PROGRESS IN CLINICAL NEUROSCIENCES 1992;869-81

SHORT COURSE CHEMOTHERAPY IN NEURO TUBERCULOSIS BRIEF REVIEW OF CLINICAL TRIALS UNDERTAKEN AT THE TUBERCULOSIS RESEARCH CENTRE, MADRAS

RAJESWARI RAMACHANDRAN, RANI BALASUBRAMANIAN, T. SANTHA DEVI

Tuberculosis Research Centre, Madras

INTRODUCTION

Tuberculosis of the nervous system can present as tuberculous meningitis, tuberculoma of brain, Potts paraplegia, tuberculosis of spine and rarely as arachnoiditis and vasculitis.

Tuberculosis is conventionally treated for 12 to 18 months to ensure adequate cure, stabilise quiescence and prevent relapses. With the introduction of rifampicin and pyrazinamide it became feasible to shorten the duration of chemotherapy to 6 to 9 months. Many controlled clinical trials conducted all over the world have confirmed the success of this approach in pulmonary tuberculosis by evolving 100% effective SCC regimens[1-5]. In a few studies especially tuberculous lymphadenitis, tuberculous abdomen and pericarditis SCC has also been used and found to be as effective as conventional regimens[6,7]. However, only recently has SCC been tried for neurotuberculosis. This presentation briefly highlights some of the chemotherapy trials conducted at the Tuberculosis Research Centre in some areas of CNS tuberculosis[8-10].

What is SCC? SCC refers to chemotherapeutic regimens containing powerful bactericidal drugs like INH, Rifampicin and Pyrazinamide, by the use of which the duration of treatment of TB is reduced from the conventional 12 to 18 months to 6 to 9 months.

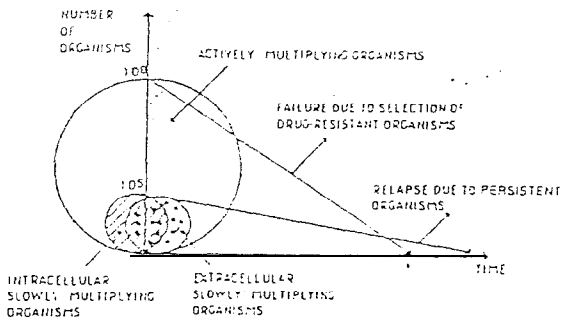
RATIONALE OF SCC :

The rationale for the use of short course chemotherapy is based on the different microbial populations in tuberculous lesions and the anti-microbial activity of different drug combinations for effective chemotherapy[11,12].

MICROBIAL POPULATION

It is possible to differentiate at least 3 different types of bacterial population[11,13]. The first is the population of organisms which actively grow at neutral pH in liquefied caseous material that covers the cavity wall, mainly drug susceptible mixed with drug resistant mutants. The second population is made up of organisms located in an acid pH environment especially inside macrophages. The organisms coated with antibody inside macrophage phagolysosomes presumably grow very slowly. The third population

consists of organisms located in solid caseous areas which multiplies slowly or intermittently or remain dormant since they are in a very unfavourable environment.



SCHEME OF THE CHEMOTHERAPY FOR TUBERCULOSIS

CHOICE OF DRUGS IN SCC[12]

SCC was made possible by the use of two drugs - Rifampicin and Pyrazinamide.

Rifampicin was found to be effective not only against actively multiplying organisms but also against dormant or persisting organisms responsible for relapses after treatment was stopped. With the rediscovery of pyrazinamide as a potent drug against organisms located in an acid environment, especially inside macrophages it became feasible to reach these difficult regions to kill the organisms. Isoniazid is very effective againstrapidly multiplying extra cellular organisms. The combination of pyrazinamide with rifampicin and isoniazid further increased the effectiveness of chemotherapy. Likewise, regimens with rifampicin in combination with isoniazid and streptomycin were almost 100% effective when given for 9 months. These findings led directly to the recommendation by the British Thoracic Association[4], American Thoracic Society[14] and others[15] of 6 months short course chemotherapy for tuberculosis. Rifampicin and pyrazinamide along with isoniazid are therefore the key sterilizing drugs in the chemotherapy of tuberculosis with SCC.

