ISONIAZID IN PRIMARY TUBERCULOSIS IN INFANCY*

A CONTROLLED CLINICAL TRIAL

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(RECEIVED FOR PUBLICATION APRIL 19, 1961)

Before the introduction of isoniazid it had been established that streptomycin was of little use in the treatment of primary tuberculosis. It did not prevent extension of the primary lesion within the lung (Lorber, 1950), and it did not prevent the occurrence of haematogenous spread or of meningitis during treatment.

When isoniazid became available it seemed essential to establish its value, if any, in the treatment of uncomplicated primary tuberculosis. As the prognosis of primary tuberculosis in English children is generally favourable, it was clear that a strictly controlled trial would be necessary to reach satisfactory conclusions. It was also clear that infants were the most suitable subjects for inclusion in such a trial, because one could be reasonably certain that the infection was of recent onset, and because in infants tuberculous infection much more commonly results in tuberculous illness than in older children. The study of a relatively small group of patients would, therefore, be sufficient to determine the value, if any, of a proposed line of treatment.

Treatment of primary tuberculosis with isoniazid might influence the course of the disease in four different ways:

- (1) it could influence the course of the primary tuberculosis itself;
- (2) it could eliminate local spread and local complications, e.g. collapse, obstructive emphysema or bronchiectasis;
- (3) it could prevent haematogenous dissemination, miliary tuberculosis and tuberculous meningitis; and
- (4) it could prevent post-primary pulmonary tuberculosis.

It will take many years of observation to reach conclusions on the last point, but it is possible to determine in a much shorter time the effect of isoniazid on the course of the primary tuberculosis

itself and its value in the prevention of the immediate post-primary complications.

Present Trial

A prospective trial was designed to answer these problems. This paper is concerned with the results obtained after five years of observation. Past experience with tuberculous infants suggested that it was ethically justifiable to withhold specific treatment from infants with uncomplicated primary tuberculosis as long as they were under strict supervision. Under these conditions any complication could be detected and treated early with an assurance of a satisfactory recovery.

Plan and Method of Analysis. The trial began in April 1952, when isoniazid became available. All tuberculin positive infants aged 24 months or less with uncomplicated and previously untreated primary tuberculosis were enrolled in the trial. The large majority of infants who were enrolled in the investigation were first seen at a Tuberculosis Contact Clinic because they had been in contact with a known case of tuberculosis. A few had been admitted to hospital for various reasons and were found to have primary tuberculosis. Once an infant satisfied the criteria for inclusion in the investigation, he was allocated by random sampling into one of two groups (Table 1). Patients in the first group ('treated cases') received isoniazid (5 mg./kg. daily), and P.A.S. (0.5 g./kg. daily) in three divided doses. No injections were given. Treatment was given for three months. Patients in the second group ('controls') received no specific treatment. Children in both groups received the same vitamin supplements. The protocol of the investigation provided that if any patient were to develop tuberculous disease which required specific treatment, such treatment was to be given by isoniazid, streptomycin or any other suitable drug.

The trial was to be run on a basis of domiciliary

* Based on a paper delivered at the Children's Hospital Medical Centre, Boston, Mass., in January 1961.

TABLE 1
PLAN AND METHOD OF INVESTIGATION

<i>Criteria for inclusion:</i> all tuberculin positive infants age 24 months or less with uncomplicated primary tuberculosis	
<i>Method of allocation:</i> random sampling	
<i>Method of initial investigation and follow-up:</i>	
<i>Treatment</i>	<i>Controls</i>
Isoniazid 5 mg./kg. daily and P.A.S. 0.5 g./kg. daily for 3 months	Vitamin supplements only
Vitamin supplements	
<i>Additional treatment</i>	as required
<i>Hospital admission</i>	exceptional

TABLE 2
SEX INCIDENCE AND AGE ON ADMISSION TO TRIAL

Age (mths)	Treated	Controls
0-6	2	5
7-12	7	9
13-18	10	10
19-24	11	5
Average age (mths) ..	16	13
Boys	15	17
Girls	15	12

TABLE 3
PRINCIPAL SOURCES OF INFECTION AND THEIR FATE

Source of Infection	Last Known Condition			Total
	Died	Still Active	Quiescent	
Mother	4	5	7	16
Father	6	3	14	23
Grandparents ..	2	3	3	8
Other relatives ..	2	2	5	9
Neighbours ..	1	0	0	1
All known sources ..	15	13	29	57

management. The large majority of the patients were not admitted to hospital except for a few days of initial clinical and bacteriological studies. Exceptionally infants were admitted for longer periods either because there was no one to look after them at home, or because they developed complications. Clinical and radiological examinations were performed in both groups at monthly intervals in the first four months; at intervals of two months up to the end of the first year, and then at three-, four- and six-month intervals up to the

end of the second, third, fourth, and fifth years respectively. More frequent examinations were performed when necessary. It was fortunate that a 100% follow-up was secured. A few infants left the district, but either attended at the appropriate time for examination even from long distances, or else attended Chest Clinics in their new areas. Information about these was then obtained from the chest physicians concerned.

Material and Clinical Features on Admission. Between April 1952 and October 1955, 59 infants (32 boys and 27 girls) were admitted to the investigation. Thirty were allocated into the group treated with isoniazid plus P.A.S., and 29 received no specific therapy at this stage ('controls'). In order to safeguard the infants in the control group, and to determine the necessary length of the investigation, concurrent analyses of the results were carried out. The investigation, therefore, could have been interrupted at any time if evidence accumulated that the treated group fared better than the controls. The investigation was concluded in October 1960. At this stage all patients had been observed for five years. Events after the fifth anniversary of the inclusion in the trial will not be considered in this paper.

The control group was accidentally weighted with small infants. On admission the average age of the treated infants was 16 months, and of the controls 13 months. There were two treated infants aged 6 months or less as compared with five controls (Table 2). Nine treated infants had a chronic cough on admission, and five of these had some degree of stridor. Six controls had a chronic cough, but only one had stridor. With regard to symptoms, therefore, the treated group was weighted with more severe cases, and this feature helped to counteract the influence of age in the opposite direction. Four treated infants and six controls showed tuberculin conversion in the two months immediately preceding their inclusion in the trial.

