ORIGINAL PAPER

MRC Working Party on Tuberculosis of the Spine

Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery

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Abstract The five-year assessment of three randomised trials of short course (6, 9 or 18 months) chemotherapy for tuberculosis of the spine is reported. In Hong Kong patients were randomised to isoniazid plus rifampicin (HR) daily for 6 or 9 months, combined with radical surgical resection with bone grafting and streptomycin for 6

months for all patients. In Madras patients were randomised to chemotherapy with HR for 6 or 9 months, or 6 months HR chemotherapy combined with surgical resection. In Korea all patients were ambulatory and were randomised to different regimens of chemotherapy 6 or 9 months HR, or 9 or 18 months isoniazid plus ethambutol

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Membership of the Working Party has been: the late Mr. D. Lloyd Griffiths (Chairman, Secretary until April 1974), the late Sir Herbert Seddon (Chairman until April 1974), the late Professor J. Ball (since April 1974), Professor J. Darbyshire (Secretary since September 1978), Professor W. Fox, Mr. H.B.S. Kemp (since April 1974), the late Mr. P.G. Konstam, Professor D.A. Mitchison (since April 1974), Professor J.G. Scadding, the late Dr. H. Stott (Secretary from April 1974 until September 1978), Dr. I. Sutherland, Ms. R. Tall, Professor P.K. Thomas (since June 1978) and Mr. G. Walker (since April 1974).

In Madras, South India, the patients were treated at the Tuberculosis Research Centre of the Indian Council of Medical Research and the following government hospitals in Madras 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), Professor S.T. Sundararaj, Professor S. Basheer Ahmed, Professor S. Soundarapandian, Professor P.V.A. Mohandas, Professor S. Rajagopal, Professor K. Sri Ram and Professor P. Soundararajan. Professor K.V. Krishanaswami, succeeded by Professor V. Rangaswamy, were the Superintendents of the Sanatorium.

The study was co-ordinated in Madras by the Tuberculosis Research Centre (TRC) and the bacteriological investigations were undertaken there. The members of the scientific staff of the Tuberculosis Research Centre with major responsibility for the work were: Dr. S.P. Tripathy, Director, succeeded by Dr. R. Prabhakar; Dr. C.V. Ramakrishnan, Dr. R. Parthasarathy and Dr. T. Santha, Medical Officers; Mr. C. Alexander, Chief Laboratory Technologist; Mr. P.R. Somasundaram and Mr. S. Sivasubramanian, Statisticians; and Mr. K.N. Gopilingam, Chief X-ray technician. The contribution of all other members of staff at the TRC, the Orthopaedic Departments and of the nursing staff who took part in the study is gratefully acknowledged.

In Korea the patients were under the clinical care of Dr. P.R.M. Pattison (whose services were kindly made available by the Overseas Missionary Fellowship). In Masan the medical superintendent of the National Hospital for Tuberculosis, Dr. O. Jung Kun, and the Minister of Health and Social Affairs of the Republic of Korea gave assistance and encouragement. Mr. L. Chong Sup, Ms. K. Young Rym, Ms. K. Young Suk, Mr. P. Sung Wong, and Mr. J. Hyun Duck were responsible for nursing, outpatient and domiciliary supervision of the patients.

We are grateful to the medical superintendents of the Pusan City Hospital, the Leprosy Mission Hospital, Taegu, and the Mokpo City Children's Tuberculosis Hospital for encouragement, co-operation and the provision of facilities.

In Hong Kong the patients were treated in and followed up from the Ruttonjee Sanatorium; Sister Mary Gabriel, Resident Physician, was the local co-ordinator, and the orthopaedic surgeons concerned were Professor A.C.M.C. Yau, the Hon. Mr. H.S.Y. Fang and Dr. L. Hsu. Dr. T.B. Teoh was the Government Pathologist in charge.

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In England the clinical coordination was undertaken in London by Ms. R. Tall and Professor J. Darbyshire. The radiographic assessments were organised by the Medical Research Council Tuberculosis and Chest Diseases Unit (TCDU), which also undertook the statistical coordination. Mr. G. Walker was the independent assessor of all the spinal radiographs and Dr. D.J. Stoker was the second assessor for radiographs presenting diagnostic problems. Dr. J.R. Bignall assessed the chest radiographs. Professor P.K. Thomas was the independent assessor of the records of lesions of the central nervous system. The results were analysed and the report written in the TCDU by Professor J. Darbyshire, Professor W. Fox, the late Mr. D. Lloyd Griffiths, Ms. S. Walker and Ms R. Tall.

(EH) or isoniazid plus PAS (PH). In all centres the results of the 6- and 9-month regimens of HR were excellent and similar to the 18-month EH and PH regimens. The 9-month EH/PH regimens were clearly inferior. In Hong Kong excellent results were achieved by the radical resection. The disease was however less extensive than in Madras, where the results after surgery were no better than with ambulatory chemotherapy. Chemotherapy is the critical factor in the management of tuberculosis of the spine. Efforts should be concentrated on ensuring that appropriate regimens are given under adequate supervision.