RELAPSES IN TUBERCULOSIS :

With adequate chemotherapy one may get sputum conversion at the end of treatment but culture becomes positive again after treatment is discontinued i.e. patient has a bacteriological relapse. Studies have shown that the majority of the patients relapse with organisms sensitive to the drugs used. With the advent of highly effective chemotherapeutic regimens with practically 100% efficiency, bacteriological relapse has become the most crucial factor in determining the relative merits of chemotherapeutic regimens[14].

To sum up, the aim in SCC is 1) to give a *bactericidal* drug combination in the initial two months, which will be effective against sensitive and resistant mutants. Aim being to achieve a rapid and total kill of the actively mutiplying bacterial population. 2) *Sterilising* drugs to prevent relapses. These act on slowly multiplying bacilli where there are no resistant mutants.

ADVANTAGES OF SCC :

1) Shortened duration, better compliance ;
2) Rapid conversion;
3) Risk of relapse less;
4) Acceptable level of toxicity; and
5) Cost effectiveness.

DOSAGE OF ANTI-TB DRUGS COMMONLY USED IN SCC :

Dosage Schedule *

Rhythm of administration	INH mg	Rif mg	PZA (G)	Emb mg
Daily	300	450	1.5	600
Thrice weekly	400	450	1.5	1000
Twice weekly	600	450	2.0	1200

* For patients weighing 40 kgs.

Though most of the trials were related to pulmonary tuberculosis the available data suggest that the approach could be extended to extra-pulmonary forms of the disease without many changes.

TRC STUDIES IN NEUROTUBERCULOSIS :

Though isolated reports on SCC in CNS tuberculosis[17] is available there are not many controlled clinical trials reported in neurotuberculosis. Encouraged by pulmonary tuberculosis studies done in TRC, we have done studies in TB spine, Pott's paraplegia, brain tuberculoma, and tuberculous meningitis. In what follows we discuss the role of SCC in TB spine, Pott's paraplegia and brain tuberculoma. Tuberculous meningitis studies are in progress and it is too early to draw any conclusions.

TUBERCULOSIS OF SPINE

Both medical and surgical approaches have been employed for the management of TB spine. Surgical approaches include debridement surgery and radical surgery (Hong Kong surgery) consisting of removal of diseased vertebrae and bridging of the gap with autologous bone graft. Chemotherapy consisted of administering streptomycin, isoniazid and PAS for 18 months with immobilisation in plaster shells. It was soon established that chemotherapy alone was as effective as surgery and patient could be treated as out--patients. In another study conducted in Hong Kong where all TB Spine patients underwent radical surgery with 6 to 9 months of chemotherapy containing INH and Rifampicin supplemented by Streptomycin twice a week, it was shown that short course chemotherapy of 6 and 9 months duration was effective[18].

Subsequent to this in the study at TRC, it was decided to compare short course chemotherapy with and without radical surgery in patients with tuberculosis of spine. Patients with clinically and radiographically active spinal tuberculosis involving the bodies of the thoracic and/or lumbar vertebrae were eligible for admission provided they

did not have obvious paraplegia. The patients were first assessed by the orthopaedic surgeon. If considered suitable for surgery, they were randomly allocated to one of the following regimens:

a Chemotherapy with isoniazid 6 mg/kg plus rifampicin 10-15 mg/kg daily for 6 months with radical surgery (Rad 6 regimen - Surgery + chemotherapy)

b Ambulatory chemotherapy with isoniazid plus rifampicin daily in the same dosages as in (a) for 6 months (Amb 6 regimen - chemotherapy alone for 6 months), and

C Ambulatory chemotherapy with isoniazid plus rifampicin daily in the same dosages as in (a) for 9 months (Amb 9 regimen - chemotherapy alone for 9 months)

In all 303 patients were admitted to the study and after excluding43 patientsfrom main analysis 260 remained in final analysis, 85 in Rad 6 series, 83 in Amb 6 series and 92 in Amb 9 series.