Contact History. A human source of infection was either known on admission or became known as a result of contact investigations in 29 of the treated and in 28 of the controls. They were mostly members of their own household, and usually they were close relatives (Table 3). The only two infants whose source of infection was not found both had primary abdominal complexes. This became apparent later when calcified mesenteric lymph nodes were demonstrated radiologically.

The principal source of infection was the mother in 16, the father in 23, a grandparent in eight,

another relative in nine and a neighbour in one. In several instances multiple sources of infection were found, but in Table 3 only the principal source is shown. These sources of infection had usually a severe disease, as shown by their subsequent progress: 15 died during the period of observation; 13 had active disease at the end of the five-year period of observation, and were still undergoing treatment. Only 29 were considered to be in the quiescent stage.

Radiological Features on Admission. The radiological changes in the lungs on admission are shown in Table 4. The distribution and the types of the lesions were very similar in the two groups. Twenty-one treated infants and 22 controls had radiologically demonstrable lung lesions at the first examination. Thirty-one of these infants had gross lesions.

Results: Clinical Course

The course of the disease was uneventful in most infants. There were no deaths either from tuberculosis or from any other causes. Twenty-five treated children and 24 controls had no tuberculous illnesses during the period of observation (Table 5).

Tuberculous Illnesses

Treated Cases. Five children who had been treated with isoniazid and P.A.S. had tuberculous illnesses at some stage. In two the illness was already present on admission into the investigation. These two (Cases 1 and 2) strictly speaking should not have been included in the investigation. In one infant the illness developed during isoniazid treatment (Case 3), and in two it occurred after the conclusion of the routine treatment (Cases 4 and 5). Only one child required additional antibiotic chemotherapy.

CASE 1 (M.N., Table 10). This girl was 22 months old when she was admitted to the investigation. At this stage she had stridor associated with obstructive emphysema of the left lung (Fig. 1). The stridor became more severe while on treatment and bronchoscopy had to be performed two weeks after admission. Although no obstruction was seen, her condition rapidly improved after bronchoscopy. She lost her stridor and made an uneventful recovery.

CASE 2 (K.S., Table 8). This boy was 11 months old on admission. His mother was in a sanatorium at the time he was brought to the clinic by a neighbour. They were unaware that the child had any subjective complaint. The baby was difficult during examination, but limitation of movement of the left shoulder joint was noted. As there was no swelling, tenderness or wasting and a

TABLE 4
RADIOLOGICAL FEATURES IN LUNGS ON
ADMISSION

Radiological Features	Treated	Controls
Negative	9	8
Hilar glandular enlargement only ..	4	7
Gross lesions	17	14
Segmental or lobar	7	6
Big or multiple opacities	9	6
Tuberculoma	1	2
Total	30	29

TABLE 5
TUBERCULOUS ILLNESSES

Illness	Treated		Controls	
	First Three Months	Later	First Three Months	Later
Meningitis	—	—	1	—
Miliary	—	1	—	—
Bronchial obstruction	2	—	1	—
Bronchial spread	—	1	—	1*
Osteitis	1†	—	—	—
Soft tissue abscess	—	—	1†	—
Phlyctenular conjunctivitis	—	—	1*	2

* These developed while receiving isoniazid and streptomycin.

† Present, but unrecognized on admission.

radiograph of the humerus and shoulder joint was normal, not enough importance was attached to the limitation of movement. Later it transpired that the mother had noticed stiffness of his left shoulder for several weeks past. Subsequently the typical changes of tuberculosis of the left shoulder joint and of the upper end of the humerus were radiologically demonstrated. Five years later this child was quite well, but he had ankylosis of his left shoulder joint. This is the only

Fig. 1.—Case 1: Obstructive emphysema of the left lung due to tuberculous glands in the left hilum.

child in the whole series of 59 who has subjective residual disability from his tuberculous infection. It is clear in retrospect that he already had tuberculosis of his shoulder joint on admission and should not have been included in the investigation. His management, nevertheless, would have been very similar.

CASE 3 (G.E., Table 10). This girl was 20 months old and symptom-free on admission. She developed acute bronchial obstruction during treatment, with gross cyanosis. An emergency bronchoscopy had to be carried out, which saved her from suffocation. Much tuberculous granulation tissue was removed from her bronchi. She then made an uneventful recovery and remained symptom-free during the next five years. A very small, well-defined calcified complex in the right lower lobe and the right hilum is the only residual evidence of her past illness.

CASE 4 (P.C., Table 8). This boy of 24 months of age remained symptom-free during chemotherapy and for nine months afterwards. Then he developed an acute febrile respiratory illness which persisted for several weeks. This illness was attributed to a massive collapse of the right middle lobe which occurred as a result of bronchial obstruction by a group of calcified glands. Subsequently he remained symptom-free for the remainder of the five-year period of observation (Figs. 2 and 3).

The following is a case of miliary tuberculosis.

CASE 5 (B.F., Table 8). This girl was 8 months old on admission. She was symptom-free and had an uncomplicated primary complex in her right upper lobe. Her progress was uneventful during the three months while she was on treatment. Although she remained well, a routine chest x-ray six months after admission showed that she now had generalized miliary tuberculosis. Tubercle bacilli were recovered from her gastric washings. She was given a six months' course of isoniazid and streptomycin treatment and she made an uneventful recovery. Five years after her admission she was perfectly well and had a calcified complex in her right upper lobe.

Controls. Five children who were not given specific treatment on admission developed tuberculous illnesses. In one the illness was probably present on admission but was not recognizable (Case 6), and in two it developed during the first three months of observation (Cases 7 and 8). Two others, whose history will not be described in detail, developed phlyctenular conjunctivitis during the second and third year of observation respectively. Of these five, two required full anti-tuberculous chemotherapy (Cases 6 and 8). All made a complete recovery.