Résumé Nous présentons les résultats jusqu'à cinq ans de trois essais randomisés de chimiothérapie courte (6, 9 ou 18 mois) pour traiter la tuberculose de la colonne vertébrale. À Hong Kong les patients ont été répartis au hasard à recevoir isoniazid plus rifampicin (HR) tous les jours pendant 6 ou 9 mois, combiné avec une résection radicale de la lésion et l'insertion de greffes osseuses, plus streptomycine pendant 6 mois pour tous les patients. À Madras les patients ont été répartis au hasard à recevoir soit la chimiothérapie avec HR pendant 6 ou 9 mois soit la chirurgie radicale plus 6HR. À Korea tous les patients étaient ambulatoires et ils ont été répartis au hasard à recevoir les régimes de chimiothérapie différentes [soit HR pendant 6 ou 9 mois soit isoniazid plus éthambutol (EH) ou isoniazid plus PAS (PH) pendant 9 ou 18 mois]. Dans tous les centres les résultats des régimes de 6 et 9 mois étaient excellents et pareils aux régimes PH et EH de 18 mois, mais les régimes PH et EH de 9 mois étaient nettement inférieurs. À Hong Kong la chirurgie radicale a donné des résultats excellents mais la maladie était moins étendue que à Madras où les résultats n'étaient pas meilleurs que ceux obtenus avec la chimiothérapie ambulatoire. La chimiothérapie est un élément critique dans le traitement de la tuberculose de la colonne vertébrale. Il faut se concentrer pour donner les régimes pertinents sous la surveillance adéquate.

Introduction

In an earlier series of studies conducted by the Working Party, ambulatory chemotherapy with a then standard 18 month chemotherapy regimen of isoniazid plus para-aminosalicylic acid (PAS) had been found to be highly effective and there had been no therapeutic benefit from the addition of certain other interventions including surgical debridement [8–10]. However, the radical operation, undertaken by its originators in Hong Kong (plus the same chemotherapy) had shown some advantages, namely less subsequent deformity, more rapid bony fusion and more rapid resolution of mediastinal abscesses [9, 10]. The results up to 3 years in Hong Kong of a second study, in which all the patients underwent a modified 'Hong Kong' radical operation have demonstrated that 6-month and 9-month short-course regimens based on isoniazid and rifampicin combined with that operation were equally effective and at least as successful as the 18-month regimen [11]. In Madras, for the first time, a

concurrent comparison was made of ambulatory treatment with the 'Hong Kong' radical operation in patients receiving a 6-month or 9-month chemotherapy regimen of isoniazid plus rifampicin. Follow-up for 3 years in Madras demonstrated no worthwhile benefits from radical surgery in that centre and indeed in terms of the overall outcome, non-surgical treatment with chemotherapy alone for 9 months achieved the best results [5]. In Korea where all patients were treated conservatively with chemotherapy alone and were to be ambulatory from the start, regimens of isoniazid and rifampicin for 6 or 9 months were compared with regimens of isoniazid plus PAS or ethambutol for 9 or 18 months [12]. Regimens containing rifampicin achieved as good results as the 18-month regimens, whereas the results of the 9-month regimens of isoniazid plus PAS or ethambutol were clearly inferior. In this report the main findings up to 5 years after the start of short-course treatment are reported for all three centres.

Patients and methods

The organisation and conduct of the studies, given in detail in the previous reports [5, 11, 12], were similar in all three centres; they are summarised below.

The main criterion for admission to the studies was clinical and radiographic evidence of active tuberculosis of any vertebral body from the first thoracic to the first sacral inclusive. Patients were ineligible if they had serious extra-spinal disease likely to affect their management or response to treatment or if they gave a history of previous anti-tuberculosis chemotherapy for 12 months or more. In Korea and Madras patients were also ineligible if they had paralysis severe enough to prevent their walking across a room (3–6 m); although this was not considered a bar to entry in Hong Kong, in fact no patients with paralysis of this degree were included.

Hong Kong

All patients underwent radical anterior resection with bone grafting [11] and were allocated at random to one of the following series:

- Rad 6HRS: isoniazid plus rifampicin in one dose daily plus streptomycin twice a week for 6 months
- Rad 9HRS: isoniazid plus rifampicin in one dose daily for 9 months plus streptomycin twice a week for 6 months

Madras

Patients were allocated at random to:

- Rad 6HR: isoniazid plus rifampicin in one dose daily plus radical anterior resection with bone grafting (as in Hong Kong)
- Amb 6HR: ambulatory chemotherapy with isoniazid plus rifampicin in one dose daily for 6 months without surgical intervention
- Amb 9HR: as Amb 6HR but for 9 months

Korea

Patients were allocated at random to:

- Amb 6HR: as in Madras
- Amb 9HR: as in Madras
- Amb 9EH: ambulatory chemotherapy with isoniazid plus ethambutol in one dose daily for 9 months
- Amb 9PH: ambulatory chemotherapy with isoniazid plus PAS in two equal doses daily for 9 months
- Amb 18EH: as 9EH but for 18 months
- Amb 18PH: as 9PH but for 18 months.

