Management and outcome of chemotherapy for childhood tuberculosis

MEDICAL RESEARCH COUNCIL TUBERCULOSIS AND CHEST DISEASES UNIT

SUMMARY  The management and outcome of chemotherapy is reported for 393 children with tuberculosis notified in 1983 (191 (49%) of white, 155 (39%) of Indian, Pakistani, or Bangladeshi, and 47 (12%) of other ethnic origins). Most (313) had respiratory disease, 65 had extrathoracic lymph node disease, and 15 had both.

Only 15 (4%) of the 390 children for whom information was available did not complete chemotherapy, 10 because of default. All except 23 (6%) of the children known to have completed chemotherapy received isoniazid and rifampicin, 194 (52%) without additional drugs, 126 (34%) with ethambutol, eight (2%) with pyrazinamide, and seven (2%) with both drugs in the initial phase. The median duration of treatment was nine months.

At the time they were last seen, all except six of the 375 children who completed chemotherapy were classified by the clinician as cured either on the primary course of chemotherapy (348, 93%) or after modification for failure or relapse (11, 3%), or toxicity (10, 3%). The remaining children were still on treatment for relapse (n=2) or had defaulted from follow up (n=4).

In recent years several highly effective chemotherapy regimens of six to nine months’ duration for the treatment of pulmonary tuberculosis in adults have been developed in controlled clinical trials and are now being recommended for use in routine services of both technically advanced and developing countries. There is, in contrast, little information on the results of short course chemotherapy in children, although it is considered that, in general, the findings in adults apply to children. However, ethambutol, a drug widely used in the initial phase of short course regimens based on isoniazid and rifampicin, is not recommended in young children because of the difficulties of detecting ocular toxicity.

In 1978/79 the Medical Research Council Tuberculosis and Chest Diseases Unit undertook a survey of notifications of tuberculosis in England and Wales to study the characteristics of disease in both children and adults, and also undertook a follow up of the adults with pulmonary tuberculosis to study their management. A further notification survey was undertaken in 1983 and the follow up, which included both children and adults, studied both management and outcome. The findings for the children with respiratory or extrathoracic lymph node tuberculosis (most of the notified cases) are reported here.

Patients and methods

The population for this survey was based on the 401 children with respiratory disease (defined as a pulmonary lesion, a pleural effusion, or intrathoracic lymph node involvement, or any combination of the three), extrathoracic lymph node disease, or both, who were notified between 1 January and 31 December 1983, that is 89% of the 452 children in the notification survey. (A further six children had respiratory or extrathoracic lymph node disease but were known to have initial resistance to one or more antituberculosis drugs and were not included as this might have affected their management.)

Approximately two years after the last child was notified, a form was sent to each clinician to obtain information on the management and outcome, in particular (a) the chemotherapy prescribed, (b) hospital admission, (c) the occurrence of adverse reactions necessitating modification of chemotherapy, and (d) the status of the child when last seen. Information was received on 399 of the 401 children but six were excluded from the analysis: one died before treatment could be started, two started treatment abroad, one developed meningitis after starting treatment (and will be reported elsewhere) and in two the notes had been lost.
Results are thus presented for 393 children. There were 313 with respiratory disease (including eight with disease involving non-respiratory sites other than extrathoracic lymph nodes) and 80 with extrathoracic lymph node disease (including 15 with respiratory disease and three with disease of other sites as well). As the management of the 15 children with both respiratory and extrathoracic lymph node disease was similar to those with extrathoracic lymph node disease alone, the findings for these two groups have been combined. There are minor differences in the number of children in some of the analyses because every item of information was not always available.

Results

ALL CHILDREN—PRETREATMENT CHARACTERISTICS

Of the 313 children with respiratory disease, 144 (46%) were white, 130 (42%) were of Indian, Pakistani, or Bangladeshi ethnic origin (subsequently referred to as Indian subcontinent), and 39 (12%) of other ethnic origins (table 1). Forty seven (59%) of the 80 children with extrathoracic lymph node disease were white, however, and only 25 (31%) of Indian subcontinent ethnic origin, the difference being greater for those with extrathoracic lymph node disease only (69% and 20% respectively). The annual notification rate for lymph node disease had declined since the previous survey in 1978/9 in children of Indian subcontinent ethnic origin but increased in those of white ethnic origin.15

The age of distribution was broadly similar for the main ethnic groups for respiratory disease (table 1) and for the males and females. The age distribution of children with extrathoracic lymph node disease differed considerably between the ethnic groups, 21% of the 47 white children being aged 10–14 years compared with 76% of the 25 Indian subcontinent children (table 1).