PRE-TREATMENT CHARACTERISTICS

The distribution of the clinical, radiological and bacteriological findings before the start of treatment was broadly similar for the 3 series.

TABLE 2 : PRE-TREATMENT CHARACTERISTICS

Pre-treatment characteristics		Total No.	Total %
Total patients		260	100
Age (Years)	0- 4	35	13
	5 - 14	52	20
	15 - 34	107	41
	35 -54	57	22
	55 or more	9	3
Sinus and/or clinically-evident Abscess		51	20
Kyphosis		219	84
Limitation of movement		246	95
Myelopathy (independent assessment)		19	7
Site of lesion Thoracic		97	37
Thoraco-lumbar		35	13
Lumbar		110	42
Lumbo-sacral		19	7
Mediastinal Psoas abscess shadow		149	57

MANAGEMENT

All patients in Rad 6 series were admitted as in-patients and 47 (60%) Amb 6 and 48 (52%) Amb 9 patients were also admitted. Out patients attended the centre twice a week and were given that day's doses under supervision and were supplied drugs for the next 2 or 3 days for self-administration. The homes of children aged below 5 years were visited daily and the drugs administered under supervision. The drug regularity was very high 97% and identical in the 3 series.

Results **Table 3**

	18 months			36 months		
	Rad6	Amb6	Amb9	Rad6	Amb6	Amb9
	%	%	%	%	%	%
Favourable	58	58	60	80	87	96
Still not favourable	33	36	38	9	7	3
Unfavourable*	9	6	2	11	6	1
Total patients	85	83	92			

"Death / Myelopathy / Additional Treatment

At 18 months the status of 58% of the Rad 6, 58% of the Amb 6 and 60% of the Amb 9 patients was classified favourable, that is they had no sinus or clinical abscess present, no myelopathy with functional impairment and had no additional operation or chemotherapy and no modification of allocated regimen; they also had no limitation of their physical activity due to the spinal lesion and their disease was radiographically quiescent. A further 28 (33%), 30 (36%) and 35 (38%) respectively had not yet attained such a favourable status radiographically; the remaining 8 (9%), 5 (6%) and 2 (2%) respectively were classified as unfavourable for reasons given in the table.

By 36 months 68 (80%), 72 (87%) and 88 (96%) of the 3 series respectively had attained a favourable status. The results of the Amb 9 series being significantly better than the Rad 6 series ($p=0.003$) but not the Amb 6 series ($p=0.07$).

CONCLUSION

The important conclusion from this study was that ambulatory chemotherapy with SCC regimens based on isoniazid and rifampicin is highly successful in the

treatment of patients with spinal tuberculosis. The most important finding at 3 years, was that the ambulatory series had better results than the radical series. These findings have a major implication in the management of this disease in developing countries where most of the cases occur. It means that operative intervention is not necessary in the majority of patients.

POTT'S PARAPLEGIA

Paraplegia used to be the most important serious complication of spinal tuberculosis and a fair proportion of beds in sanatoria and orthopaedic towards, were occupied by patients who had Pott's paraplegia. With the advent of effective chemotherapy and early diagnosis of TB the number of cases of Pott's paraplegia has come down. In order to compare SCC with surgical procedures in the management of Pott's Paraplegia a controlled clinical trial was carried out by TRC.

The aim of the study was to assess the efficacy of multi-drug 9-month regimen with or without surgery in the treatment of Pott's paraplegia. Patients with clinical or radiological evidence of active tuberculosis of vertebral bodies below D3 and paraplegia of recent onset within one month were eligible for admission to this study.

Initially ten patients were treated with a 9 month regimen combined with radical surgery within a week of starting treatment. The chemotherapy consisted of streptomycin 0.75g plus isoniazid 300 mg plus rifampicin 12 mg/kg body-weight plus pyrazinamide 35mg/kg plus ethambutol 25 mg/kg daily for 2 months, followed by rifampicin 12 mg/kg plus isoniazid 15 mg/kg twice-weekly for the next 7 months (2RSHZEmb daily/2RHtw).

