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Unreliability of the Mantoux test using 1 TU PPD in excluding childhood tuberculosis in Papua New Guinea

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SUMMARY 139 children with bacteriological or histological proof of active tuberculosis were given the Mantoux tuberculin test while they were inpatients at Port Moresby General Hospital. Only half (70) of the children had positive results (induration of at least 5 mm). Of the 35 children under 2 years, 25 (71%) showed no reaction whatsoever. Malnutrition, assessed by weight for age, did not appear to influence the response although nearly all children under 5 weighed less than the Harvard mean. Previous BCG immunisation had no significant effect on the reaction to tuberculin. General debility, recent measles, treatment with corticosteroids, or early stage of illness may account for some negative reactions, but whatever the cause, the high proportion of negative results means that the tuberculin test as currently practised in Papua New Guinea cannot be relied on to exclude active tuberculosis in children.

Tuberculosis continues to be a problem among children in developing countries, but the circumstances regarding its diagnosis and management are very different from those in Western countries.

In many Third World countries facilities for diagnosis of tuberculosis are limited and the tuberculin test would appear to be the ideal diagnostic tool. However, studies in tropical countries have shown that reactions to tuberculin are not as clearly 'positive' or 'negative' as they are in temperate climates; there are many intermediate reactions which are thought to be due to agents antigenically similar to human tubercle bacilli.[1] This makes interpretation of test results difficult, particularly if trying to provide clear guidelines for use by paramedical staff that will be relevant for adults and children. To reduce the number of false-positive results the standard test recommended by the World Health Organisation (WHO) is 1 tuberculin unit (1 TU) of purified protein derivative (PPD) with Tween 80 (equivalent to 5 TU without Tween 80) but in fact WHO no longer supports the use of the tuberculin test for diagnostic purposes (WHO, 1979, personal communication).

In Papua New Guinea, there continues to be dependence on the Mantoux test for confirmation of tuberculosis. In an attempt to prevent overloading the TB control services with patients who do not have tuberculosis it was suggested that the diagnosis should be excluded by means of a Mantoux test using the WHO standard of 1 TU PPD with Tween 80.[2] This recommendation posed enormous problems for paediatricians working in Papua New Guinea as they were clinically aware that there were many children with active tuberculosis who had negative results to Mantoux tests. Therefore it was felt important that the extent of unreliability of the test, using this recommended dose of 1 TU PPD, should be assessed in a situation where the diagnosis could be established bacteriologically or histologically.

Patients and methods

Port Moresby is the capital of Papua New Guinea and the general hospital with 96 paediatric beds serves a population of 120 000 and acts as the referral centre for the Central Province. Children suspected of having tuberculosis are admitted whenever possible for full investigation before treatment is begun.

Between June 1975 and May 1978, 388 such children were admitted to hospital; mycobacteria reported as *Mycobacterium tuberculosis* were isolated from 131 of these children. The cultures were from gastric aspirates (92), gland biopsies (21), discharging sinus swabs (6), CSF (4), pleural aspirates (3), ear swabs (3), umbilical swab (1), and lung aspirate (1). Identification of the mycobacteria was based on the

growth characteristics of the organisms on standard medium and no further typing was done. Gland biopsies showing the typical histology of active tuberculous lymphadenitis, but which were not cultured, were obtained from a further 33 children. Thus in 164 children the diagnosis of tuberculosis was considered proved and they constitute the study group.

The children's ages ranged from 3 months to 12 years with a peak between 1 and 2 years (Fig. 1). Seven out of 80 boys and 13 out of 84 girls died.

Of the 164 children in the study group 98 (60%) had pulmonary lesions, and 54 of these 98 children had visibly enlarged cervical glands; 34 (21%) children had lymphadenitis alone, while miliary and meningeal tuberculosis accounted for a further 16 (10%) and 8 (5%) respectively. The remaining 4% had tuberculous otitis media (4 cases), abdominal tuberculosis (3 cases), and joint tuberculosis (1 case) (Table 1).

The BCG experience of each child was obtained by noting the presence or absence of a scar on the left upper arm, and if possible this was confirmed by checking his (or her) health record book.