As in the earlier report [12] the findings for the 9EH and 9PH regimens and those for the 18EH and 18PH regimens have been combined and are referred to as the 9P/EH and 18P/EH regimens, respectively.

The dosages of the drugs were as follows: isoniazid: 6 mg/kg body weight orally (maximum 300 mg); rifampicin: 15 mg/kg body weight orally (maximum 600 mg); streptomycin: 20 mg/kg body weight intramuscularly (maximum 1 g); ethambutol: 15–25 mg/kg according to age and PAS: 0.2 g/kg body weight orally (maximum 10 g). In Madras the dosage schedules of both isoniazid and rifampicin were modified because of the occurrence of jaundice in 18 patients receiving relatively high doses [5].

Progress was assessed monthly for the first 3 months, 3 monthly up to 24 months, then 6 monthly to 5 years. At each assessment full clinical examination and radiography of the spinal lesion were performed, with bacteriological examinations if indicated. In Korea, although it was originally planned to follow up all patients to 5 years, the follow-up was terminated when the project leader (PRMP) left Korea. All patients had been followed for 3 years and 95% for longer.

Results

Hong Kong

In Hong Kong 60 patients were admitted to the study, 9 being excluded before treatment or in the first 3 years for reasons given earlier [11]. One further patient (Rad 6HRS) was excluded between 3 and 5 years; he defaulted after attending for 4 years when his spinal disease was clinically and radiographically quiescent. After these exclusions, there remain 50 (24 Rad 6HRS, 26 Rad 9HRS) patients in the main analysis.

Pretreatment characteristics of the patients are given in Table 1. The characteristics of the patients in the two series were similar (data not shown). Two patients

(1 Rad 6HRS, 1 Rad 9HRS) underwent additional surgery during the first 3 years [11] because of sinuses [one (9HRS) also receiving additional chemotherapy]. No patient had additional chemotherapy or surgery between 3 and 5 years.

Sinuses or clinically evident abscesses were observed in 8 patients (5 Rad 6HRS, 3 Rad 9HRS), in all except 1 (Rad 9HRS) on admission. All these lesions had healed by 12 months [11] and no sinuses or clinically evident abscesses developed subsequently up to 5 years.

Two patients (1 in each series) had myelopathy without functional impairment and 1 (Rad 9HRS) a cauda equina lesion on admission. All had resolved by 9 months and no patient developed central nervous system involvement subsequently.

Complete bony fusion was present at 3 years in all 50 patients (Table 2). The mean total vertebral body loss, as assessed on the pretreatment radiographs, was 0.50 in both series (Table 3). At 5 years there was a further mean loss of 0.15 vertebral bodies in the Rad 6HRS series and of 0.05 bodies in the Rad 9HRS series.

On admission the mean angle of kyphosis was 17.7° for the 14 Rad 6HRS patients with a thoracic or thoracolumbar lesion and 23.5° for the 14 Rad 9HRS patients. By 5 years the mean increase in kyphosis was 12.5° for the Rad 6HRS with a mean decrease of 1.6° for the Rad 9HRS (1 patient had a reduction in angle of 44°; if he is excluded the mean change in the Rad 9HRS series is an increase of 1.6°) (Table 3).

At 5 years 23 of the 24 Rad 6HRS and 25 of the 26 Rad 9HRS patients had a favourable status, defined as full physical activity with radiographically quiescent dis-

Table 1 Pretreatment characteristics

Characteristics	Hong Kong		Madras		Korea	
	No	%	No	%	No	%
Total patients assessed	50	100	250	100	151	100
Age (years)						
0–14	13	26	84	34	88	58
15–54	28	56	158	63	60	40
55 or more	9	18	8	3	3	2
Sinus and/or clinically evident abscess	7	14	49	20	49	32
Radiographic abscess shadow	29	58	142	57	93	62
Myelopathy ^a	2	4	19	8	19	13
with functional impairment	0	0	19	8	11	7
Radiographic site of lesion ^b						
thoracic	18	36	93	37	62	41
thoraco-lumbar	4	8	33	13	32	21
lumbar or lumbo-sacral	28	56	124	50	57	38
Number of vertebrae involved						
1 or 2	44	88	172	69	63	42
3 or 4	5	10	69	28	58	38
5 or more	1	2	9	4	30	20
Total vertebral body loss						
less than 1	47	94	180	72	65	45
1–2	3	6	69	28	66	46
more than 3	0	0	0	0	13	9
Angle of kyphosis ^c						
0–20	10	50	35	29	8	10
21–40	8	40	67	55	38	48
41 or more	2	10	20	16	34	42

^a Defined as involvement of the spinal cord, with or without functional impairment;

^b based on patients with an assessable radiograph (50 Hong Kong, 249 Madras, 144 Korea);