In the main study 25 patients were treated with one of the following three regimens :

1. - CHEM series : Streptomycin 0.75g plus isoniazid 300 mg plus ethambutol 25 mg/kg daily plus rifampicin 12 mg/kg twice-weekly for 2 months, followed by rifampicin 12 mg/kg plus isoniazid 15 mg/kg twice-weekly for the next 7 months (2RtwSHEmb daily/7RHtw), or,

2. RAD Series : As in (1) and with radical excision of the diseased vertebrae, or

3. CT Series : As in (1) and with costotransversectomy

Combining the pilot study and the main study, 35 patients (17 RAD, 4 CT, 14 CHEM) were considered for the study. Of the total of 35 patients, 2(1RAD, 1CHEM) were excluded (1(CHEM) died early in treatment: 1 (RAD) had no bony lesion on admission). There remained 33 patients (16 RAD, 4 CT, 13 CHEM) for analysis.

Condition on admission : Of the 33 patients, 15 were males; 6 patients were aged 14 years or less and 16 were aged 35 years or more. The bladder was involved in 11 of the 33 (33%). Sixteen (48%) patients had a chest X-ray lesion suggestive of pulmonary tuberculosis but none had positive sputum by culture.

Neurological examinations, : Neurological assessment was clinical. All patients were assessed at start, then daily for 3 days, and thereafter, on alternate days till 2 weeks, weekly till 3 months, monthly till 9 months, 3-monthly till 3years and 6-monthly thereafter. The surgery group patients were assessed, in addition, before the operation and at 8 hours, 24 hours, and on the 2nd, 3rd, 5th and 7th days after the operation.

Management : Initially, all patients were hospitalised and the drugs were given under the direct supervision of a staff member. After discharge from the hospital, the patients collected the drugs once in 15 days as ambulant out-patients. The mean time taken to become ambulant i.e. able to walk unaided was 128 days in the CHEM series (range 25-367) and 85 days in the surgery series (range 9-122). The drug regularity was very high. The coverage for the follow-up at the various time points ranged from 90-100%.

TABLE 4

Status	Patients	
	No.	%
Total patients	33	–
Non-tuberculous death	2	–
Patients with assessable response	31	100
Paraplegia resolved	28	90
Unfavourable response *	3	10

* Rx extended beyond 9 months – 1
Death associated with spinal TB – 2

The table above gives the status at the end of 9 months of chemotherapy Of the 31 with an assessable response, 28 had resolution of paraplegia.

Speed of resolution: The speed of resolution with respect to motor power, spasticity and bladder involvement, amalgamating the findings in the 3 regimens, is presented in the table below. Considering motor power, 18 of 29 (62%) resolved by 3 months, 26 (90%) by 6 months and 28 (97%) by 9 months. Regarding spasticity, 14 (48%) resolved by 6 months, 17 (59%) by 6 months, 17 59%) by 9 months and 21(72%) by 12 months. Bladder recovery was complete in as many as 6 patients by 3 months, and in all by 6 months.

TABLE 5

	No. of	Resolved by months			
	pts.	3	6	9	12
Bladder	9	6	9	9	9
Motor power	29	18	26	28	28
Spasticity	29	3	14	17	21

CONCLUSION :

Of 29 patients alive at the end of treatment, all had their paraplegia resolved completely with or' without surgery. One died 11 months after treatment due to myocardial infarction and two patients due to accidents at 54th month and 36th month. The remaining patients were doing well at 60th month. There were no relapses. In this study, the numbers are small and needs to be confirmed by a larger series. The present study clearly demonstrates that Pott's Paraplegia can be effectively treated using a SCC regimen of 9 months duration. This finding has the same implications as that of the treatment of TB spine using SCC in that the duration of treatment is drastically reduced and the services of skilled neuro and orthopaedic surgeons may not be required.