All 164 children were given the Mantoux test on admission. The test was read and recorded in 139 children; 108 in whom the diagnosis was confirmed bacteriologically and 31 in whom it was confirmed histologically. The test was performed using 1 TU of PPD RT23 with Tween 80 given intradermally into the flexor surface of the left forearm. Most tests were done by one paramedical worker who had been trained in the technique, and all tests were read between 48 and 72 hours either by me or by the resident medical officer. A test was considered positive if there was an induration of at least 5 mm. In the other 25 patients, Mantoux tests were performed but the outcome not recorded; there was a tendency to fail to record negative reactions.

Tests were repeated on 7 negative reactors by me and were again found negative. The PPD dilution was checked by a WHO team against a standard dilution with the conclusion that there was no difference in the potency of the two dilutions.

Results

Of the 139 patients who had a Mantoux test completed satisfactorily only 70 showed reactions of more than 5 mm induration; 69 had a negative Mantoux test and 63 of these showed no induration whatsoever to the dose used (Fig. 2).

Of the 20 children who died 13 had had a Mantoux test. In 9 the results were negative, 3 showed a 5 mm reaction, and 1 a 10 mm reaction.

Children under 2 years were significantly less likely to have a positive result than older children ($P<0{\cdot}005$) (Table 2).

Fig. 1 *Age distribution of children with proved tuberculosis.*

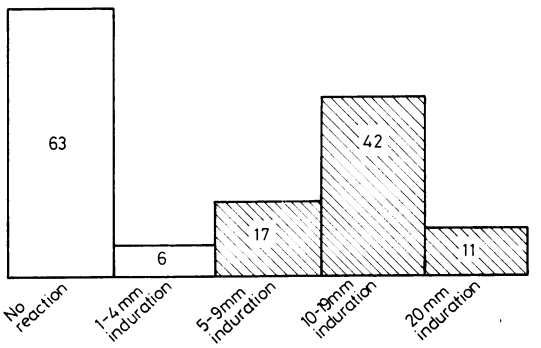

Fig. 2 *Results of Mantoux test for 139 children with proved tuberculosis.*

Table 1 *Site of tuberculosis in 164 children in study group*

Type of tuberculosis	*No of cases*
Pulmonary	44
Combined pulmonary and lymphadenitis	54
Lymphadenitis	34
Miliary (3 also had meningitis)	16
Meningeal	8
Tuberculous otitis media	4
Abdominal	3
Joint	1

Table 2 *Mantoux results according to age in children with proved tuberculosis*

Age of children (months)	*Mantoux test*			
	Positive		*Negative*	
	No	(%)	*No*	(%)
<12	4	(29)	10	(71)
12–23	6	(29)	15	(71)
24–59	23	(53)	20	(47)
60–>144	37	(61)	24	(39)

Table 3 *Mantoux test results according to weight*

Harvard standard	*Mantoux test*			
	Positive		*Negative*	
	No	(%)	*No*	(%)
>100% (n=1)	1			
80–100% (n=16)	7	(44)	9	(56)
60–80% (n=43)	17	(40)	26	(60)
<60% (n=17)	7	(41)	10	(59)

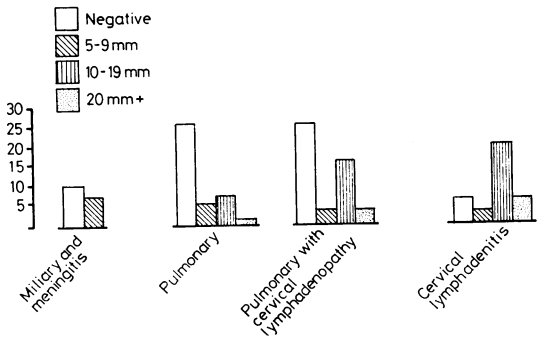

Fig. 3 *Results of Mantoux tests according to site of infection.*

Table 4 *BCG and Mantoux results*

	Negative		*Indurations*			*Total positive*	
	No	(%)	*5–9 mm*	*10–19 mm*	*>20 mm*	*No*	(%)
BCG	44	(52)	9	25	6	40	(48)
No BCG	13	(43)	4	10	3	17	(57)

The admission weights of the children under 5 years showed only one child whose weight was above the Harvard mean.[3] The weights of 16 children were between 80 and 100% of the mean, 43 were between 60 and 80%, and 17 were below 60% of the Harvard mean (Table 3). In this group of patients there appeared to be no association between low weight and a negative response to the Mantoux.

