in patients aged less than 15 years with an initial angle of kyphosis of more than 30° whose kyphosis increased substantially.

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The patients were treated in Chennai (Madras), South India, at the Tuberculosis Research Centre of the Indian Council of Medical Research, and the following government hospitals in Chennai city: General Hospital, Stanley Hospital, Royapettah Hospital, Institute for Child Health and Hospital for Children, Kilpauk Medical College Hospital and Tuberculosis Sanatorium, Tambaram. The orthopaedic surgeons were Professor M. Natarajan succeeded by Professor T. K. Shanmugasundaram (Principal Investigator), the late Professor S. T. Sundararaj, Professor S. Basheer Ahmed, Professor S. Soundarapandian, Professor P. V. A. Mohandas, Professor S. Rajagopal, Professor K. Sriram and Professor P. Soundararajan.

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Resection of the tuberculous focus and anterior spinal fusion, the modified 'Hong Kong' operation, is a surgical procedure for the treatment of tuberculosis of the spine. This operation, in combination with long-term (18 months) chemotherapy consisting of isoniazid plus p-aminosalicylic acid was investigated in Hong Kong. In many developing countries it may not be possible to undertake this surgery because of limited facilities, inadequate hospital beds and financial constraints. Under such circumstances the best available method of treatment for spinal tuberculosis appears to be chemotherapy on an ambulant basis.^{2,3}

Short-course (6 or 9 months) regimens of chemotherapy, based on daily isoniazid and rifampicin are highly effective in smear-positive pulmonary tuberculosis.^{4,5} A six-month regimen of daily isoniazid and rifampicin^{6,7} was expected to be effective in spinal tuberculosis, because of its paucibacillary nature.

Based on the available knowledge in the 1970s, a randomised, concurrent, controlled clinical trial was undertaken in Chennai (formerly known as Madras), South India, to compare ambulant short-course (six months) chemotherapy with anterior spinal fusion plus six months of chemotherapy. In case this ambulant regimen proved to be less effective than anterior spinal fusion it, was extended to nine months in another group to observe whether the results would be better.

This was a collaborative investigation, the participants being the Indian Council of Medical Research (Tuberculosis Research Centre, Chennai), the British Medical Research Council and orthopaedic surgeons attached to six government hospitals in Chennai. The period of intake for the study was from May 1975 to December 1978. The three- and five-year results have already been reported.^{8,9} This report describes the findings up to ten years.

Organisation and conduct of the study

Full details have been given in earlier reports^{8,9} and are summarised here.

Eligibility criteria. Patients with clinically and radiologically active tuberculosis of the spine involving any vertebral body from the first thoracic to the first sacral,

inclusive, were eligible for admission to the study. Patients were ineligible if they had paralysis of the lower limbs severe enough to prevent them from walking across a room, serious extraspinal disease (tuberculous or non-tuberculous), a history of previous specific chemotherapy for 12 months or more, or had already had major surgery for the spinal disease.

Pretreatment assessments. In brief, the assessments at the start consisted of a detailed clinical examination, antero-posterior and lateral radiographs of the whole spine and posteroanterior films of the chest.

Detailed bacteriological examinations of sputum, pus, urine and specimens removed at surgery were also conducted when applicable.

Allocation to treatment. Patients were allocated, at random, to one of the following three treatment series.

1) Rad6. Surgery plus isoniazid (5 to 7 mg/kg body-weight) and rifampicin (10 to 15 mg/kg) together in one dose daily for six months. The surgery consisted of radical excision of the tuberculous focus and repair of the resultant gap with autologous bone grafts, according to a technique developed in Hong Kong. It was carried out within one month of the start of chemotherapy.

2) Amb6. Ambulatory chemotherapy with isoniazid plus rifampicin (drug dosages as in Rad6) daily in one dose for six months.

3) Amb9. As in 2) but for nine months.

Assessments of progress. The details of assessments of progress up to five years have been described previously.⁹ Between five and ten years the patients were assessed annually by the same methods. If a patient did not report for follow-up, appropriate retrieval action was taken.