BRAIN TUBERCULOMA

Brain tuberculoma is now being suspected much more often than in the past, probably due to increased awareness of the disease among physicians and the greater availability of the CT scan. Traditionally Brain Tuberculoma were treated by neurosurgeons by biopsy, decompression or total removal. With the advent of anti-tuberculosis drugs medical treatment of brain tuberculoma was established using combination regimens which had to be administered for atleast 18 months. There are reports which suggest that chemotherapy alone may be effective even for large brain tuberculomas with increased intracranial tension; however, no reports are available on the use of short-course chemotherapy for brain tuberculoma. A controlled study was undertaken to evaluate the efficacy of short-course chemotherapy in the management of brain tuberculoma.

A circumscribed hyperdense lesion compared to the surrounding brain, with a volume of 1000 cu.mm. or more, enhancing with contrast and having adjacent oedema on CT scan, was taken as tuberculoma for admission to the study.

All cases admitted to the study were randomly allocated to one of the following 9-month regimens:

Chemotherapy consisted of 3 drugs daily, rifampicin, isoniazid and pyrazinamide for 3 months, in Regimen 1 and thrice-weekly in Regimen II, followed by 2 drugs, rifampicin and isoniazid for 6 months, twice-weekly in both the regimens.

Regimen I : 3RHZ7/6RH2 (daily)

Regimen II : 3RHZ3/6RH2 (intermittent)

The following investigations were done on admission: CT scan, radiographs of the chest and skull, CSF culture, culture of sputum and urine, Mantoux, liver function tests and haematological examinations. CT scan was repeated at 1 month, 2 months and every 2 months thereafter till 2 consecutive scans were normal. If the size of the mass at the second month scan was more than 80% of the mass on admission, a biopsy of the mass was done for histopathology and culture examinations.

In all, 144 patients (121 from General Hospital and 23 from the Railway Hospital) were admitted to the study. The following analysis is based on 113 patients who have completed treatment, after excluding 31 for various reasons, including 13 who were

diagnosed as having a non-tuberculous lesion or where the scan criteria was not fulfilled, and 5 who had chemotherapy terminated for serious toxicity in the first 3 months. Table 6 gives the characteristics on admission.

TABLE 6

Date on admission		3RHZ7/6RH2		3RHZ3/6RH2		Both	
		No.	%	No.	%	NO.	%
Sex	Male	23	40	21	38	44	39
	Female	35	60	34	62	69	61
Age	–15	21	36	28	51	49	43
(years)	15-24	16	28	15	27	31	27
	35-44	7	12	4	7	17	10
	–45	1	2	4	7	5	4
Lesion	Single	43	74	45	82	88	78
	Multiple	15	26	10	18	25	22
Mantoux	0-9	25	43	28	51	53	47
(mm)	10-19	16	28	11	20	27	24
	–20	11	19	11	20	22	19
	Not tested	6	10	5	9	11	10
	Total	58	100	55	100	113	100

Of a total of 113 patients, 58 were allocated to the daily regimen and 55 to the intermittent regimen; 44 (39%) were males, 43% were less than 15 years of age, and only 4% were above the age of 44; and 88 (78%) patients had a single lesion in the CT scan. The characteristics in the 2 regimens were similar.

TABLE 7

Svmptoms and signs	Daily		Intermittent		Both	
	No.	%	No.	%	No.	%
Convulsion	47	81	45	82	92	81
Headache	40	69	31	56	71	63
Vomiting	20	34	19	35	39	35
Limb weakness	21	36	13	24	34	30
Fever	13	22	11	20	24	21

Visual disturbances	14	24	12	22	26	23
Unsteady gait	8	14	6	11	14	12
Others	6	10	5	9	11	10
Normal	26	45	29	53	55	49
Papilloedema	11	19	9	16	20	18
Deficit	10	17	9	16	19	17
Papilloedema plus deficit	11	19	8	15	19	17
Total patients	58	100	55	100	113	100

CLINICAL PRESENTATION :

Of the 113 patients, 20 presented with papilloedema only (Table 7), 19 had papilioedema with neurological deficit, 19 had only neurological deficit and 55 had only symptoms. Convulsion (81%) and headache (63%) were the main presenting symptoms (Table 7); 35% complained of vomiting and 30% of limb weakness.