CASE 6 (E.R., Table 11). This 11-month-old boy was symptom-free on admission but had an extensive shadow in his left upper lobe which showed incipient central

calcification (Fig. 4). He also had enlarged calcifying cervical glands. A week after admission he developed a swelling over the lower half of his sternum, almost in the mid-line. This later became fluctuant. Neither at this stage nor at any other time was there any clinical or radiological evidence of an underlying bony disease of either the sternum, the ribs or the vertebrae. When the swelling appeared the infant was put on isoniazid and streptomycin treatment and this treatment was given for six months. The soft tissue abscess was incised and tubercle bacilli were cultured from the pus. The abscess healed well. This infant also developed phlyctenular conjunctivitis both during and after the conclusion of his chemotherapy. At the end of five years of observation he was perfectly well, but he had extensive calcifications in his cervical, thoracic and abdominal lymph nodes as well as in his spleen, and he had a persistent segmental collapse in his left upper lobe (Figs. 4-6).

CASE 7 (S.S., Table 9). This boy was 4 months old on admission. He developed bronchial obstruction with stridor and general signs of ill health during the first three months of observation. He made a rapid recovery without any active measures being taken, but had several brief episodes of stridor during the first year. He had no subjective symptoms during the next four years. At the end of five years he was perfectly well, but had extensive calcified lesions in both lung fields, in both hila and in the abdomen (Figs. 7-9).

The following is a case of tuberculous meningitis.

CASE 8 (S.B., Table 9). This boy was 10 months old on his admission. He was symptom-free but had an extensive recent lesion in his right upper lobe and enlarged glands in the right hilum (Fig. 10). During the first three months of observation he became slightly off colour. For this reason his cerebrospinal fluid was examined. It showed minimal changes characteristic of 'serous tuberculous meningitis' (Lincoln, 1947). Gradually the changes in the cerebrospinal fluid developed into the typical findings of tuberculous meningitis and tubercle bacilli were then recovered on direct smear and also cultured. He was treated with intramuscular and intrathecal streptomycin plus P.A.S. for six months and made an uneventful recovery. He never had any neurological signs. Five years after admission he was perfectly well, had a normal intelligence, normal hearing and a normal electroencephalographic tracing. He had a calcified complex in his right upper lobe (Figs. 10-12).

The infants who developed haematogenous complications were under 12 months of age, and all had *gross* radiological changes on admission. One treated infant and two controls required anti-tuberculous chemotherapy above that laid down in the plan of the investigation.

Non-tuberculous Illnesses. The efficiency of chemotherapy, if any, might have shown itself by the improved general health of the infants and a reduced liability to non-tuberculous illnesses. In

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 2.—Case 4 (P.C.) (Table 8): Collapse of right middle lobe one year after admission.

FIG. 3.—Case 4: Bilateral calcified complexes five years later.

FIG. 4.—Case 6 (E.R.) (Table 11): Extensive opacity with faint calcifications, occupying the whole of the left upper lobe, on admission.

FIG. 5.—Case 6: Slight improvement one year later, with persistent segmental collapse.

FIG. 6.—Case 6: Five years later; small segmental collapse persists. There are calcified hilar lymph nodes.

FIG. 6.

FIG. 7.—Case 7 (S.S.) (Table 9): Large mottled shadows in right mid-zone and hilum, on admission.

FIG. 8.—Case 7: Increased mottled shadowing in right lung, plus enlargement of the left hilar nodes, and some mottling of the left lung three months later.

FIG. 9.—Case 7: Bilateral large, dense calcified complexes five years later.

FIG. 10.—Case 8 (S.B.) (Table 9): Extensive recent primary complex in right upper lobe on admission.

FIG. 11.—Case 8: Much worse one year later. The whole upper lobe is involved.

FIG. 12.—Case 8: Large calcified complex in right upper lobe five years after admission.

TABLE 6
NON-TUBERCULOUS ILLNESSES

Disease	Treated	Controls*
Measles	18	13
Pertussis	4	6
Upper respiratory infections, including sore throat ..	19	28
Lower respiratory infections ..	14	19
Other illnesses	43	35
All illnesses	98	101

* Excluding two patients who were later given chemotherapy.

TABLE 7
AVERAGE GAIN OF WEIGHT

	Average Weight Gain (kg.)	
	Treated	Controls*
During first 3 months	0.8	1.0
At 1 year	2.6	2.9
At 2 years	4.6	5.0
At 3 years	7.4	7.0
At 4 years	9.0	8.3
At 5 years	10.8	10.7

* Excluding two patients who were later given chemotherapy.

fact, no significant difference was found between the groups in this respect (Table 6). Not counting common colds, the 30 treated patients had 98 intercurrent illnesses and 27 controls (having excluded two who had to have chemotherapy) had 101 illnesses. The distribution of the illnesses was very similar. Measles was followed by a considerable temporary worsening of the radiographic appearance of the lung lesion in two treated infants. No other child suffered any detectable clinical or radiological exacerbation of his condition following an intercurrent illness.

Weight Gain. There was very little difference between the two groups with regard to weight gain either during the initial three-month period or subsequently (Table 7).

Radiological Changes. The radiological changes in the lungs which occurred during the period of observation are described below, related to the findings on admission:

- (1) 17 infants whose radiographs appeared normal;
- (2) 11 infants who showed enlarged hilar lymph nodes;
- (3) 31 infants who had gross radiological changes. In each group the changes in the treated children

are described first, separate consideration being given to events during the first three months after admission.

(1) *17 Infants with Negative Radiographs on Admission.* There were 17 infants whose radiographs of the chest were normal on admission. Nine were treated and eight were controls. Three treated infants and four controls developed intrathoracic calcification either of the hilar lymph nodes or of the whole primary complex (Table 13). None of these had a demonstrable active lesion at any time and the calcifications were the first signs of an intrathoracic lesion. The calcifications became visible approximately three years after admission, and were very small. One child in each group had temporary lobar consolidation five months and four years after admission, respectively. These cleared quickly and completely and were not followed by calcification. These lesions were considered to be non-tuberculous.