Table I. Details of the 235 patients available for the ten-year analysis

	Patients (%)			
	Rad6	Amb6	Amb9	All
Age in years				
0 to 14	32	45	28	35
15 to 34	41	38	39	40
35 or more	21	17	33	26
Site of lesion*				
Thoracic	33	37	41	37
Thoracolumbar	15	15	11	14
Lumbar	44	42	39	42
Lumbosacral	8	5	9	7
Number of vertebrae involved*				
1 or 2	64	73	66	68
3 or 4	32	23	30	29
5 or 6	4	4	4	4
Total vertebral body loss*				
0.0 to 0.9	68	66	80	71
1.0 to 1.9	26	27	18	23
2.0 to 2.9	6	6	3	5
Angle of kyphosis (degrees)*†				
0 to 30	61	56	65	60
31 to 60	39	44	35	40
Total	78	78	79	235

* based on independent radiological assessments

† for patients without a lordotic angle and with lesions up to L2 only (28 Rad6, 41 Amb6, 38 Amb9)

Results

Study population. In all, 304 (100 Rad6, 101 Amb6, 103 Amb9) patients were admitted. Of these, 54 were excluded from the five-year analysis⁹ since 13 did not have active tuberculosis, six were unfit for surgery or anaesthesia or refused surgery, 13 had died from non-tuberculous causes, 16 had their chemotherapy changed because of toxicity or had missed their drugs for more than six weeks, five had additional chemotherapy for extra spinal tuberculosis and one had the operation at the wrong level. A further 15 (4 Rad6, 4 Amb6, 7 Amb9) were excluded between five and ten years: five (2 Rad6, 2 Amb6, 1 Amb9) had died from non-tuberculous causes, three (all Amb9) were retreated (1 for tuberculosis meningitis, 1 for pleuropulmonary glandular tuberculosis, 1 for recurrent discharging sinus) and seven (2 Rad6, 2 Amb6, 3 Amb9) were lost to follow-up, but had quiescent spinal disease at the last assessment. Of the total of 69 patients excluded (23%), 22 (22%) had been allocated to Rad6, 23 (23%) to Amb6 and 24 (23%) to Amb9. There remained 235 (78 Rad6, 78 Amb6, 79 Amb9) patients for ten-year analyses.

Follow-up. During the ten-year period follow-up was con-

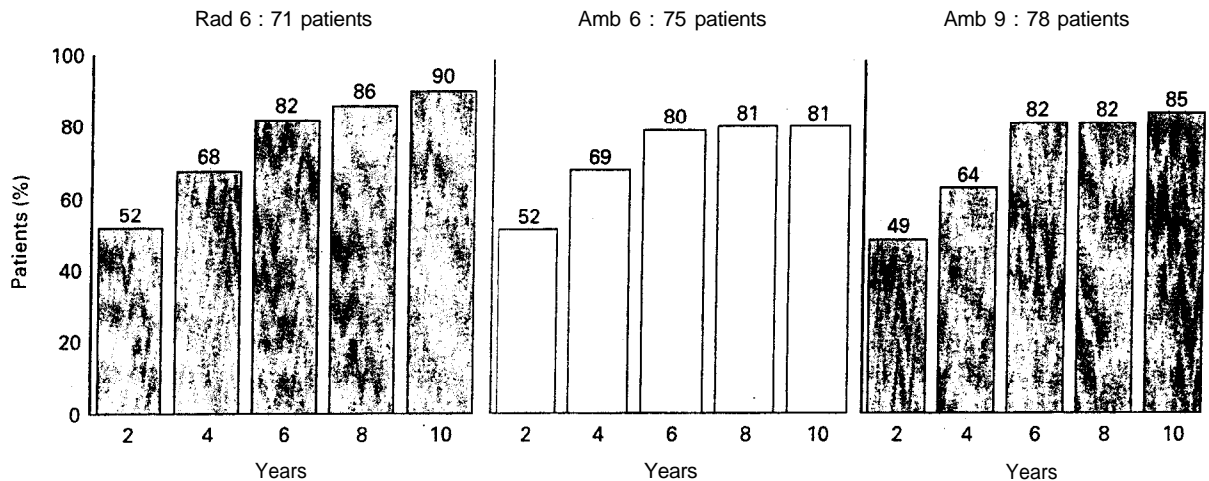


Fig. 1

The percentage of patients with complete bony fusion in the three treatment groups up to ten years

sistently very high and similar (95% to 100%) in the three series.¹⁰

Characteristics on admission. The distributions of the patients were broadly similar in the three series (Table I). Of the 235 patients 35% were aged less than 15 years. The site of the lesion was thoracic or thoracolumbar in 51%. The number of vertebrae involved was three to six in 33%, and the total loss of vertebral body was one or more in 28%. The angle of kyphosis¹¹ was more than 30° but 60° or less in 40% of the patients.