^c thoracic or thoraco-lumbar lesions only (20 Hong Kong, 122 Madras, 80 Korea)

Table 2 Occurrence of bony fusion

Cumulative % with bony fusion by month	Hong Kong		Madras		Korea				
	Rad 6HRS % of 24 patients	Rad 9HRS % of 26 patients	Rad 6HR % of 77 patients	Amb 6HR % of 79 patients	Amb 9HR % of 85 patients	Amb 6HR % of 38 patients	Amb 9HR % of 36 patients	Amb 9P/EH % of 33 patients	Amb 18P/EH % of 37 patients
6	(38)	42	10	15	15	8	0	9	5
12	(58)	81	34	33	29	18	3	21	11
24	(92)	96	55	52	51	37	31	33	35
36	(100)	100	65	66	58	47	36	39	46
42	(100)	100	68	67	62	50	39	39	49
48	(100)	100	69	70	66	53	44	39	49
54	(100)	100	73	70	72	55	53	42	51
60	(100)	100	77	75 ^a	74	58	56	48	62
Partial fusion at 60	(0)	0	21	15	18	16	28	30	19
No fusion at 60	(0)	0	3	10	8	26	17	21	19

^a Including 3 patients assessed as only partially fused at 36 months, and fused at 60 months; numbers in parentheses indicate % based on less than 25 patients

ease, with neither sinuses nor clinically evident abscesses and with no myelopathy with functional impairment and no modification of the allocated regimen (Table 4). Forty-seven of the 48 patients had already achieved a favourable status by 3 years, the remaining patient (Rad 9HRS) having been considered to have disease not yet quiescent radiographically at that stage, although in all other respects his status was favourable. Only 2 patients (1 in each series) could not be classified as favourable at 5 years, both because of modification of their allocated regimen, their status being favourable in every other respect at 3 and 5 years. Therefore, all 50 patients had a favourable status clinically and radiographically at 5 years.

Madras

A total of 304 patients (100 Rad 6HR, 101 Amb 6HR, 103 Amb 9HR) were admitted to the study in Madras, 44 being excluded in the first 3 years for reasons detailed in the earlier report [5]. Ten more patients, all with clinically and radiographically quiescent disease, were excluded between 3 and 5 years (3 Rad 6HR, 1 Amb 6HR, 6 Amb 9HR). Five of these died from non-tuberculous causes; 4 patients had received additional chemotherapy for tuberculosis at other sites and one defaulted from follow-up. There remain 250 patients in the analysis at 5 years (82 Rad 6HR, 82 Amb 6HR, 86 Amb 9HR).

Pretreatment characteristics are given in Table 1. The characteristics of patients in the three series were broadly similar (data not shown). Eleven patients had additional chemotherapy or surgery before 3 years [5] but none subsequently.

Sinuses and clinically evident abscesses were present on admission in 49 patients (16 Rad 6HR, 21 Amb 6HR, 12 Amb 9HR). Resolution of the lesions was slower in the earlier months in the two Amb series compared to the Rad series [5], but by 9 months the lesions had resolved in all except 1 patient (Amb 9HR). A further 32 patients (5 Rad 6HR, 12 Amb 6HR, 15 Amb 9HR) developed abscesses (25) or sinuses (7) evident only after starting treatment, the lesions resolving within 12 months in all except 1 Rad 6HR patient. This patient developed a sinus at the site of the operation that persisted until the graft was removed in the 31st month. The sinus, although not present at 36 months recurred at 42 months and then healed without further recurrence. No other patient had a sinus or clinically evident abscess between 3 and 5 years.

Myelopathy was present on admission or developed within the first 6 months in 19 patients (5 Rad 6HR, 5 Amb 6HR, 9 Amb 9HR), 13 having functional impairment at some time [5]. One patient (Rad 6HR) died with complete paralysis in the 5th month. Only 2 patients (Rad 6HR) had residual myelopathy at 3 years; one had developed a myelopathy at 6 months that resolved by 15 months but recurred at 21 months; he had weakness of one leg at 3 years but this resolved by 42 months. The other patient had myelopathy with functional impairment

Table 3 Changes in total vertebral body loss and angle of kyphosis from 0 to 5 years

Change in total vertebral body loss and angle of kyphosis 0 to 5 years	Hong Kong		Madras		Korea			
	Rad 6HRS % of total patients	Rad 9HRS % of total patients	Rad 6HR % of total patients	Amb 6HR % of total patients	Amb 9HR % of total patients	Amb 6HR % of total patients	Amb 9HR % of total patients	Amb 18P/EH % of total patients
Vertebral body loss								
Improvement: reduction in loss of 0.25 or more	8	20	7	0	0	3	0	6
No change: change of +/- 0.24	54	56	61	51	65	53	31	31
Deterioration: further loss of:								
0.25-0.49	21	16	15	20	16	8	16	16
0.50-0.99	17	8	15	24	16	25	38	34
1.0 or more	0	0	3	5	4	11	16	12
Total patients assessed	24	25	75	75	82	36	32	32
Angle of kyphosis								
Improvement: reduction of 11° or more	0	7	3	0	4	(6)	(4)	(10)
No change: change of +/- 10°	36	79	62	58	51	(56)	(38)	(52)
Deterioration: increase of:								
11°-30°	64	14	32	36	35	(28)	(42)	(33)
31° or more	0	0	6	2	10	(11)	(17)	(5)
Total patients assessed	14	14	34	45	51	18	24	21
Numbers in parentheses indicate % based on less than 25 patients								