Seven infants (three treated and four controls) who had no pulmonary lesion at any time, developed calcified mesenteric lymph nodes approximately two years after admission.

In the remaining three infants (all treated) no active or calcified tuberculous lesion was discovered at any time up to five years after their admission. The only evidence of their tuberculous infection was a repeatedly positive tuberculin reaction.

It is seen, therefore, that radiologically the progress of all these 17 infants was uneventful.

(2) *11 Infants with Hilar Glandular Enlargement on Admission.* Eleven infants (four treated and seven controls) on admission presented with unequivocal and often gross hilar enlargement, but without a radiologically demonstrable parenchymal lung lesion. In three of the four treated infants the lesions regressed and calcification took place up to three years after admission. In one treated infant a temporary collapse of the left lower and of the right middle lobe occurred 22 months after admission. This was not associated with any illness, and the collapse was not present two months later. The final picture in all four treated infants was that of a small, single calcified primary complex.

None of the seven children in the control group showed any progressive enlargement of the glands or an extension of the lesions into the lung parenchyma in the acute stage, nor did they develop segmental collapse. On the final radiograph they all had calcified primary complexes. In three these were single and small, in three double primary calcified foci of moderate size were seen in two

different lobes either in the same lung, or in the opposite lung. In the seventh child extensive bilateral calcification developed. This infant had a completely uneventful clinical course.

(3) *31 Infants with Gross Pulmonary Lesions on Admission.* Thirty-one infants had more extensive pulmonary lesions. There were three different types. In 15 infants (nine treated and six controls) the lesions consisted of single or multiple primary complexes in which the pulmonary components were sufficiently large to produce a clearly definable shadow on the radiograph of the chest. In 13 infants (seven treated and six controls) large opacities or translucencies of lobar or segmental distribution were seen and were attributed to consolidation, and/or collapse or to obstructive emphysema. Three infants (one treated and two controls) each had a solitary, very large round parenchymal

lesion without correspondingly large hilar enlargement. These three lesions were considered to be tuberculomas. These 31 infants constitute the most important group. Their radiological changes are described individually, in some detail, together with brief clinical notes in Tables 8-12.

(a) 15 INFANTS WITH LARGE OR MULTIPLE PRIMARY COMPLEXES

Treated Cases: There was one infant among the nine treated cases (Table 8) (J.A.) whose lung lesion showed significant deterioration in spite of isoniazid and P.A.S. treatment during the first three months. This deterioration immediately followed an attack of measles (Figs. 13 and 14). In two other children (P.C. and D.C.) deterioration occurred during the months following the conclusion of treatment and one of them (P.C.) had a temporary lobar collapse (Figs. 2 and 3). The most spectacular complica-

TABLE 8
RADIOLOGICAL PROGRESS IN NINE TREATED INFANTS WITH LARGE OR MULTIPLE
PRIMARY COMPLEXES ON ADMISSION

Name	Age O/A (mths)	Radiological Features					Clinical Course
		On Admission	At Three Months	At One Year	Later	Special Features	
P.C.	24	Fresh primary complex right middle lobe, right hilum and focus in left lower lobe	Incipient calcification on right	Much worse; collapse of right middle lobe; calcification progressing (Fig. 2)	Extensive calcified shadows right middle, right lower and left lower lobes and both hila 3-5 yrs (Fig. 3)	Lobar collapse after conclusion of treatment	Uneventful
R.W.	18	Large complex right mid-zone and right hilum; enlarged left hilum	Same	Same	Calcification of both hila and of primary focus in left lower lobe 3-5 yrs	—	Uneventful
S.R.	16	Massive opacities right upper and right middle lobes and grossly enlarged paratracheal glands (Fig. 15)	Right upper lobe lesion and paratracheal glands; much smaller—dense opacity persists in right middle lobe	Minimal shadows in right upper lobe; no other lesions	Normal by 2 yrs; no calcification developed by 5 yrs (Fig. 16)	Remarkable and complete clearing of extensive lesions	Slight intermittent stridor during first year
M.M.	10	Several opacities in left upper lobe; enlargement left hilum; early calcification	Much clearer; several calcifying shadows left upper lobe, left lingula and left hilum	Progressive calcifications	Dense calcified lesion at 2 years with progressive absorption up to 5 years	Final radiograph virtually normal	Uneventful
D.C.	9	Very large right upper lobe and right mediastinal complex	Slight improvement	Mass increasing in size; central calcification	Gradual calcification ending up with small calcified complex 3-5 years	—	Uneventful
J.A.	20	Ill-defined shadows left lung and primary complex left lower lobe with early calcification (Fig. 13)	Much worse—gross opacity of entire left upper lobe (Fig. 14)	Well calcified complex left upper lobe and left hilum	Gradual calcification resulting in small calcified complex at 5 years	Segmental lesion during treatment following measles	Uneventful
K.S.	11	Primary complex right upper lobe; incipient calcification right hilum	Progressive calcification	Calcified complex right upper lobe	—	—	Tuberculous shoulder (See Case 2)
B.F.	8	Primary complex right upper lobe	Considerable regression	Incipient calcification right upper lobe	Calcified complex right upper lobe 2 years onwards	Miliary tuberculosis at 6 months	See Case 5
S.G.	18	Calcifying complexes both upper lobes and hilum	Calcification progressing	Dense bilateral calcifications	Calcification persisting, but decreasing in size at 5 years	Cervical lymph node calcification	Uneventful

FIG. 13.—J.A. (Table 8): Ill-defined shadows in left lung and primary complex in left lower lobe with incipient calcification on admission.

FIG. 14.—J.A.: Three months later: extension of opacity which occupies the whole of the left upper lobe.

tion occurred in B.F. who developed miliary tuberculosis six months after admission.

Dramatic and eventually complete or almost complete clearing of initially extensive lesions occurred in two infants (M.M. and S.R.) (Figs. 15 and 16). In the remaining children the course

of events was one of slow resolution followed by calcification. Five years after admission one of the nine has a clear chest radiograph, one has minimal calcification of the hilar lymph nodes on one side, four have single calcified complexes and three have extensive multiple bilateral calcifications.