Deaths associated with spinal tuberculosis. Four (all Rad6) patients died, all within the first six months. Three were in the postoperative period and the other had complications of postoperative paraplegia.⁸

Modification of treatment. A total of 11 (5 Rad6, 5 Amb6, 1 Amb9) patients had modification of treatment, all within the first three years.⁸ Of the five Rad6 patients, surgery was abandoned in two for technical reasons, two required additional surgery, for posterior displacement of the bone graft in one and for a persistent postoperative sinus in the other, and one who died with paraplegia was given additional chemotherapy. Of the six ambulant patients, additional chemotherapy was given to two (both Amb6) for clinically evident abscesses, and further surgery carried out in four (3 Amb6, 1 Amb9), including two (both Amb6) with additional chemotherapy also, because of neurological deficit.

Sinuses and/or clinically evident abscesses. The prevalence, incidence and resolution of sinuses and/or clinically evident abscesses have been reported elsewhere.¹² Patients in the Rad6 series had a faster resolution ($p < 0.001$ at two months) and a lower incidence ($p = 0.03$) than those in the ambulant series. There was no recurrence of the lesions during the ten-year period.

Involvement of the central nervous system. Myelopathy was present on admission or developed within the first two months in 17 of 235 patients (7%). Of these, 16 recovered (four with additional chemotherapy and/or surgery) and all

were alive and normal at ten years. The other patient developed postoperative paraplegia and died in the fifth month.

Myelopathy developed after the first two months in two patients, but resolved without additional chemotherapy or surgery. Both were alive and normal at ten years.

Bony fusion. Complete bony fusion occurred in similar proportions of patients in the three series up to six years, about 50% by two years, rising to about 80% by six years (Fig. 1). There was very little change after six years. At ten years, the rates were 90% for 71 Rad6, 81% for 75 Amb6 and 85% for 78 Amb9 patients. The difference between the radical and the ambulant series combined was not significant ($p > 0.1$).

Partial bony fusion occurred in five (7%) Rad6 and 21 (14%) ambulant (11 Amb6, 10 Amb9) patients. The five Rad6 patients had no functional disability. Among the 21 ambulant patients, five children under ten years of age had considerable worsening of the kyphosis to 40° or more during the adolescent growth spurt.

At ten years there was no bony fusion in 3% of patients (2 Rad6, 3 Amb6, 2 Amb9). In the two Rad6 patients this was due to failure of the bone graft. The five ambulant patients had partial involvement of the vertebral bodies without total destruction of intervertebral disc spaces; they had excellent functional results without increase in the deformity.

Spontaneous fusion of the posterior elements of the spine was found in eight patients (1 Rad6, 7 Amb6 + Amb9); all were asymptomatic.

Angle of kyphosis. There were 107 (28 Rad6, 41 Amb6, 38 Amb9) patients with thoracic or thoracolumbar lesions. The mean angles of kyphosis on admission (Fig. 2) were broadly similar at 26° to 30°. The mean angles at ten years were also similar, ranging from 41° to 47°. There was an increase in the mean angle of kyphosis in these patients over the ten years (Fig. 3). None of the differences between

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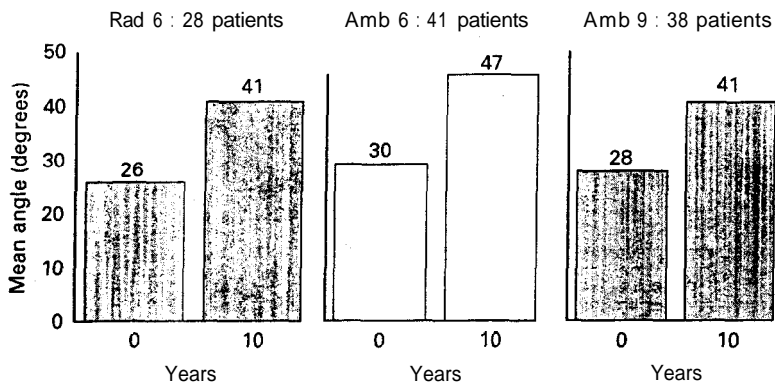


Fig. 2

Mean angle of kyphosis for patients with thoracic or thoracolumbar lesions on admission and at ten years.