Table 4 Status at 5 years

Status	Hong Kong				Madras				Korea ^a			
	Rad 6HRS		Rad 9HRS		Rad 6HR		Amb 6HR		Amb 9HR		Amb 6HR	
	No	%	No	%	No	%	No	%	No	%	No	%
Favourable	23	96	25	96	72	88	75	91	84	98	35	90
Still not favourable: not quiescent radiographically	0	0	0	0	2	2	2	2	1	1	3	8
Unfavourable: death due to or associated with spinal disease	0	0	0	0	4	5	0	0	0	0	0	0
sinus present	0	0	0	0	0	0	0	0	0	0	1	3
additional chemotherapy	1	4	1	4	2	2	5	6	1	1	0	0
and/or surgery for spinal disease	0	0	0	0	2	2	0	0	0	0	0	0
radical operation abandoned	0	0	0	0	2	2	0	0	0	0	0	0
Total patients assessed	24	100	26	100	82	100	82	100	86	100	39	100

^a A further 3 patients had an unfavourable status at their last assessment, namely 1 (Amb 18P/EH) with a sinus and 2 (1 Amb 9HR, 1 Amb 18P/EH) with myelopathy with functional impairment. In addition 8 not assessed at 3 years had undergone additional chemotherapy because of the spinal lesion (1 Amb 6HR, 1 Amb 9HR, 5 Amb 9P/EH, 1 Amb 18P/EH)

on admission, this resolved by 9 months but recurred without functional impairment at 36 months only. No patient developed myelopathy between 3 and 5 years.

The rate of occurrence of bony fusion was similar in the 3 series (Table 2). At 5 years 75% of the patients had complete fusion; 3% in the Rad series and 9% in the ambulatory series having no evidence of fusion and the remainder having partial bony fusion.

The mean total vertebral body loss on admission was 0.77 of a vertebrae for the Rad 6HR, 0.83 for the Amb 6HR and 0.65 for the Amb 9HR series (Table 3). At 5 years there was a mean further loss of 0.18, 0.35 and 0.24 vertebral bodies, respectively. Most of the loss occurred early with little or no change after 18 months [5].

The mean angle of kyphosis (for patients with thoracic or thoraco-lumbar lesions not extending below L2) on admission was 26.5° for the Rad 6HR, 28.2° for the Amb 6HR and 25.2° for the Amb 9HR series (Table 3). At 5 years, there was a mean increase in the angle of kyphosis in all three series of 10.0°, 11.9° and 10.5°, respectively.

At 5 years (Table 4), 72 of the 82 Rad 6HR, 75 of the 82 Amb 6HR and 84 of the 86 Amb 9HR had a favourable status. Of the 14 patients classified as unfavourable, 4 (all Rad 6HR) had died from reasons associated with the spinal lesion, all within 6 months [5]. The remaining 10 patients (4 Rad 6HR, 5 Amb 6HR, 1 Amb 9HR) were classified as unfavourable solely because of modification of the allocated regimen (all before 3 years) [5]. Four of the patients had died from non-tuberculous causes, but their status at the time of death and the status of the other 6 patients at 5 years was, in all other respects, favourable.

At 3 years 219 patients had reached a favourable status and all these were classified as favourable at 5 years. Of the 16 classified as still not favourable at 3 years, 5 were classified as still not favourable at 5 years because their disease was not yet quiescent radiographically and the other 11 had a favourable status. Of the 15 patients classified as unfavourable at 3 years, 1 had a favourable status at 5 years and 10 had clinically and radiographically favourable status after modification of the allocated regimen (the remaining 4 patients had died before 3 years). Thus, no patient deteriorated between 3 and 5 years.

Korea

Of the 359 patients admitted to the study in Korea, 94 were excluded before 3 years [12]. A further 2 patients (1 Amb 6HR, 1 Amb 9PH) were excluded after 3 years because of further chemotherapy for pulmonary tuberculosis, and 13 patients were not seen after 3 years. Because the follow-up was terminated before all patients had reached 5 years, the results presented here are restricted to patients seen at 53 months or later, a total of 151 patients (39 Amb 6HR, 40 Amb 9HR, 33 Amb 9P/EH, 39 Amb 18P/EH). In addition the status at the last assessment after 3 years and details of any complica-

tions or additional chemotherapy are presented for all 250 patients seen after 3 years.

Pretreatment characteristics are given in Table 1. The characteristics of the four series were broadly similar (data not shown).