TABLE 9

RADIOLOGICAL PROGRESS IN SIX CONTROL INFANTS WITH LARGE OR MULTIPLE PRIMARY COMPLEXES ON ADMISSION

Name	Age O/A (mths)	Radiological Features					Clinical Course
		On Admission	At Three Months	At One Year	Later	Special Features	
S.S.	4	Large mottled shadow right middle and right hilum (Fig. 7)	Worse; left hilum also enlarged; diffuse mottling both sides (Fig. 8)	Large calcifying focus right upper lobe; calcified mass in right hilum; calcified left hilar glands	Dense calcified masses both upper lobes, right lower lobes, both hila and in mesenteric lymph nodes 2-5 years (Fig. 9)	Multiple intra-thoracic and abdominal primary complexes	Repeated stridor (See Case 7)
K.R.	7	Large soft shadows right middle and upper lobes and right hilum	Considerable regression of all shadows	Large calcified mass right middle and upper lobe, and right hilum	No change up to 5 years	Double primary complex	Uneventful
J.C.	23	Opacity left upper lobe and large left hilar nodes	Much better	Hard opacity of left hilum	Returned and remained normal 2-5 years	—	Uneventful
S.B.*	10	Extensive recent complex right upper lobe and right hilum (Fig. 10)	Worse; * ?miliary spread	Much worse; * right upper lobe completely opaque with early calcification (Fig. 11)	Gradual regression of soft shadows, leaving a large calcified complex in right upper lobe at 5 years (Fig. 12)	Deterioration and lobar lesion during treatment	T.B.M. (See Case 8)
S.C.	13	Very extensive fluffy shadows right upper lobe and right hilum	Almost clear	Opacity whole of right middle lobe and large hilar glands again	Regression of pulmonary shadows leaving minimal right hilar calcification only; gross abdominal calcification by 2 years	Double intra-thoracic and abdominal primary foci, lobar collapse at 1 year	Uneventful
L.McB.	13	Fresh large primary complex right upper lobe and right hilum	Slight regression	Incipient calcification in regressed complex	Well calcified small complex right upper lobe 2-5 years	—	Uneventful

* Treated with streptomycin and P.A.S. from second month onwards.

FIG. 15.—S.R. (Table 8): Massive opacity in the right upper and middle lobes with grossly enlarged hilar lymph nodes.

FIG. 16.—S.R.: Normal radiograph four years later: no calcifications.

Controls: Two of the six controls (Table 9) showed significant deterioration during the first three months of observation (S.S. and S.B.). The possibility of miliary tuberculosis was considered in both, but remained unconfirmed. One of these infants developed tuberculous meningitis (S.B., Case 8) and although his meningitis responded rapidly to treatment with streptomycin and P.A.S. his lung lesions showed progressive deterioration (Figs. 10-12). Eventually complete healing took place. The other infant recovered without specific treatment, but the extent of his intrathoracic and abdominal calcifications made it clear that he had had disseminated tuberculous lesions (Figs. 7-9). An infant who was 13 months old on admission (S.C.) developed a temporary collapse of his right middle lobe at one year. His clinical course was uneventful. On his final radiograph only a minimal hilar calcification was demonstrable. The latest radiographs in this group of six show that one (J.C.) has a clear chest x-ray, one has minimal calcification of his hilar lymph nodes, one has a small and another a large, single calcified complex and two have large multiple calcified pulmonary complexes. Two children have calcified abdominal glands in addition to their intrathoracic lesions.

(b) 13 INFANTS WITH LOBAR OR SEGMENTAL LESIONS

Treated Cases: Three of the seven treated infants (Table 10) showed significant extension of their disease during the three months of treatment. In one of these a segmental collapse became lobar collapse (G.E.), in the second the lesions in the right

middle lobe became more extensive (D.H.), and in the third an already pronounced lobar obstructive emphysema became of extreme degree (J.B.) (Figs. 17 and 18). All the other four infants showed considerable improvement by the time treatment was concluded. In one of these (J.G.) remarkable fluctuations occurred during treatment, large opacities completely disappearing in a matter of days, only to reappear and disappear again in rapid succession (Figs. 19-22).

One year after admission the radiographs were better in all children than at any time earlier. The latest radiographs five years after admission were normal in three children; three had a well calcified single pulmonary complex and one had bilateral calcified complexes. Calcification of the cervical lymph nodes persisted in one child whose pulmonary complex first calcified and later became absorbed (C.M.).

Controls: One of the six controls (Case 6, E.R.) (Table 11) developed a haematogenous soft tissue abscess soon after admission and had to be treated with isoniazid and streptomycin. There was only little and slow radiological improvement during the six months of treatment and at the end of five years he still had a segmental collapse in his left upper lobe. This is the only persistent segmental lesion in the entire series of 59 (Figs. 4-6). He also has calcified abdominal lymph nodes.

The remaining five infants in this group required no specific treatment. None deteriorated during the first three months, or at any time later, with the possible exception of B.S. This infant's original lesion showed consistent improvement, but he

TABLE 10

RADIOLOGICAL PROGRESS IN SEVEN TREATED INFANTS WHO PRESENTED WITH LOBAR OR SEGMENTAL LESIONS OR OBSTRUCTIVE EMPHYSEMA ON ADMISSION