Bacteriological confirmation of the diagnosis was obtained in 58 (19%) of the 313 children with respiratory disease only, 54 from respiratory specimens (usually gastric aspirate (n=30) or sputum (n=17)). A pulmonary lesion at independent radiographic assessment was present in 122 (44%) of the 277 with a radiograph available and involved an area of more than one sixth of a lung field in 34 (12%). A further 114 (41%) had enlarged intrathoracic nodes without a pulmonary lesion (but in nine (3%) a pleural effusion was present), 12 (4%) had an effusion only, and in 29 (10%) the radiograph was considered to be within normal limits. The pretreatment characteristics of the white and Indian subcontinent children were similar (data not tabulated here).

Of the 80 children with lymph node disease, bacteriological confirmation was obtained in eight (in seven from the node). In a further 46 there was histological confirmation. Of the 47 white children, only one (2%) had a positive culture from the lymph node, a further 35 (74%) having positive histology; the corresponding figures for the 25 children of Indian subcontinent ethnic origin were six (24%) and seven (28%). There were 11 (23%) white and 11 (44%) Indian subcontinent children who had neither bacteriological nor histological confirmation of the diagnosis of tuberculosis.

Of the 393 children, 249 (63%) were notified by chest physicians and 123 (31%) by paediatricians, although management may well have been undertaken jointly in some of them.

CHEMOTHERAPY

Completion of chemotherapy

Only 15 (4%) of the 390 children assessed did not complete chemotherapy (table 2), the main reason being default or poor compliance (n=10). One child died from congenital tuberculosis. In a further 58 (15%) children, chemotherapy was completed but not as planned by the clinician in charge, the com-
monest reasons being default or poor compliance (n=21), toxicity (n=10), and slow response or deterioration (n=10). Thus most (81%) of the children completed chemotherapy as planned by the clinician in charge. The findings were very similar for the children with respiratory and those with extrathoracic lymph node disease.

Individual drugs and regimens prescribed
All except two of the 391 children who started treatment were prescribed isoniazid, and all except nine rifampicin. Forty per cent received ethambutol, but only 5% pyrazinamide, and 4% streptomycin.

Almost all (352, 94%) of the 375 children who completed chemotherapy were prescribed regimens based on isoniazid and rifampicin (table 3); 52% had no additional drug. Over a third of the children had ethambutol as a third drug either in the initial phase only (30%) or throughout (4%). Only 15 (4%) had pyrazinamide in the initial phase, seven with ethambutol as well. The findings were similar for the children who completed chemotherapy as planned by the clinician in charge. A higher proportion of the patients with extrathoracic lymph node disease received one or two additional drugs (either in the initial phase or throughout), namely 48% compared with 35% of those with respiratory disease. There was evidence that the choice of regimen was influenced by the radiographic characteristics of the respiratory disease; for example 20 (59%) of the 34 children with a pulmonary lesion involving more than one sixth of a lung field were prescribed regimens containing ethambutol or pyrazinamide (or both drugs) in addition to isoniazid and rifampicin, compared with 38% of those with smaller pulmonary lesions and 23% of those with enlarged intrathoracic nodes only.

No child was prescribed intermittent chemotherapy.