Children with cervical lymphadenitis were particularly sensitive to tuberculin. They had a higher percentage of positive results and larger areas of induration than children without cervical gland involvement (Fig. 3).

The BCG experience of 114 children was recorded. Previous BCG immunisation did not significantly affect sensitivity to tuberculin ($P>0\cdot1$) (Table 4).

Discussion

It was suggested by members of a visiting WHO consulting team[2] that too much reliance was placed on the isolation of mycobacteria from gastric aspirates and, in the presence of a negative tuberculin test, such mycobacteria were probably atypical. 47 children diagnosed from gastric lavage had a negative reaction to the Mantoux test but 25 had chest *x*-rays which were considered by the radiologist to be diagnostic of tuberculosis; these consisted of a typical miliary pattern (8), tuberculous bronchopneumonia (5), pleural effusion (7), and hilar gland enlargement (5). Four of the children with positive gastric aspirates and nondiagnostic chest *x*-ray changes had additional evidence of tuberculosis—3 had CSF changes typical of tuberculous meningitis and 1 had a gland biopsy showing caseous tuberculous lymphadenitis. Of the remaining 18 children, 9 had a strong family history of tuberculosis; in each case this comprised at least one parent and up to 5 other members of the household. Four had pulmonary complications after measles and their condition did not improve until antituberculous therapy was begun. In retrospect, the diagnosis of tuberculosis could be disputed in only 5 of the 47 children with positive gastric aspirates and a negative Mantoux test, although even in these 5 there were sufficient clinical grounds—such as continuing fever and persistent weight loss—to warrant treatment.

All the patients studied were inpatients at the hospital so one would expect a high proportion of cases difficult to diagnose in whom there had been a disproportionate effort made to find mycobacteria. During the same period there were 96 children, 29 of whom were seen only as outpatients, with a good clinical and *x*-ray evidence of tuberculosis from whom mycobacteria were not isolated. This group included patients with hilar lymphadenopathy (41), pleural effusion (18), cervical lymphadenitis (16), meningitis (10), Pott's disease (8), and miliary tuberculosis (3); 37 (39%) of these 96 children had a negative Mantoux test, and in 59 (61%) results were positive. Thus the proportion of positive results was not significantly different from those from whom mycobacteria were isolated ($P>0\cdot05$).

Other series have also shown that children with cervical lymphadenitis are more sensitive to tuberculin;[4] anyway these children are less likely to be missed as they are easier to diagnose clinically.

Several factors may be responsible for the large number of tuberculin nonreactors:

(1) The Mantoux test may have been done too early in the disease for the test to be positive;[11] 11 children had repeat tests 6–8 weeks after starting TB treatment, and 6 of these had become positive by the second test. This cannot however be the whole explanation, as in developing countries many cases present late in the course of the disease. In this study for instance,

33 of the 69 with negative Mantoux reactions had had symptoms for more than 2 months before admission.

(2) A number of patients were debilitated and a negative tuberculin test is well recognised in such children, particularly if they have miliary or meningeal tuberculosis.[6] However, many negatives were found in children who were not severely ill but none the less yielded positive cultures.

(3) Malnutrition is considered a cause of failure of tuberculous patients to react to tuberculin.[5 7] In the study group wasting was common and 78% of the children under 5 years were below 80% of the Harvard mean, but there was no clear association between degree of weight deficit and tuberculin sensitivity.

(4) Some patients were so ill at the time of admission that antituberculous drugs and corticosteroids were started immediately. Of 15 patients who were Mantoux tested at the same time, or soon after, corticosteroids were started, 6 were Mantoux positive and 9 negative. So corticosteriods were not a major cause of negative tuberculin reactions in the study group.[8]

(5) Measles is known to make a child nonreactive to tuberculin for some weeks after infection[9] and this may have been responsible for some negative reactions. A history of measles was sought in every case. Only 6 children were known definitely to have had a recent attack of measles and all 6 had a negative Mantoux. A possible history of measles was obtained from a further 3 children: 2 were Mantoux negative and the other had a reaction of 10 mm.

(6) Polio vaccine has also been found to reverse the tuberculin reaction temporarily;[10] the immunisation records are not available but this may have been a factor in the children under 2 years.

Whatever the cause of a negative tuberculin reaction the effect on its usefulness in diagnosis is the same. A negative result is difficult to interpret both in clinically mild and severe illness and cannot be accepted as excluding the diagnosis of tuberculosis. It might be considered that, when doubt exists, start of treatment should be delayed, but this can be dangerous, particularly in young children who may deteriorate with frightening rapidity or develop complications, as illustrated by the following case histories.