Name	Age O/A (mths)	Radiological Features					Clinical Course
		On Admission	At Three Months	At One Year	Later	Special Features	
G.E.	20	Segmental collapse right middle lobe; glandular mass right hilum	Collapse of whole right middle lobe; glandular mass in right hilum increased; slight right pleural effusion	Much better; faint opacity in region of right middle lobe	Well calcified single complex in right costophrenic angle and right hilum from 2-5 years	Deterioration during treatment; good end result	(See Case 3)
J.G.	6	Complete consolidation of left upper lobe, confluent with left hilar shadow (Fig. 19)	Very slight shadow in left mid-zone	Few calcified specks in the left lingula	Calcifications absorbed; normal radiograph at 4 and 5 years	Remarkable fluctuations during first 3 months (Figs. 19-22)	Uneventful
D.H.	16	Consolidation of right middle lobe; massive glands right hilum; enlarged left hilum	Worse; fresh shadow in right upper lobe and patchy shadowing left upper lobe in addition to previous shadows	Much better; both hila calcifying; small focus right middle and left upper lobes	Well-developed double calcified primary complex right middle and left upper lobes	Deterioration during treatment; good end result; double primary complex	Uneventful
S.C.	9	Consolidation left upper lobe and enlarged mediastinal glands	Considerable regression	Calcified speck left upper lobe, otherwise normal	Calcification absorbed by 3 years, leaving normal radiograph	—	Uneventful
C.M.	9	Large opacity occupying left lingula and enlarged glands left hilum with early calcification	Regression of pulmonary shadows; extensive calcification left hilar and mediastinal lymph nodes	Densely calcified complex left lingula and hilum	Calcification of cervical lymph nodes; pulmonary calcifications absorbed by 5 years	Temporary increase of left perihilar shadows at 15 months; double primary complex	Uneventful
M.N.	22	Obstructive emphysema of entire left lung; big glands left hilum (Fig. 1)	Much better; only considerably enlarged left hilar lymph nodes	Further decrease in left hilar shadow	Calcified complex left upper lobe developing between 2 and 5 years	Rapid improvement ? due to bronchoscopy	(See Case 1)
J.B.	12	Lobar opacity left upper lobe; obstructive emphysema left lower lobe; mass of left hilar glands (Fig. 17)	Worse; gross increase in obstructive emphysema with deviation of mediastinum to right (Fig. 18)	Much improved; minimal emphysema on left	Well calcified primary complex left costophrenic angle and left hilum at 2-5 years	Temporary worsening during treatment; good end result	Uneventful

FIG. 17.—J.B. (Table 10): Lobar opacity of left upper lobe and obstructive emphysema of the left lower lobe due to gross hilar lymphadenopathy.

FIG. 18.—Gross increase in degree of obstructive emphysema three months later.

FIG. 19.

FIG. 20.

FIGS. 19-22.—J.G. (Table 10): Rapidly fluctuating lesions in the left upper lobe and left lingula during the first three months after admission.

FIG. 21.

FIG. 22.

developed a lobar consolidation in his other lung on two widely separated occasions. On each occasion this lesion resolved quickly and there was no evidence that it was tuberculous. In three of the five children substantial improvement occurred by three months and in all five by one year. The last radiograph, five years after admission, was normal in two children. Small calcified complexes persisted in the other three.

(c) THREE INFANTS WITH PULMONARY TUBERCULOMATA

Finally, there were three infants who had a solitary, large round lesion without comparable degree of enlargement of the hilar lymph nodes (Table 12). The rate of shrinking of the lesion, the degree and type of calcification and the final outcome were similar in the one treated infant and in the two controls. None showed improvement by three months, but a reticular type of calci-

fication developed and the tuberculoma started to contract by one year. This process continued and now all three have a dense calcified mass which is much smaller than the original lesions. Small adjacent calcified primary complexes became demonstrable in all three (Figs. 23-31).

(4) *Summary of Radiological Changes.* There were nine infants with no demonstrable pulmonary lesions at any time. Seven of them had primary abdominal complexes. Among the remaining 51 children there were 20 who had either no demonstrable lesion on admission or had hilar glandular enlargement only. No subsequent deterioration was seen in any of these. They all developed pulmonary calcified complexes, irrespective of whether they were treated with isoniazid or not.

All the important changes occurred among the 31 who already had gross lesions on admission. The most serious complications seen were miliary

TABLE 11

RADIOLOGICAL PROGRESS IN SIX CONTROL INFANTS WHO PRESENTED WITH LOBAR OR SEGMENTAL LESIONS ON ADMISSION

Name	Age O/A (mths)	Radiological Features					Clinical Course
		On Admission	At Three Months	At One Year	Later	Special Features	
E.R.*	11	Extensive opacity with central calcification occupying the whole left upper lobe; calcifying glands in neck (Fig. 4)	Decreasing mass left upper lobe with extensive calcification in it; splenic and mesenteric calcifications ++	Left upper lobe collapse; additional calcified focus in left lower lobe, otherwise same (Fig. 5)	Segmental collapse of left upper lobe persisted at 5 yrs; extensive calcifications in left upper, left lower lobes, left hilum (Fig. 6); cervical and mesenteric nodes* in spleen	Deterioration during isoniazid treatment, persistent collapse; multiple ? primary foci; splenic calcifications	(See Case 6)
L.W.	6	Massive opacity occupying the pectoral segment of right upper lobe, glands, right hilum	Substantial general improvement	Small calcifying focus, right upper lobe; glandular mass denser	Well calcified double but small primary complex right upper lobe from 2-5 years	Rapid improvement	Uneventful
J.D.	18	Opacity occupying the whole of the left lingula	Substantial improvement	Small calcifying focus left lingula and left hilar nodes	Very small calcified complex left lingula persisting at 5 years	Rapid improvement	Uneventful
D.G.	13	Consolidation of right middle lobe	No improvement	Much better; only right hilar enlargement	Returned to normal at 2 years and remained so at 5 years; no calcification	Complete clearing of big lesion	Uneventful
L.Z.	4	Segmental opacity left upper lobe; enlarged glands left hilum	No improvement	Opacity smaller and denser; glands not demonstrable	Minimal calcified complex left upper lobe at 3 years, and normal at 5 years	—	Uneventful
B.S.	3	Enlarged gland left hilum; obstructive emphysema left lower lobe	Much improved—emphysema less obvious	Large calcified gland left hilum	Small calcified complex left lower lobe at 2-5 years	Intercurrent symptomless consolidation of whole of right middle lobe at 5 and 15 months after admission with complete clearing within 1 month each time	Uneventful

* Treated with isoniazid and streptomycin for 6 months, starting one week after admission.