Duration of chemotherapy
Table 4 shows the distribution of the duration of chemotherapy for the children who completed chemotherapy as planned for the two regimens most commonly prescribed, namely isoniazid and rifampicin alone or with ethambutol in the initial phase. Although the median duration was nine months for both regimens there was some evidence that those not receiving ethambutol in the initial phase were treated for a shorter time (32% compared with 8%...
Management and outcome of chemotherapy for tuberculosis

Table 4  Duration of isoniazid+rifampicin and isoniazid+rifampicin+ethambutol/isoniazid+rifampicin regimens for children who completed chemotherapy as planned

<table>
<thead>
<tr>
<th>Duration (months)</th>
<th>Isoniazid+rifampicin No (%)</th>
<th>Isoniazid+rifampicin+ethambutol/isoniazid+rifampicin No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6</td>
<td>36 (21)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>7, 8</td>
<td>18 (11)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>9</td>
<td>59 (35)</td>
<td>48 (50)</td>
</tr>
<tr>
<td>10, 11</td>
<td>15 (9)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>12</td>
<td>26 (15)</td>
<td>15 (16)</td>
</tr>
<tr>
<td>13-15</td>
<td>8 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>9 (5)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Total No children assessed</td>
<td>171 (100)</td>
<td>96 (100)</td>
</tr>
<tr>
<td>Median (months)</td>
<td>9.0</td>
<td>9.0</td>
</tr>
</tbody>
</table>

The duration of chemotherapy has been calculated so that, for example, nine months represents from 8.5 to 9.5 months.

Table 5  The use of ethambutol in the initial (or only) phase for the 151 patients in whom the dosage and duration were known

<table>
<thead>
<tr>
<th>Duration (months)</th>
<th>No of children prescribed dosage (mg/kg)</th>
<th>Total children No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-12</td>
<td>13-17</td>
</tr>
<tr>
<td>≤ 1</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>7-9</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>10-12</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>&gt;12</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total No children assessed</td>
<td>32</td>
<td>76</td>
</tr>
</tbody>
</table>

The use of ethambutol was more than 15 mg/kg compared with 37% of 106 aged 5 to 9 and 15% of 136 aged 10 to 14 years.

Adverse reactions
In all, 11 (3%) of the 390 children for whom information was available were reported to have adverse reactions necessitating modification of their chemotherapy. No child had more than one type of reaction. Five children had vomiting, two had abnormal liver function tests without symptoms of hepatitis, three had rashes, and one developed possible ocular toxicity (it was not possible to determine whether or not this was confirmed at ophthalmological assessment). In six children one or more drugs were stopped, in three treatment was interrupted, and in two the drug dosage was reduced.

INITIAL HOSPITAL ADMISSION
Less than half (46%) of the 313 children with respiratory disease were admitted to hospital initially compared with 75% of the 80 with extrathoracic lymph node disease. For both groups the main reason for admission was for investigation and diagnosis (77% and 95% respectively). For those with respiratory disease, other main reasons were severity of disease (5%), emergency (4%), and social factors (3%).

Hospital stay was reported to be prolonged for reasons other than tuberculosis in 14 (10%) of the children with respiratory disease and three (5%) of those with extrathoracic lymph node disease, the main reasons being coexisting disease (n=6) and social reasons (n=6).

The median duration of hospital stay for tuber-
closus (table 6) was only four days for children with extrathoracic lymph node disease compared with nine days for those with respiratory disease, 15% and 29% respectively being in hospital for more than two weeks.

**OUTCOME OF CHEMOTHERAPY**

*Duration of follow up*

The date of last attendance was known for 366 of the 375 children who completed chemotherapy; 15% were last seen at the time chemotherapy was completed, 27% within 6 months after completion, 31% from six to 12 months, 16% from 12 to 18 months, and 11% more than 18 months. Some of the children had been discharged from follow up but many were still attending.

**Outcome in the children who completed chemotherapy**

Most (93%) of the 300 children with respiratory disease were classified by the clinician as cured on the primary chemotherapy (table 7) and a further 5% after modification of chemotherapy. There were 11 children who could be considered to be therapeutic failures because they had modification of chemotherapy or a further course for slow response, deterioration, or relapse, although nine were classified as cured when last seen. In at least two of the 11, poor compliance was considered to have contributed to the therapeutic failure. Of the six children whose chemotherapy was modified because of a slow response to treatment, three had persisting enlargement of the hilar nodes with middle lobe consolidation (n=1) or partial obstruction of the right main bronchus (n=1) or trachea (n=1); the last patient was also prescribed steroids. One patient had a large effusion that was slow to resolve; chemotherapy was modified and steroids were added. The remaining two patients were reported to be slow to respond clinically. Two children had chemotherapy modified because of clinical and radiographic deterioration and three relapsed after stopping chemotherapy.