Of the total of 250 patients assessed after 3 years, 16 (2 Amb 6HR, 2 Amb 9HR, 11 Amb 9P/EH, 1 Amb 18P/EH) had had a major modification of their allocated regimen before 3 years [12]. Four patients (1 Amb 6HR, 2 Amb 9P/EH, 1 Amb 18P/EH) had an additional course of chemotherapy after 3 years, 3 for sinuses and the fourth because of radiographic deterioration.

Of the 265 patients followed up to 3 years [12], 88 had sinuses or clinically evident abscesses on admission (49 of the 151 followed up to 5 years in Table 1) and a further 33 patients developed such lesions during the first 3 years. Sinuses were still present at 3 years in 4 patients; the sinus had resolved in two (both Amb 18P/EH) by 48 and 60 months, respectively. The remaining 2 patients (1 Amb 9P/EH, 1 Amb 18P/EH) still had sinuses at their last assessment at 54 months. In addition, 2 patients (both Amb 9P/EH), whose initial lesion had resolved by 3 years, had recurrences of sinuses. In 1, the original lesion had resolved by 21 months but recurred at 48 months. After additional chemotherapy the sinus resolved by 52 months. In the other patient, whose abscess had resolved by 24 months, a sinus developed at 44 months and resolved with additional chemotherapy by 52 months. Two further patients developed sinuses for the first time after 3 years; one (Amb 9P/EH) developed an abscess and a sinus at 42 months that resolved without further chemotherapy. The second (Amb 6HR) had a sinus at 54 months and was given further chemotherapy with PAS and isoniazid; the sinus was still present at 5 years.

Myelopathy was present on admission or developed by 6 months in 33 patients (6 Amb 6HR, 12 Amb 9HR, 5 Amb 9P/EH, 10 Amb 18P/EH), 22 of them (4 Amb 6HR, 8 Amb 9HR, 3 Amb 9P/EH, 7 Amb 18P/EH) with functional impairment at some time [12]. The myelopathy had resolved by 18 months without additional chemotherapy and surgery in 23 but recurred in 4 (2 Amb 9HR, 1 Amb 9P/EH, 1 Amb 18P/EH) and persisted at 3 years in 2 of them. In a further 2 patients (1 Amb 6HR, 1 Amb 9HR) resolution had occurred by 3 years with additional chemotherapy. In the remaining 8 patients (1 Amb 6HR, 4 Amb 9HR, 3 Amb 18P/EH) myelopathy persisted at 3 years, in 2 with functional impairment. These two patients had weakness in one (Amb 9HR) or both (Amb 18P/EH) legs when last seen at 42 months. Of the other 6 who had myelopathy without functional impairment at 3 years, 5 had residual neurological signs at the last attendance (42, 48 and 3 at 60 months). The remaining patient (Amb 18P/EH) had no neurological abnormalities when last seen at 48 months.

At 3 years, complete bony fusion was present in less than half the patients in all four series; by 5 years the proportion had increased to half in all except the Amb 9P/EH series. However, an appreciable number of patients in all 4 series still had no bony fusion at 5 years (Table 2).

The mean total vertebral body loss on admission was equivalent to 1.2 vertebral bodies for the Amb 6HR, 1.4 for the Amb 9HR, 1.0 for the Amb 9P/EH and 1.2 for the Amb 18P/EH series. At 5 years there was a mean further loss in all 4 series of 0.4, 0.5, 0.9 and 0.5 bodies respectively, most of the loss having occurred early (Table 3). The mean angle of kyphosis (for patients with thoracic or thoraco-lumbar lesions) on admission was 47.3° for the Amb 6HR, 41.5° for the Amb 9HR, 33.7° for the Amb 9P/EH and 35.7° for the Amb 18P/EH series, the increase at 5 years being 10.9°, 15.4°, 27.0° and 9.9°, respectively. Most of the further increase had occurred early by 18 months [5].

Of patients assessed at 5 years, 35 of the 39 Amb 6HR, 34 of the 40 Amb 9HR, 24 of the 33 Amb 9P/EH and 35 of the 39 Amb 18P/EH series had a favourable status (Table 4). Of the 8 patients classified as having unfavourable status because of additional chemotherapy for their spinal lesion, 7 had a favourable status in all other respects at 5 years, and the eighth was clinically favourable but his disease was considered not yet quiescent radiographically.

Of the 114 patients who had a favourable status at 3 years, all except one had a favourable status at 5 years. This patient (Amb 6HR) had a sinus which had developed, for the first time, at 54 months. By 5 years 13 of the 26 patients (8 Amb 6HR, 9 Amb 9HR, 3 Amb 9P/EH, 6 Amb 18P/EH) who had been classified as still not favourable at 3 years had achieved a favourable status, the remaining 13 (3 Amb 6HR, 5 Amb 9HR, 1 Amb 9P/EH, 4 Amb 18P/EH) still not being considered favourable as their disease was considered to be not yet quiescent radiographically. Of the 12 patients classified as unfavourable at 3 years, 2 had sinuses, one of which was still present at 5 years (Amb 9P/EH), the other (Amb 18P/EH) having resolved. The other 8 patients were classified as unfavourable solely because of modification of their allocated regimen because of the spinal disease; at 5 years, 7 had a favourable status in all other respects and the eighth (Amb 9P/EH) in all respects except that the disease was not considered to be quiescent radiographically.