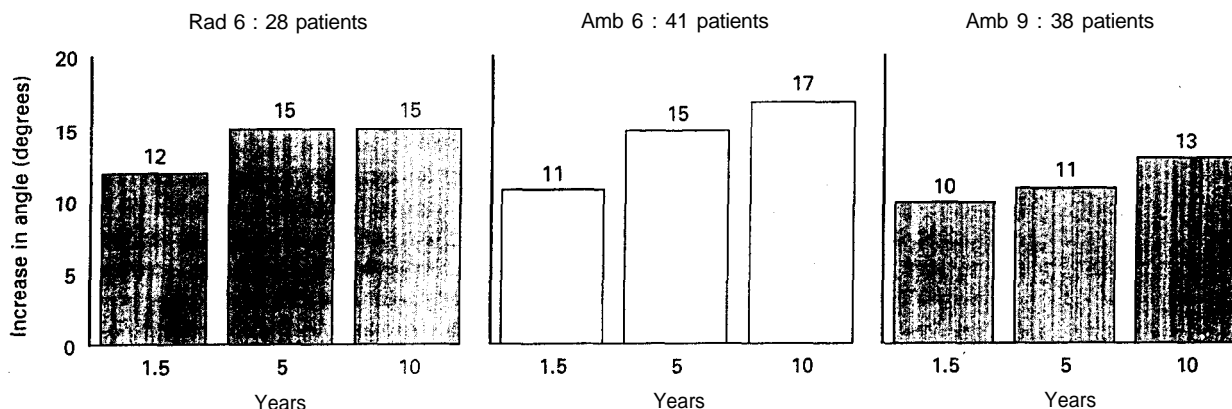


Fig. 3

Mean increases in angle of kyphosis for patients with thoracic or thoracolumbar lesions during ten years.

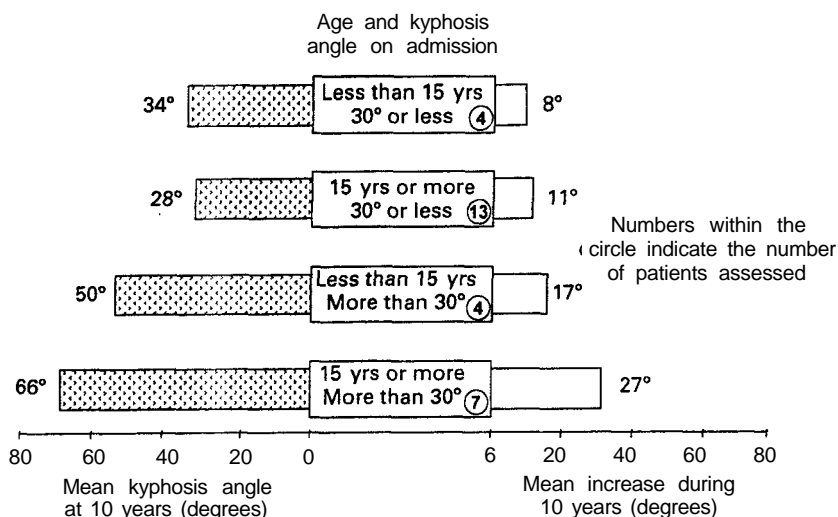


Fig. 4

The mean angle of kyphosis at ten years and the mean increase over ten years related to the age and angle on admission for patients in the Rad6 group.