Only five of the 75 children with extrathoracic lymph node disease were not classified as cured on the primary course of chemotherapy (table 7). Two had modification of the chemotherapy for slow response, one because of persisting lymphadenopathy (who also received steroids) and one because of lack of clinical improvement with weight loss. Three children had chemotherapy modified for toxicity. Although 16 of the 75 children who completed chemotherapy were reported to have residual palpable lymph nodes when last seen, none of these were considered to be clinically important.

**CLINICAL COURSE OF EXTRATHORACIC LYMPH NODE LESIONS**

Of the 80 children with lesions, 25 (31%) had an abscess or sinus on admission, the proportion being higher for the white (18, 38%) than for the Indian subcontinent children (three, 12%). A further seven (9%) developed an abscess or sinus for the first time after starting treatment (five (11%) of the white and one (4%) of the Indian subcontinent children). One or more nodes increased in size during chemotherapy in five (6%) children and new nodes appeared in 11 (14%).
CORTICOSTEROIDS
Corticosteroids were prescribed for seven (2%) of the 393 children for reasons associated with their tuberculosis; four for persistently enlarged lymph nodes (two with hilar nodes resulting in collapse of the right upper lobe in one and the right middle lobe in the other, one with enlarged paratracheal nodes resulting in severe tracheal compression, and one with both paratracheal and cervical nodes). Two children had pleural effusions and the seventh child had respiratory disease which was slow to respond to chemotherapy. Four of the seven children also had modification of their antituberculosis chemotherapy (see above).

OTHER DISEASES
In all, 41 of the 393 children were reported to have one or more coexisting diseases, the commonest being asthma in 19. Six children had anaemia, three had congenital heart lesions (one coarctation of the aorta and two ventricular septal defects), one had Down's syndrome, one thalassaemia, one haemophilia, and three had other congenital abnormalities. Other diseases, each occurring in one child, were bronchiectasis, coeliac disease, epilepsy, encephalitis, and diabetes, and two were reported to have unspecified psychiatric illnesses.

FACTORS AFFECTING MANAGEMENT
Stepwise multiple regression analysis restricted to children notified by chest physicians or paediatricians (95% of the children) were used to examine possible associations between pretreatment factors and patient management. The independent variables studied were age, sex, ethnic origin, the results of smear examination and of culture of sputum, the presence of a pulmonary lesion or enlarged intrathoracic nodes at independent assessment, whether notified by the paediatrician or chest physician, and the type of lesion (respiratory or extrathoracic lymph node).

An analysis of the total duration of chemotherapy based on 288 children who completed chemotherapy as planned and were prescribed regimens based on isoniazid and rifampicin identified four significant factors associated with a longer duration of chemotherapy, namely, notified by a paediatrician, a positive culture, extrathoracic lymph node disease, and Indian subcontinent ethnic origin.

Duration of hospital stay in the 174 children admitted initially and whose stay was not prolonged for reasons other than tuberculosis was significantly associated with two factors, namely the diagnosis of respiratory disease and a pulmonary lesion at independent assessment (both associated with a longer duration).

In neither the analyses of duration of chemotherapy nor those of hospital stay did the independent variables account for more than 14% of the total variation and it is likely that most of the remaining variation is due to differences in methods of management of the large number of clinicians involved.

Discussion
This survey has provided information on the routine management of children diagnosed as suffering from respiratory or extrathoracic lymph node tuberculosis in England and Wales in 1983, almost all of whom were managed by respiratory physicians or paediatricians. Information was collected at least two years after the start of treatment and the results of treatment were, on the whole, excellent. Only 4% of 390 children did not complete a course of chemotherapy, usually because of default or poor compliance, and of those completing treatment 93% were reported to be cured on the primary course of chemotherapy, a further 6% being cured after modifications, which were frequently minor.

At most, only 13 (3%) of the children could be regarded to have responded unsatisfactorily, 11 with respiratory and two with extrathoracic lymph node disease. In eight (including the two with lymph node disease) the only problem was a slow response to the initial chemotherapy. Of the remaining five, two were reported to have deteriorated during chemotherapy and three to have relapsed after stopping chemotherapy. Poor compliance was considered to have contributed to therapeutic failure in at least two of the patients and all except the two still on treatment at the time of the follow up were considered to be cured after modification of the chemotherapy or a further course.