Case 1. A boy aged 9 months, whose mother had died at birth. He was bottle fed successfully by his grandmother and his growth curve rose steadily above 80% of the Harvard mean. He presented at outpatients on 30 November 1977 with a history of diarrhoea. He was not clinically dehydrated and there were no abnormal clinical findings but his weight was noted to have fallen 0·8 kg during the preceeding 4 weeks, so he was admitted. A chest *x*-ray showed some consolidation in the right upper and mid-zones but the Mantoux test was negative; there was no family history of tuberculosis and a BCG scar was seen on his left arm. He was treated with antibiotics, but he remained unwell and ran a slight fever. His weight had dropped a further 0·4 kg by 21 December and a repeat *x*-ray showed increased consolidation and small bilateral effusions. It was decided on this evidence to start antituberculous therapy.

His grandmother unexpectedly took him away on 25 December and did not return with him until 1 January, when he was severely ill with gross meningeal signs. Treatment included chemotherapy for tuberculosis and corticosteriods but he died 2 days later. Necropsy showed widespread tuberculosis.

Case 2. A boy of 12 years, was first seen on 12 April 1976 with a 2-week history of cough. He was not very ill and apart from a few small cervical glands there were no abnormal clinical findings. The chest *x*-ray suggested tuberculosis with perihilar consolidation and widening of the mediastinum to the right but, as the Mantoux test was negative, it was decided to delay treatment and review him as an outpatient.

He did not return until 25 June, when he was complaining of pain in his back. On examination he had a slight kyphosis at the level of the 1st and 2nd lumbar vertebrae which was tender on palpation. *X*-ray of the lumbar spine showed moderate erosion of the 2nd lumbar vertabra.

The proportion of positive results in this study group could have been increased if all negative reactors had had a repeat test 6–8 weeks after starting therapy but a belated positive result would have been no help in the initial decision to start treatment. In any case, in practice, repeating the Mantoux test routinely is impossible in Papua New Guinea because many children return to their villages (up to 80 miles from Port Moresby) to continue treatment at the nearest aid post.

Conclusion

The generally accepted policies of tuberculosis control do not include identification and treatment of sick children. This is because they are not a hazard to the community as they generally swallow their sputum and thus are not infectious. Health workers treating children have other priorities and there is a strong feeling that because of the danger of miliary,

meningeal, or spinal tuberculosis developing in children it is better to overdiagnose the infection rather than leave a case until it is too late. A negative Mantoux result does not necessarily exclude tuberculosis and the decision to start treatment often rests on clinical criteria.

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References

1. Nyboe J. The efficacy of the tuberculin test. *Bull WHO* 1960; **22:** 5–37.
2. World Health Organisation Regional Tuberculosis Control Team. *Assignment report.* ICP/BVD/001–E (Papua New Guinea). Geneva: WHO, 1977.
3. Jelliffe D B. *The assessment of the nutritional status of the community.* World Health Organisation Monograph Series No 93. Geneva: WHO, 1966.
4. Miller F J W, Seal R M E, Taylor M D. *Tuberculosis in children.* London: Churchill, 1963.
5. Lloyd A V C. Tuberculin test in children with malnutrition. *Br Med J* 1968; **iii:** 529–31.
6. Illingworth R S. Miliary and meningeal tuberculosis—difficulties in diagnosis. *Lancet* 1956; **ii:** 646–9.
7. Harland P S E G. Tuberculin reactions in malnourished children. *Lancet* 1965; **ii:** 719–21.
8. Salomon H, Angel J H. Corticotrophin induced changes in the tuberculin skin test. *Am Rev Respir Dis* 1961; **83:** 235–42.
9. Starr S, Berkovich S. Effects of measles, gammaglobulin modified measles, and vaccine measles on the tuberculin test. *N Engl J Med* 1964; **270:** 386–91.
10. Brody J A, Overfield T, Hammes L M. Depression of the tuberculin reaction by viral vaccines. *N Engl J Med* 1964; **271:** 1294–6.
11. Kent D C, Schwartz R. Active pulmonary tuberculosis with negative tuberculin skin reactions. *Am J Respir Dis* 1967; **95:** 411–8.

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