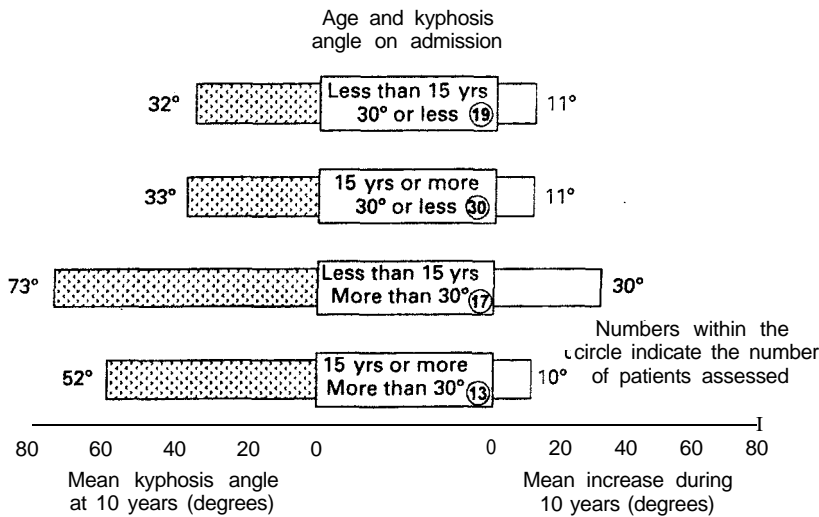


Fig. 5

Mean angle of kyphosis at ten years and mean increase over ten years related to the age and angle on admission for patients in the Amb6 and Amb9 groups.

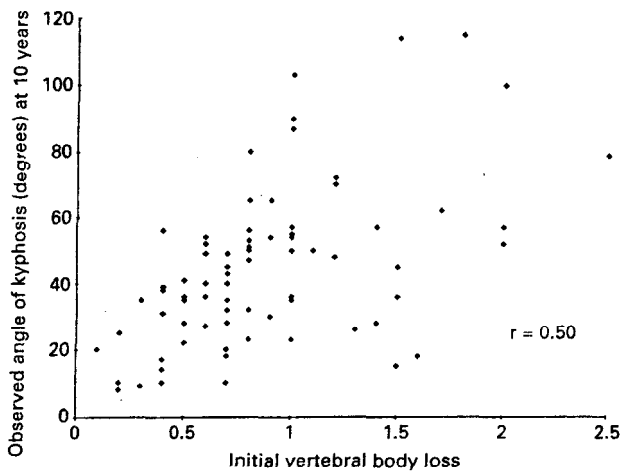


Fig. 6

Scatterplot of the observed angle of kyphosis at ten years and the initial vertebral body loss in the 79 Amb6/Amb9 patients.

the groups was significant ($p > 0.1$ for all the comparisons). Most of the increase occurred within the first 18 months. The increase in the angle was similar in those with thoracic and thoracolumbar lesions in the radical and ambulant series.

Analyses were undertaken to see if changes in the angle of kyphosis during the ten years were related to the initial angle of kyphosis and to age. It was not possible to assess the influence of age in the Rad6 patients (Fig. 4) because of

the small numbers. Seven patients aged 15 years or more and having an initial angle of more than 30° showed a mean increase of 27°. In all, there was failure of the bone graft which spanned three or more disc spaces.

In the two ambulant series, patients with an initial angle of 30° or less, irrespective of age, had similar changes in the angle of kyphosis. In patients with an initial angle of more than 30°, however, the change in the angle of kyphosis was related to age. In patients aged less than 15 years, the mean increase by ten years (Fig. 5) was 30°, compared with 10° in those aged 15 years or more (Student's *t*-test, $p = 0.001$); the mean angles at ten years (Fig. 5) were 73° and 52°, respectively. Furthermore, an increase of more than 30° (not shown in the figure) was observed in seven and none, respectively (Fisher's exact test, $p = 0.01$).

In all, 13 patients (3 Rad6, 10 Amb6 + Amb9) had an increase of more than 30° during the ten-year period.

Influence of initial vertebral body loss on the angle of kyphosis at ten years.

A regression line was fitted for predicting the angle of kyphosis at ten years (Y) from the initial vertebral body loss (X) in ambulatory patients. The equation derived was of the form $Y = 22.1 + 25.0 X$. The correlation coefficient, however, was only 0.50. Also, the predicted angle was within $\pm 10^\circ$ of the observed angle in only 34 (43%) of 79 ambulatory patients (Fig. 6).

Results at ten years. At ten years, 90% of 78 Rad6, 94% of 78 Amb6 and 99% of 79 Amb9 patients had a favourable status (Table II), with no sinus or clinically evident abscess,

Table II. Status at ten years for the 235 patients available for follow-up

Status	Surgery		Ambulatory chemotherapy			
	Rad6		Amb6		Amb9	Amb6 + Amb9
	Number	(%)	Number	(%)	Number	(%)
Favourable*	70	90	73	94	78	99
Unfavourable†	8	10	5	6	1	1
Total assessed	78	100	78	100	79	100

* as defined in text

† defined as death due to or associated with spinal tuberculosis, additional surgery and/or chemotherapy, or radical operation abandoned for technical reasons

no myelopathy and no modification of the allocated regimen. Further, they had no limitation of their physical activity due to the spinal lesion and their disease was radiologically quiescent. The difference between the Rad6 and Amb9 series was significant ($p = 0.03$). The differences between the Rad6 and Amb6 series and that between the Amb6 and Amb9 were not significant ($p = 0.2$).