The regimens currently recommended for the treatment of pulmonary tuberculosis in adults in England and Wales are a nine month regimen of isoniazid and rifampicin with a two month initial supplement of ethambutol, or a six month regimen in which pyrazinamide is also given for the first two months. The role of pyrazinamide in the initial phase in short course chemotherapy is well established in adult pulmonary disease, and the risk of hepatic toxicity in these regimens is very low. There is much less experience with pyrazinamide in children, although it has been used in children with tuberculous meningitis in Hong Kong and Madras. In the present survey only 5% of children were given pyrazinamide initially, compared with 23% of 1068 adults with pulmonary tuberculosis notified in the first six months of 1983. It will be important to assess how widely the six month regimen containing
pyrazinamide becomes adopted in clinical practice in the next few years, both in children and adults and to monitor both the acceptability and toxicity in routine practice. In the present survey the regimen most commonly prescribed for both respiratory and lymph node disease was isoniazid and rifampicin without a third drug (in 52%). In view of the low incidence of initial resistance\textsuperscript{15} and the limited extent of disease in most children it is likely that treatment with such a regimen is adequate for most children in England and Wales and this is borne out by the results. Even in adults with extensive smear positive pulmonary disease in East Africa, a regimen of isoniazid and rifampicin for six months was highly effective with a relapse rate of only 7\% in 164 patients in two years of follow up.\textsuperscript{20} Studies in Hong Kong have shown that adult patients with smear negative pulmonary disease (whether culture positive or culture negative) and small radiographic lesions can be cured by regimens of four months' duration,\textsuperscript{21} and this group of patients may correspond more closely to many of the paediatric cases than the more extensive, culture and frequently smear positive pulmonary disease in patients with whom short course chemotherapy has usually been investigated. The results achieved in the present survey suggest that durations of less than nine months, even without pyrazinamide, were effective.

The evidence is that the main role of ethambutol when given in addition to isoniazid and rifampicin is the prevention of the emergence of further resistance in the small proportion of patients with initial resistance to one or more antituberculosis drugs.\textsuperscript{22} As the incidence of initial resistance to isoniazid is low in children in the United Kingdom (although higher in those of Indian subcontinent than those of white ethnic origin\textsuperscript{15}) there is little, if any, place for ethambutol in the treatment of tuberculosis in children. Indeed, because of the risks of ocular toxicity associated with this drug and the difficulties of detecting such toxicity in children, it has been recommended that it should not be used in young children.\textsuperscript{9} In this survey, however, only one possible case of ocular toxicity was reported in 151 children receiving the drug, many in dosages higher than those recommended and for a longer period.

Adverse reactions to the antituberculosis drugs requiring modification of chemotherapy were rare, occurring in only 11 of the 390 children for whom information was available. There were only two children who had chemotherapy modified because of abnormal liver function tests; neither had symptoms of hepatitis. In one child (aged six years) possible ocular toxicity was reported but we were unable to ascertain whether it was confirmed on ophthalmological examination. The commonest reactions were vomiting (n=5) and skin rashes (n=3). Appropriate dosages of individual antituberculosis drugs for adults are well established but there has been considerable variation in the dosages recommended for children. In the present survey there was a wide range in the dosages of isoniazid, rifampicin, and ethambutol prescribed on a mg/kg body weight basis. Although most were within an acceptable range, an appreciable proportion were prescribed dosages below or above the range. The recommended dosage of ethambutol is the same as the adult dosage but for isoniazid and rifampicin higher dosages are usually recommended. For isoniazid 10 mg/kg is the standard dosage,\textsuperscript{23} although up to 20 mg/kg is sometimes recommended.\textsuperscript{8} and recent reports have suggested that lower dosages may be adequate.\textsuperscript{24} In the survey 25\% of the children received dosages of 5 mg/kg or less and 4\% had 15 mg/kg or more. The recommended dosage of rifampicin is 10–20 mg/kg,\textsuperscript{8,23} and there is evidence that dosages in the higher end of the range should be prescribed in children (but not in neonates).\textsuperscript{25} However, a study of children with tuberculous meningitis in India demonstrated that there is an appreciable risk of hepatic toxicity particularly if rifampicin is given in association with isoniazid in high dosage.\textsuperscript{19} In the present survey, 19\% of children were prescribed dosages of less than 10 mg/kg and 7\% more than 20 mg/kg. For ethambutol, where dosage is of particular importance because of its association with ocular toxicity, 22\% received less than 13 mg/kg and 30\% more than 17 mg/kg, 12\% receiving more than 17 mg/kg for more than two months. In view of the difficulty of detecting ocular toxicity in very young children, it is of particular concern that 36\% of those aged less than 5 years were prescribed ethambutol.