Of the 99 patients assessed after 3 years but not after 52 months, 11 had an unfavourable status at their last attendance, namely 1 of the 21 Amb 6HR, 2 of the 28 Amb 9HR, 5 of the 24 Amb 9P/EH, and 3 of the 26 Amb 18P/EH patients. One patient (Amb 18P/EH) had a sinus at his last attendance at 52 months and 2 (1 Amb 9HR, 1 Amb 18P/EH) had myelopathy with functional impairment at their last attendances, both at 42 months. The remaining 8 patients had had additional chemotherapy for their spinal disease, their status being favourable in all other respects at their last attendance.

Discussion

This report summarises the findings of a series of studies undertaken by the MRC Working Party on Tuberculosis

of the Spine in collaboration with the Indian Council of Medical Research in Madras, and with groups in Hong Kong and Korea. It brings together unique information on the role of short-course chemotherapy and radical surgery in the management of patients with widely differing characteristics. Over half (58%) of the patients were children in Korea compared with a third in Madras and 26% in Hong Kong and there was both clinical and radiographic evidence that the disease was most severe in Korea and least in Hong Kong. Sinuses or clinically evident abscesses were present on admission in 32% of the Korean patients but only 20% of those in Madras and 14% in Hong Kong, and myelopathy in 13%, 8% and 4%. The spinal lesion more often involved the thoracic and thoraco-lumbar spine in Korea and the lesions were, on average, more extensive, involving five or more vertebrae in 20%. Bony destruction and deformity, as measured by the angle of kyphosis was also greatest in the Korean patients. The regimens studied in the three centres reflected the very different surgical and medical facilities available.

The most important assessment of outcome of treatment used was achievement of a favourable status, for which patients had to have full physical activity with clinically and radiographically quiescent disease, with no sinuses, abscesses or myelopathy with functional impairment, all without modification of the allocated regimen. In all three centres the results achieved by the 6- and 9-month regimens of isoniazid plus rifampicin were excellent in terms of the proportion of patients achieving a favourable status by 5 years, most of whom had already achieved it by 3 years. The results of the 18-month regimen of isoniazid plus PAS or ethambutol in Korea were very similar but the 9-month regimen of isoniazid plus PAS or ethambutol in the same centre was clearly inferior. Thus, short-course regimens including rifampicin were demonstrated to be as effective as those regimens of longer duration that were also investigated in the first series of studies undertaken by the Working Party [8-10]. A reduction from 18 months to 6 or 9 months of treatment represents a major advance in terms of the need for organisation of chemotherapy and patient compliance. This is particularly important in developing countries, where most of the cases of tuberculosis of the spine now occur. The difficulties of ensuring that patients take chemotherapy for long periods of time has been one of the major problems of tuberculosis control [2, 3] and although shortening the total period by half or even two-thirds reduces the burden on both the patient and the treatment services considerably, the need for adequate supervision of chemotherapy remains. The need for further developments such as shortening the total duration even further or the use of widely spaced intermittent regimens that can be given as infrequently as once a week under full supervision, is widely accepted by all those involved in the management of tuberculosis. However, the large body of research in pulmonary tuberculosis indicates that with presently available drugs, regimens of less than 6 months' duration are not likely to be

adequate[4]. Several new rifampicin derivatives with much longer half lives than rifampicin are being developed and may make highly effective widely spaced intermittent regimens a practicable proposition [14]. Since the present studies were planned the role of pyrazinamide in the initial phase of short-course chemotherapy regimens has been demonstrated in numerous studies of pulmonary tuberculosis [7]. As it is thought to have a special sterilising role different from that of rifampicin its addition to the 6-month regimen of isoniazid and rifampicin in this study would be expected to give even better results. This regimen is currently recommended for the treatment of all forms of tuberculosis by the World Health Organisation and the International Union against Tuberculosis and Lung Disease (IUATLD) [6, 16] and for pulmonary tuberculosis by the American Thoracic Society (ATS) and British Thoracic Society (BTS) [1, 13, 15].