In all, 14 (8 Rad6, 5 Amb6, 1 Amb9) of 235 patients had an unfavourable status at ten years. All have been described in detail earlier.

Progress of patients excluded from the main analyses. In all, 69 (22 Rad6, 23 Amb6, 24 Amb9) patients were excluded from the ten-year analyses. Of these, 56 (19 Rad6, 16 Amb6, 21 Amb9) had active spinal disease. A total of 28 patients (8 Rad6, 10 Amb6, 10 Amb9) could not be assessed at ten years. Of these, 18 had died from non-tuberculous causes, but had quiescent spinal disease at their last assessment; two refused surgery at the start and eight defaulted from follow-up. Of the remaining 28 (11 Rad6, 6 Amb6, 11 Amb9) patients, 16 (7 Rad6, 4 Amb6, 5 Amb9) had a favourable result at ten years.

Discussion

The British Medical Research Council investigated anterior spinal fusion in Hong Kong¹³ and ambulant short-course chemotherapy in Korea¹⁴ in the treatment of tuberculosis of the spine involving the bodies of thoracic and lumbar vertebrae without paraplegia. A concurrent comparison of ambulant short-course chemotherapy (Amb6, Amb9) with anterior spinal fusion, in addition to short-course chemotherapy (Rad6), was conducted at the Tuberculosis Research Centre, Chennai (Madras).⁸

At ten years, 94% of the Amb6 and 99% of the Amb9 series had a favourable status, the difference not being significant ($p = 0.2$). The Rad6 regimen was less effective than Amb9 ($p = 0.03$), 90% of patients having a favourable status. This difference was due to surgical complications.

The outcome of the two ambulant regimens was confirmed by a Korean study.¹⁴ Using the same criteria, an unfavourable response at three years was observed in 2% of 65 patients given daily isoniazid and rifampicin for six months and in 4% of 71 given the same drugs for nine months. Treatment with two drugs may no longer be acceptable because of the current high levels of initial drug resistance,¹⁵⁻¹⁷ the emergence of multi-drug-resistant tuberculosis and co-infection with HIV.^{18,19} Under the Revised National Tuberculosis Control Programme in India, the regimen recommended for severe forms of tuberculosis is isoniazid, rifampicin, pyrazinamide and ethambutol, administered three times a week for two months, followed by isoniazid and rifampicin given three times a week for four months.²⁰

Anterior spinal fusion was also investigated in Hong Kong in combination with 18 months of isoniazid plus *p*-aminosalicylic acid¹ or with six or nine months of isoniazid

plus rifampicin.¹³ The overall results were satisfactory, a favourable status occurring in 86% by ten years²¹ and 96% by three years,¹³ respectively. Anterior fusion is expected to confer two particular benefits, namely, rapid bony fusion and arrest of progression of the gibbus deformity.¹ Unlike in Hong Kong, bony fusion in the surgically treated patients was not rapid in Chennai even although the pretreatment characteristics of the patients in the first study in Hong Kong were similar. Fusion occurred by one year in 34% in the Chennai study, 69% in the first Hong Kong study²¹ and 56% in the second Hong Kong study.¹³

The angle of kyphosis increased in all three treatment groups in the present study, the mean increase being 15° for the Rad6, compared with 17° for the Amb6 and 13° for the Amb9 series ($p > 0.1$ for all three comparisons). Thus, surgery did not arrest the progression of the gibbus deformity and neither was correction achieved in the two Hong Kong studies. In the first study the mean angle at ten years was virtually the same as that on admission and in the second study it had increased by 11° at three years.¹³ Moon²² concluded that "it was unwise to rely solely on the anterior strut graft to prevent vertebral collapse". Posterior instrumentation followed by anterior fusion was successful in correcting the gibbus and maintaining it for a mean period of 3.6 years.²³