The initial chest radiograph was suggestive of pulmonary tuberculosis in 11. Of these, 2 were culture-positive by sputum examination, with drug-sensitive organisms.

Table 8 shows the progress between 0 and 9 months as assessed by CT scan in 92 patients (45 daily, 47 intermittent) for whom readings were available. It was observed that in both series taken together.

TABLE 8

Progress (0-9 months)	Daily		Intermittent		Both	
	No.	%	No.	%	No.	%
Lesion disappeared	36	77	34	76	70	76
Lesion decreased						
by > 50%	2	4	3	7	5	5
by < 50%	6	13	6	13	12	13
Static	2	4	0	0	2	2
Lesion increased						
by > 50%	0	2	1	2	1	2
by < 50%	1		0		1	
New lesion appeared	0	0	1	2	1	1
Total patients	47	100	45	100	92	100

Tuberculomas had totally disappeared in 70 (76%) of the patients. In 17 (18%), a decrease in the size of the lesion was observed. In 2 patients, the lesion remained static. In 2 (2%) other patients, the lesions had increased in size and in another patient, a new lesion had appeared. Of the two patients with increased lesions, one refused surgery and continued to have hemiparesis and papilloedema. The two patients whose lesions remained static and the patient who had a new lesion were clinically doing well without additional chemotherapy.

The patients are being followed up till 60 months, and the clinical status at 24 month for 100 patients who have completed 24 months follow-up is given in table 9. Of these, 48 had no neurological deficit at the start of treatment and 52 patients had clinical signs – 19 with papilloedema plus deficit. At 24 months, 91 patients were normal clinically; 8 patients continued to have papilloedema and/or neurological deficit. None of the patients had a relapse of tuberculoma.

TABLE 9

Clinical status	Initial		At 24 months	
Normal	48		91	
Papilloedema	19		1	
Neurological deficit	16	52	1	8
Papilloedema plus deficit	17		6	
Total patients	100		99	

CONCLUSION :

At the end of chemotherapy, the results with the daily and intermittent regimens were similar. In all, 77% and 76%, respectively, showed total scan clearance. Clinically, 90% in the intermittent regimen and 91% in the daily regimen were normal. Residual deficit was seen in 6% in the intermittent regimen and 5% in the daily regimen. The results of SCC of 9 months' duration in the treatment of brain tuberculoma appear encouraging from the available data; and suggest that SCC may become the treatment of choice for brain tuberculoma.

In the management of brain tuberculoma using SCC the following points need to be kept in mind.

1. New lesions may appear and existing lesions may enlarge a phenomenon which has been noticed in the management of other extra pulmonary TB lesions. e.g. TB Lymph adenitis (Such events do not warrant any change in the management. (2) The role of surgery is restricted to shunt surgery, biopsy and decompression following clinical deterioration.

Although scan deterioration at the end of two months was an indication for surgery it was not resorted to unless there was concomittant clinical deterioration.

ADVERSE REACTIONS :

Jaundice was the most common adverse reaction seen, and was more common in daily regimens and in those patients who underwent surgery. (TB spine 18% in RAD series, 10% in AMB series, paraplegia 6% in RAD, 6% in CT series, Tuberculoma 22% in daily and 5% in intermittent) The occurrence of jaundice does not warrant stoppage of ATT. Effective management consists of stopping potentially hepatotoxic drugs like Rif, PYZ and INH and replacing them with SM and ethambutol. Rif, INH & PYZ may be reintroduced safely once jaundice has abated. Other less commonly encountered adverse reactions include Arthralgia, 'Flu syndrome' and GIT disturbances which are easily manageable using simple symptomatic drugs.