TABLE 12

RADIOLOGICAL PROGRESS IN THREE INFANTS WHO PRESENTED WITH PULMONARY TUBERCULOMA ON ADMISSION

Name	Age O/A (mths)	Radiological Features					Clinical Course
		On Admission	At Three Months	At One Year	Later	Special Features	
(a) Treated T.W.	21	Very large uniformly dense mass in region of right middle lobe; no apparent glandular enlargement (Fig. 23)	Same	Shadow smaller; dense reticular calcification throughout its substance (Fig. 24)	Progressive shrinking of lesion with increasing dense calcification; very dense contracted mass at 4-5 years; minimal hilar gland calcification 3-5 years (Figs. 25-26)	—	Uneventful
(b) Controls N.K.	17	Dense round opacity occupying left lingula; no apparent glandular enlargement (Fig. 27)	Same	Reticular calcification throughout substance of lesion; small calcifying gland in left hilum (Fig. 28)	Progressive shrinking of lesion with increasingly dense calcification; small calcified gland left hilum 3-5 years (Figs. 29-31)	—	Uneventful
P.B.	13	Large round shadow in right middle lobe without apparent glandular enlargement	Same	Reticular calcification developing in shrinking tuberculoma; additional small calcifying complex right lower lobe and hilum	Progressive shrinking and increasing calcifications at 5 years	—	Uneventful

FIG. 23.

FIG. 24.

FIG. 25.

FIG. 26.

FIG. 27.

FIG. 23.—T.W. (Table 12): Fresh tuberculoma in right middle lobe, on admission.

FIG. 24.—T.W.: Reticular calcification taking place one year later.

FIGS. 25 and 26.—T.W.: Dense residual calcified mass five years later.

FIG. 27.—N.K. (Table 12): Fresh tuberculoma in left lingula on admission.

FIG. 28.—N.K.: Reticular calcification one year later.

FIG. 30.

FIG. 29.

FIG. 31.

FIGS. 29-31.—N.K.: Progressively dense calcification and regression.

tuberculosis in a treated infant, three months after the conclusion of treatment; and persistent segmental collapse in a control who had to be given a prolonged course of treatment starting soon after his admission. Considerable but temporary deterioration occurred during the first year after admission in six treated infants and in three controls.

The latest radiographs (Table 13) show that of the 30 treated children 10 have no detectable lung lesion, 20 have intrathoracic and four extrapulmonary calcification. These figures compare with seven out

of 29 controls with negative radiographs of the chest, and 22 with calcified intrathoracic lesions. Seven children have calcified abdominal lymph nodes, including three who have intrathoracic as well as abdominal calcifications. This number includes two children who had to receive chemotherapy. These two have the most extensive residual lesions.

Discussion

This investigation failed to indicate that isoniazid associated with P.A.S. conferred any demonstrable

TABLE 13
INCIDENCE OF CALCIFIED LESIONS ON THE FINAL RADIOGRAPHS

	Treated				Controls			
	Number	Lung Calcification	Abdomen or Neck Calcifications	No Lesion	Number	Lung Calcification	Abdomen or Neck Calcifications	No Lesion
Initially negative	9	3	3	3	8	4	4	—
Hilar glandular enlargement only	4	4	—	—	7	7	—	—
Single or multiple primary lesions	9	8	—	1	6	5*	2*	1
Segmental or lobar lesions	7	4*	1*	3	6	4†	1†	2
Tuberculomas	1	1	—	—	2	2	—	—
Total	30	20*	4*	7	29	22*†	7*†	3

* Multiple calcified foci.

† One child treated with INH and SM almost from beginning.

benefit on infants suffering from uncomplicated primary tuberculosis. The absence of significant differences between the two groups, however, was not so much due to the failure of treatment, as to the fact that primary tuberculosis even in these very young infants is usually a benign condition in this country. It is possible that if the duration of isoniazid treatment had been longer, the miliary tuberculosis which occurred after the conclusion of treatment might have been avoided. In the same way the single case of tuberculous meningitis might not have occurred if the infant had been on prophylactic isoniazid. If it had been possible to study a much larger group of children more conclusive differences might have emerged. The number of cases of primary tuberculosis in our community, however, was diminishing so rapidly that the continuation of this investigation would hardly have added enough new children to reach more definite conclusions. Nevertheless, the data from this investigation are sufficient to show that the course of the primary infection and the evolution of the primary lesion itself are not favourably influenced by antibiotic treatment.

It is still important to know whether isoniazid, used prophylactically in infected children, is likely to prevent local extension of the disease, haematogenous spread or tuberculous meningitis. Some answers are available to this problem from a similar, but large-scale co-operative investigation performed in the United States and initiated by Dr. E. M. Lincoln. A preliminary communication (Ferebee, Mount and Anastasiades, 1957) has been published. Twenty-one clinics enrolled 2,750 children between January 1955 and June 1957. They were tuberculin positive and those over 3 years of age also had to have radiological evidence of tuberculosis, though in practice this was not always adhered to. Children

were allocated by the random sampling method into two groups. In one group treatment was given by isoniazid (4-6 mg./kg. body weight) daily for 12 months. The other group received identical placebo tablets and the physicians treating the children were not aware to which group their patients belonged.

The initial analysis of the results showed that during the first year of observation six cases of tuberculous meningitis occurred among the controls and only one among the treated. There were, however, two cases of miliary tuberculosis in the treated and one among the controls. Five controls and one treated child developed skeletal tuberculosis. Altogether 26 controls and five treated children had some extrapulmonary complications. These differences are statistically significant, but it must be remembered that to prevent these 21 clinical cases, many of which were trivial, nearly 1,400 children had to be treated for a whole year with a drug which is not free of toxic side-effects. Further, we do not know what influence, if any, this treatment will have on the late development of adult type of tuberculosis, nor do we know the outcome of further antibiotic treatment in those who have already had one year's treatment and may harbour resistant organisms. The incidence of meningitis and miliary tuberculosis in the controls was only 0.5%, even though little over one-fifth (296 out of 1,356) were children of white stock. The report does not subdivide the results according to race, though this may be of importance.