Considering the Rad6 patients, problems relating to the bone graft were responsible for failure of fusion in two of 71 patients and a substantial (27°) increase in the angle of kyphosis by ten years in seven patients aged 15 years or more who had an initial angle of more than 30°. Upadhyay et al²⁴ reported dislodgement of the graft after anterior fusion in ten (10%) of 104 patients, and an increase in the angle by 20° or more by one year in all. Bailey et al²⁵ followed up 100 consecutive children with spinal tuberculosis who were operated on and reported graft complications in 35%, including fracture in 12%. Rajasekaran and Soundarapandian²⁶ found that the graft failed most often in patients in whom it spanned three or more disc spaces. When the anterior strut graft is long, the spine is mechanically unstable and the graft fails because of fracture, displacement or absorption. To achieve mechanical stability of the spine and help in the early incorporation of the graft, the anterior fusion must be supplemented by posterior fusion,^{25,27} preferably with instrumentation.²³ Present techniques such as CT and MRI can define the number of diseased vertebrae and the involvement of posterior elements, and thus help in the planning of surgery.²⁸

The management of the patients would be improved if the final angle of kyphosis could be predicted at the start of treatment. Rajasekaran and Shanmugasundaram²⁹ derived an equation for doing this, based on the initial vertebral loss. An analysis of the angle of kyphosis at ten years in the ambulant patients in our study, showed that the agreement ($\pm 10^\circ$) between the angle predicted and the observed angle was only 34% using their equation, and 43% with a revised equation derived by us. We conclude that the angle of

kyphosis at ten years cannot be accurately predicted based on the initial vertebral loss in most patients. All patients undergoing ambulant chemotherapy should be monitored for progression of the deformity during the active phase of the disease.

Our study gives valuable information on the influence of age and the initial angle of kyphosis on the changes in the gibbus deformity among the ambulant patients. Those aged less than 15 years who had an initial angle of more than 30° had the highest mean angle (73°) at ten years, due to an increase of 30°. Therefore surgery is indicated in addition to chemotherapy in these patients.

A gibbus deformity, if severe, can give rise to cardio-respiratory failure³ and late-onset paraplegia.^{30,31} Neither of these occurred in our study. A longer period of follow-up is needed to monitor the patients for such complications. Leong³⁰ pointed out that a severe worsening of kyphosis with an increase of more than 30° occurred in about 20% of conservatively treated patients in Korea, yet this had not been taken into account in assessing the response to treatment.³² In our study, there were 13 (3 Rad6, 6 Amb6, 4 Amb9) such patients among 107. If these are reclassified as having had an unfavourable response, the revised figures for favourable status at ten years become 86% for Rad6, 86% for Amb6 and 94% for Amb9, the differences between the three series not being significant ($p \geq 0.2$ for all comparisons).

We conclude that ambulant chemotherapy with daily isoniazid and rifampicin for six months was very effective for tuberculosis of the thoracic or lumbar spine without paraplegia, except in patients aged less than 15 years who had an initial angle of kyphosis greater than 30°. The efficacy of the six-month regimen was not enhanced by the addition of anterior spinal fusion.

The following recommendations for treatment are made for patients with active tuberculosis of the thoracic or lumbar spine without paraplegia.

1) Patients with an initial angle of kyphosis of 30° or less should be started on ambulant chemotherapy. All patients, especially children, should be assessed periodically for an increase in the deformity, by comparing the most recent radiograph with the initial one.

2) Chemotherapy should consist of isoniazid, rifampicin, pyrazinamide and ethambutol, given three times a week for two months, followed by two drugs, namely isoniazid and rifampicin, given three times a week for four months.²⁰

3) Surgery, in addition to chemotherapy, is indicated for:

- patients aged less than 15 years, in whom the initial angle of kyphosis is more than 30°;
- patients started on ambulant chemotherapy who develop progressive kyphosis;
- children aged less than ten years with destruction of vertebral bodies who have partial or no fusion even during the adolescent growth spurt; and
- patients with compression of the spinal cord in whom the neurological status deteriorates in spite of chemotherapy.

4) Radical excision with anterior spinal fusion with a stable strut graft is the operation of choice. If the graft is expected to span three or more disc spaces, or the posterior elements are diseased, the procedure should be supplemented by posterior fusion, preferably with instrumentation. Preoperative evaluation with CT and MRI when possible, is of value in the planning of the surgery.

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