In Summary :

1. Short course chemotherapy of 6 to 9 months is an effective management schedule for neuro tuberculosis.
2. Both children and adults can be treated with SCC.
3. The relapse rates after short course chemotherapy regimens vary from 0 to 7% in pulmonary TB and almost nil in CNS TB showing the sterilising capacity of SCC regimens.
4. Role of surgery is minimised or relegated to the background as shown in TB spine and brain tuberculoma.
5. Jaundice is the most common side effect and this is clinically manageable.
6. Intermittent drug regimens are less toxic and as effective as daily regimens.
7. Patient's compliance was not a problem in the above studies. So we can confidently say that SCC has come to stay in the management of central nervous system tuberculosis.

References

1. Fox W., Short-Course Chemotherapy for pulmonary tuberculosis and some problems of its programme application with particular reference to India, Bulletin of the International Union against Tuberculosis 1985, 60, 40.
2. Fox W., Whither Short-Course Chemotherapy? Br. J. Dis Chest, 1981, 75, 331.
3. British Thoracic Association. A controlled trial of 6 months chemotherapy in pulmonary tuberculosis. First report: results during chemotherapy. British Journal of Diseases of the Chest, 1981, 75:141-53.
4. British ThoracicSociety. A controlled trial of6 month chemotherapy in pulmonary tuberculosis. Final Report: results during the 36 months after the end

of chemotherapy and beyond. British Journal of Diseases of the Chest, 1984, 78:330-6.

5. Balasubramanian R. et al., Five year results of a 3 month and two 5 month regimens for the treatment of sputum positive pulmonary tuberculosis in South India. Tubercle, 1990, 71:253.

6. Jawahar, M.S., Sivasubramanian, S., Vijayan, V. K. Short course chemotherapy for tuberculous lymphadenitis in children. British Medical Journal, 1990, 301:359.

7. Balasubramanian R., Rajeswari; R. et al. Interim results of a controlled clinical study of abdominal tuberculosis. Indian Journal of Tuberculosis, 1989, 36, 117.

8. Indian Council of Medical Research/British Medical Research Council Working Party Study in Madras, South India. A controlled trial of short-course regimens of chemotherapy in patients receiving ambulatory treatment or undergoing radical Surgery for tuberculosis of the spine, Ind. J. Tub., 1989, 36, suppl.

9. Rajeswari, et al., Short-Course Chemotherapy in the treatment of Pott's Paraplegia, Ind. J. Tub., 1959. 36:113.

10. Rajeswari, S. Kalyanraman S., Short course chemotherapy in the treatment of brain tuberculoma – a controlled clinical trial. Neurology India, 1989, Suppl Vol. 37, 512E03.

11. Grosset, J.H. Present and new drug regimens in chemotherapy and chemoprophylaxis of tuberculosis. Bulletin of International Union Against Tuberculosis and Lung Diseases, 1990. 65:86 to 90.

12. Grosset J.H. Present status of chemotherapy for tuberculosis. Review of Infectious Diseases. 1989. 11 (suppl 2) S347-S352.

13. Mutchison, D.A. The action of anti-tuberculosis drugs in short course chemotherapy. Tubercle. 1985. 66:219.

14. American Thoracic Society and Centers for Disease Control. Treatment of tuberculosis and tuberculosis infection in adults and children. American Review of Respiratory Disease, 1986, 134:355-63.

15. Societe francaise de Pneumologie. Recommendations pour le traitement de la tuberculose en France. Revue des Maladies Respiratories, 1984, 1:59-62.

16. Tripathy, S.P. Relapse in Tuberculosis. The Indian Journal of Tuberculosis, 1981, Vol. XXVIII. No. 2, 45-57.

17. Gowri Devi, M., Satis Chandra, P., et al. Is there a need for long treatment of tuberculous meningitis? Abstract, 37th Annual Conference of, Neurological Society of India. 1989, 73-74.

18. Medical Research Council working party on Tuberculosis of the spine. A controlled trial of six months and nine months regimens of chemotherapy in patients undergoing radical surgery for tuberculosis of the spine in Hong Kong. Tubercle 1986, 67, 243-259.