There was no significant difference between the two groups with regard to the development of adverse pulmonary changes developing during the first year, though only 21 of those treated with isoniazid developed these as compared with 34 controls. An analysis of the results in the controls

showed that children under 1 year of age were at the greatest risk of developing meningitis. This risk was 33 per 1,000 for those with normal roentgenograms, 100 per 1,000 for those with hilar or paratracheal involvement, and 182 per 1,000 for those with parenchymal involvement. It is not stated how many infants were of this age group, nor how many were of European stock, so that too much should not be read into these figures. The risk of developing meningitis in children over 1 year of age was trivial.

There is now a very large volume of literature on the treatment of primary tuberculosis. The only other major attempt at a controlled therapeutic trial was organized by the Institut National d'Hygiène in Paris and other French cities (Lotte, Noufflard, Debré and Brissaud, 1960). Unfortunately, in this trial, individual physicians were given the liberty to treat or not treat children, according to their clinical judgment, so there were admittedly no real controls. Altogether 5,526 children were enrolled, many retrospectively. In this trial chemotherapy consisted of isoniazid (20 mg./kg. per day) plus P.A.S. (300 mg./kg. per day) for a minimum of six months. The incidence of extrapulmonary complications was commonest in the controls who were under 5 years of age (0.7% versus 12.6%), but pulmonary complications were commoner in the treated children. Out of 153 treated cases, 21 developed atelectasis (13.8%). No systematic or serial gastric washings were performed, but strains of tubercle bacilli were cultured from 14 patients after three months of treatment. Two strains were highly resistant and one slightly resistant to isoniazid.

Lincoln, Harris, Bovornkitti and Carretero (1958) studied 156 children (111 under 2 years of age) with primary tuberculosis with serial bronchoscopy. They found that endoscopic evidence of bronchial tuberculosis was commonest in children under 4 years. Three-quarters of their patients had had chemotherapy, but endobronchial involvement persisted for one to over three years in spite of it, and 50 of the 156 developed gross abnormalities of the bronchial tree as shown on bronchogram. They conclude: 'There is no evidence that antimicrobial therapy shortens the course of tuberculous endobronchitis due to encroachment of caseous nodes in the bronchi. Specific therapy does not diminish the incidence of sequelae in the bronchi or the parenchyma. Nevertheless, there is justification for treating children with tuberculous endobronchitis in the hope of diminishing the dangers of bronchogenic spread.' Lorrman and Bentley (1959) had similar experience and came to similar conclusions,

as did Frostad (1959), who noted perforation of the bronchial wall by caseous lymph nodes in 23 children two to 14 months after the beginning of chemotherapy.

Lambert (1959), in reviewing the evidence in favour of prophylactic treatment with isoniazid in symptomless children, concludes that it is undesirable because of our ignorance of its effects on the patients' subsequent immunity and their liability to harbour drug-resistant bacilli. Tuberculin reversion took place in four infants aged 7 to 24 months after six months of isoniazid treatment (Robinson, Meyer and Middlebrook, 1955).

Conclusions

In conclusion, it seems evident that at the present the immediate prognosis of primary tuberculosis in even very young English children is generally favourable and specific treatment of complications is so successful that it is not essential or perhaps even desirable to treat symptomless tuberculous infants with specific drugs, or admit them to hospital as long as they are under adequate outpatient supervision and the parents and their doctors are conversant with the earliest symptoms which might indicate extrapulmonary spread of the tuberculosis which will demand treatment. A watchful expectant policy can be justified, knowing the actual treatment of the complications is little different from the so-called prophylactic treatment and that the outcome of therapy is excellent, if it is applied early. Adopting such a policy, one will only need to treat perhaps one in 10 infants and a much smaller proportion of older children. These conclusions do not necessarily apply under different racial, social or economic conditions in different parts of the world.

Summary

A strictly controlled therapeutic trial in the treatment of primary tuberculosis in infancy is reported. Fifty-nine infants were enrolled and observed for five years. Thirty were treated with isoniazid and P.A.S. and the others served as controls.

A detailed analysis of their progress failed to disclose that the antibiotic treatment conferred any benefit on the treated infants.

The indications for prophylactic chemotherapy are discussed.

I am happy to acknowledge the help received from physicians of the Sheffield Chest Clinic who referred most of the cases; Dr. Llywelyn Roberts, Medical Officer of Health and his staff of Health Visitors who

arranged the children's attendance and kept an eye on potential defaulters; Dr. T. Lodge and his staff for the many radiographs, and Professor R. S. Illingworth for his encouragement of this work and for his critical comments.

REFERENCES

- Ferebee, S. H., Mount, F. W. and Anastasiades, A. A. (1957). Prophylactic effects of isoniazid on primary tuberculosis in children. *Amer. Rev. Tuberc.*, 76, 942.
- Frostad, S. (1959). Segmental atelectasis in children with primary tuberculosis. *Ibid.*, 79, 597.
- Lambert, H. P. (1959). Chemoprophylaxis of tuberculosis. *Ibid.*, 80, 648.
- Lincoln, E. M. (1947). Tuberculous meningitis. Part II. Serous tuberculous meningitis. *Ibid.*, 56, 95.
- , Harris, L. C., Bovornkitti, S. and Carretero, R. W. (1958). Endobronchial tuberculosis in children. A study of 156 patients. *Ibid.*, 77, 39.
- Lorber, J. (1950). Streptomycin and the primary lung lesion in tuberculosis in children. *Lancet*, 1, 389.
- Lorrman, G. and Bentley, F. J. (1959). The incidence of segmental lesions in primary tuberculosis in childhood. *Amer. Rev. Tuberc.*, 79, 756.
- Lotte, A., Noufflard, H., Debré, R. and Brissaud, H. E. (1960). Treatment of primary tuberculosis in childhood. *Pediatrics*, 26, 641.
- Robinson, A., Meyer, M. and Middlebrook, G. (1955). Tuberculin hypersensitivity in tuberculous infants treated with isoniazid. *New Engl. J. Med.*, 252, 983.