Of the 80 children with extrathoracic lymph node disease, 6\% had a temporary increase in size of one or more nodes during chemotherapy, 9\% developed abscesses or sinuses, and 14\% developed new nodes. None of these children were given corticosteroids, although they were prescribed for four children with persistently enlarged intrathoracic nodes. Residual lymph nodes were reported in 16 children at the time the child was last seen but none was considered clinically significant and all the children were classified as cured by the clinician. Such problems in the clinical course of lymph node disease are well known and, in a study conducted by the British Thoracic Society in adults,\textsuperscript{26} were as common during and after treatment with an 18 month regimen of isoniazid and rifampicin as with a nine month regimen, and were rarely due to a relapse or reactivation of the tuberculosis.
Initial admission to hospital was usually for investigation and diagnosis (in just under half of the children with respiratory disease but three quarters of those with extrathoracic lymph node disease). In most of the children with lymph node disease it was related to surgical procedures and the median duration of stay for tuberculosis was only four days. In respiratory disease the median duration of admission for tuberculosis was nine days, 29% of the children being in hospital for more than two weeks and 10% for more than four weeks. Thus hospitalisation was usually for specific indications and for short periods.

This survey has shown that the results of treatment of childhood respiratory and extrathoracic lymph node tuberculosis in England and Wales in patients diagnosed in 1983 were, on the whole, excellent. Chemotherapy was based on the highly effective combination of isoniazid and rifampicin in most patients, although the high proportion of children, even of those aged less than 5 years, receiving ethambutol gives some cause for concern. However, no confirmed ocular toxicity was documented. A third drug may be desirable in circumstances where there is likely to be a high risk of initial drug resistance. Pyrazinamide has been shown to result in a more potent regimen of shorter duration in adults but experience of pyrazinamide in children is relatively limited. The evidence is that it is well tolerated.18 19 and has a low incidence of side effects, and therefore its use should be considered as a third drug in the initial phase of chemotherapy even in young children. Recent recommendations about the treatment of tuberculosis in adults and children have recommended the use of chemotherapy based on isoniazid, rifampicin, and pyrazinamide,3,8 and the Joint Tuberculosis Committee of the British Thoracic Society is currently preparing a similar recommendation for Britain.

The survey was undertaken by Mr AJ Nunn, Mr SP Byfield, Dr JH Darbyshire, and Professor W Fox, Medical Research Council Tuberculosis and Chest Diseases Unit, Dr KM Citron (consultant physician) and Dr JO Warner (consultant paediatrician), Brompton Hospital. Radiological assessments were made by Dr M Caplin. The contribution of the Communicable Disease Surveillance Centre (Dr NS Galbraith) and the Mycobacterium Reference Unit (Dr PA Jenkins) of the Public Health Laboratory Service was coordinated by Dr ON Gill.

References
1 Fox W. Short-course chemotherapy for pulmonary tuberculosis and some problems of its programme application with particular reference to India. Bull Int Union Tuberc 1985;60:40–9.
Correspondence to Dr JH Darbyshire, MRC Cardiothoracic Epidemiology Group, Brompton Hospital, Fulham Road, London SW3 6HP.

Accepted 4 January 1989
Management and outcome of chemotherapy for childhood tuberculosis. Medical Research Council Tuberculosis and Chest Diseases Unit.

Arch Dis Child 1989 64: 1004-1012
doi: 10.1136/adc.64.7.1004

Updated information and services can be found at:
http://adc.bmj.com/content/64/7/1004

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/