In the first series of studies conducted by the working party, the radical operation developed in Hong Kong of resection of the spinal focus and bone grafting showed some advantages over a simple surgical debridement. Surgical debridement, however, had no appreciable therapeutic advantages over ambulatory chemotherapy. In the present series of studies, very good results were achieved by the radical operation plus chemotherapy in Hong Kong, but this is likely to be at least in part related to the fact that the disease was least extensive on admission. In Madras, where the operation had not been introduced until the start of the study, the results achieved were no better than those of the ambulatory regimens and there were four deaths related to the operation. There are problems in introducing a new major surgical procedure even in an orthopaedic centre, which in the light of the excellent results achieved by chemotherapy alone suggest that it need not and should not be introduced. The need for surgical intervention in technically advanced countries is often in relation to diagnosis rather than to treatment in view of the excellent results achieved by chemotherapy alone. Although not investigated in the present series of studies, other methods of treatment such as bed rest or plaster jacket had no therapeutic benefit in addition to chemotherapy in the first series of studies [8] and therefore their use cannot be recommended. Chemotherapy is, without doubt, the critical factor in the management of tuberculosis of the spine and all efforts should be concentrated on ensuring that appropriate regimens are given under adequate supervision.

If, as may be expected from the longer-term results of the first series of studies, the 5-year results of chemotherapy prove to be permanent, short-term chemotherapy based upon rifampicin in patients ambulatory from the start would appear to be the best available method of treatment for this disease. Indeed, the main indication for any form of surgery would appear to be difficulty in diagnosis in patients whose condition cannot be correctly diagnosed by simpler methods, and in that case, again apart from special centres, debridement should be an ad-

equate operative technique with fewer complications than the radical operation. The advantages of radical surgery do not seem to justify its widespread adoption; it should be confined to centres adequately equipped in all respects.

However, the recent evidence of increasing incidence of tuberculosis in association with the HIV pandemic and in the homeless and in other deprived populations, even in the technically advanced centres, together with an increase in resistance to the key drugs, rifampicin and isoniazid, are of major concern. The introduction of fully supervised therapy (or 'directly observed therapy') has led to a reduction in the problem of drug resistance in several countries and the development of new drugs would obviously improve the options for those patients with multi-drug resistant disease. Even if these threats significantly increase, ambulant outpatient chemotherapy without resort to splintage or to open operation is likely to remain the best option for the management of spinal tuberculosis in the large majority of patients.

References

1. American Thoracic Society (1994) Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 149:1359–1374
2. Fox W (1983) Compliance of patients and physicians: experience and lessons from tuberculosis – I. *BMJ* 287:33–35
3. Fox W (1983) Compliance of patients and physicians: experience and lessons from tuberculosis – II. *BMJ* 287:101–105
4. Fox W (1984) Short-course chemotherapy for pulmonary tuberculosis and some problems of its programme application with particular reference to India. *Lung India* 11:161–174
5. Indian Council of Medical Research/British Medical Research Council Working Party Study (1989) A controlled trial of short-course regimens of chemotherapy in patients receiving ambulatory treatment or undergoing radical surgery for tuberculosis of the spine. *Indian J Tuberculosis* 36 [Supp]:1–21
6. International Union against Tuberculosis and Lung Disease, Antituberculosis regimens chemotherapy (1988) Recommendation from the committee on treatment of IUATLD. *Bull Union Tuberc Lung Dis* 63:60–64
7. Leading Article (1984) The role of pyrazinamide in primary chemotherapy for pulmonary tuberculosis. *Tubercle* 65:1–4
8. Medical Research Council Working Party on Tuberculosis of the Spine (1985) A 10-year assessment of controlled trials of inpatient and outpatient treatment and of plaster-of-Paris jackets for tuberculosis of the spine in children on standard chemotherapy. *J Bone Joint Surg [Br]* 67:103–110
9. Medical Research Council Working Party on Tuberculosis of the Spine (1978) Five-year assessments of controlled trials of ambulatory treatment, debridement and anterior spinal fusion in the management of tuberculosis of the spine. *J Bone Joint Surg [Br]* 60:163–177
10. Medical Research Council Working Party on Tuberculosis of the Spine (1982) A 10-year assessment of a controlled trial comparing debridement and anterior spinal fusion in the management of tuberculosis of the spine in patients on standard chemotherapy in Hong Kong. *J Bone Joint Surg [Br]* 64:393–398
11. Medical Research Council Working Party on Tuberculosis of the Spine (1986) A controlled trial of six-month and nine-month regimens of chemotherapy in patients undergoing radical surgery for tuberculosis of the spine in Hong Kong. *Tubercle* 67:243–259
12. Medical Research Council Working Party on Tuberculosis of the Spine (1993) Controlled trial of short-course regimens of chemotherapy in the ambulatory treatment of spinal tuberculosis. *J Bone Joint Surg [Br]* 75:240–248
13. Subcommittee of the Joint Tuberculosis Committee (1992) Guidelines on the management of tuberculosis and HIV infection in the United Kingdom. *BMJ* 304:1231–1233
14. Tam CM, Chan SL, Lam CW, Leung CC, Kam KM, Morris JS, Mitchison DA (1998) Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis. Initial report. *Am J Respir Crit Care Med* 157:1726–1733
15. Tuberculosis Committee of the British Thoracic Society (1998) Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 53:536–548
16. World Health Organisation Tuberculosis Unit Division of Communicable Diseases (1991) Guidelines for tuberculosis treatment in adults and children in national treatment programmes. WHO Geneva; WHO/TB/91: 1–61