RECOGNITION OF TUBERCULOSIS IN CHILDREN UNDER 2 YEARS

BY

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Modern therapy is so effective that the diagnosis of tuberculous meningitis or miliary tuberculosis is a matter of urgency. Yet if we rely upon the traditional methods diagnosis would be made too late for effective treatment. We must therefore try to recognize primary tuberculosis before serious complications occur, and our purpose in this paper is to demonstrate the ways in which tuberculosis becomes manifest in young children and to discuss the diagnosis. To do this we use records of 313 children known to have been infected in the first two years of life and seen in either the children's departments or the tuberculosis contact clinics in Newcastle-upon-Tyne between 1946 and 1950. Of these 313 children, 150 were admitted to hospital ill when first seen and 163 were examined initially as contacts, 62 of the latter being admitted to hospital during the subsequent period of observation. In all, therefore, 212 children were admitted to hospital and 101, though infected, remained at home.

We begin with a reminder of the development of the primary complex and its characteristics in young infants.

Natural History of Tuberculous Infection in Early Childhood

Whenever or wherever the first infection with tuberculosis occurs there is a local lesion at the site with enlargement and caseation of the nearest lymph nodes. The primary focus and enlarged nodes are together known as the primary complex. Although this complex is a constant anatomical finding, the results of infection vary with the age of the child. The major fear is the development of haematogenous dissemination or tuberculous meningitis.

The child of 2 years has not developed his full capacity to localize infection (Burnet, 1952), and the risk of generalized tuberculosis or tuberculous meningitis is certainly greater than after infection in older children. Serious complications occur in at least 5% and possibly as many as 10% of children infected in the first two years of life (Cammock and Miller, 1953). Of children who get tuberculous meningitis or miliary tuberculosis, 85% do so in the first year after infection, and either complication is uncommon more than two years afterwards (Wallgren, 1948). For the same reason the risk of bone disease in the first two years is probably greater than the average risk (1-2%) in all children infected under 5 years (Cammock and Miller, 1953).

The regional lymph nodes caseate and often soften; in superficial glands giving abscesses, and in the mediastinum ulceration and destruction of the walls of adjacent bronchi, often allowing either the aspiration of caseous material or, if the mass of material is harder and larger, obstruction with consolidation or collapse of the lung beyond.

In contrast to the increased risk of haematogenous spread and progressive lung disease, the young infant is not so likely to develop erythema nodosum or phlyctenular conjunctivitis. Nor does the young infant develop the three-weeks febrile illness ("fever of onset") without localizing signs seen so often in older children (Wallgren, 1948).

Epidemiology.—In Newcastle 2% of children are infected before the age of 2 (Cammock and Miller, 1953). The lung is the commonest site; 253 of our 313 children had radiological evidence of lung infection, while only six had evidence of abdominal infection, and two of these had been in contact with an adult with "open" phthisis. In 28 cases the first sign was swelling of lymph nodes in the neck, and these almost certainly had nasopharyngeal infections. Only seven had ever consumed "raw" milk, but 14 had lived in close contact with infective adults. Almost all the 313 children lived in urban or industrial surroundings, and in 256 (82%) we knew of contact with an infective adult; 217 of the infectors lived in the same house as the child and 201 were relatives. Contact was known in 86 of the children admitted immediately to hospital, and by systematic examination of families 15 new and hitherto unsuspected cases of active phthisis were found, making 101 in all.

Diagnosis

How can we use these few basic facts of epidemiology and natural history to recognize tuberculosis earlier? Diagnosis is suspicion confirmed. Let us therefore consider when we should suspect and how we can confirm or disprove our suspicions.

When should Tuberculosis be Suspected?—From the beginning we must distinguish two groups of children: those infected with tuberculosis but symptomless and apparently healthy, and those with manifest illness.

Symptomless Primary Complex.—First the child with symptomless primary complex: in infants, indeed in children generally, symptomless primary infection is usually discovered by routine tuberculin-testing in infant welfare centres, hospital out-patient departments, or tuberculosis contact clinics. Sometimes such testing is rather thoughtlessly said to be "unnecessary" or even "meddlesome"; but on reflection we see that it is enormously important for the family doctor to know the child is infected, and this knowledge may be of great assistance in making an early diagnosis if complications unfortunately do occur; we should therefore encourage rather than discourage the routine use of tuberculin tests in clinics and in family practice.

Presenting Illness in 150 Infected Children Under 2 Years Admitted to Hospital Suffering from Tuberculosis

Tuberculous meningitis	48	32.0%
Pulmonary disease, including miliary (14)	56	37.3%
Lymphadenitis: cervical or other superficial	28	18.7%
Bone and joint	10	6.7%
Abdominal tuberculosis	4	
Skin { Primary infection	2	5.3%
Erythema nodosum	2	
	150	100%

Manifest Disease

In the Table we show the illnesses in 150 children on admission to hospital. In a third the symptoms were caused by the primary lung complex or its local complications. In another third the presenting illness was tuberculous meningitis. Sometimes the child has been in good health until the onset of meningitis; at other times there had been vague ill-health or failure to thrive for some weeks previously. Nearly one-fifth had superficial tuberculous lymphadenitis. Bone or joint disease was seen comparatively infrequently, and under urban conditions abdominal tuberculosis is now quite uncommon. Erythema nodosum was the presenting sign in only two cases, and phlyctenular conjunctivitis was not recorded as the presenting sign in any case.

Primary Lung Infection.—Sweating or haemoptysis practically never occurs; almost always, if clinical signs are present, the primary lung lesion is to be suspected by one or more of the following: (1) *Failure to gain* or loss of weight, with vague ill-health in the absence of abnormal physical signs or acute illness. (2) *Cough*:—Suspect any harsh dry cough which is not whooping-cough and is unaccompanied by upper respiratory infection. Sometimes the cough is spasmodic and occasionally is followed by vomiting, so that differentiation from whooping-cough is almost impossible on clinical grounds alone. (3) *Wheeze*:—In

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young infants, as mediastinal glands enlarge and press upon the trachea there may be a gentle inspiratory and expiratory wheeze. Made louder on crying, it may disappear altogether in sleep. The wheeze may be mistaken for "asthma," but true sensitivity asthma is unusual under 2 years of age.

Many children with chronic upper respiratory infection, especially if they are fat, get attacks of wheezing or recurrent bronchitis. But any child who does wheeze and continues to do so for more than a week or so should have a tuberculin test. Sometimes primary tuberculous infection and non-tuberculous recurrent wheezy bronchitis occur together. Widespread rales and rhonchi can then be heard over both lungs; otherwise gross physical signs are usually absent unless the primary focus is enlarging and lung tissue is being destroyed or there is extensive lung collapse. Indeed, the more signs heard in the chest the less likely is the underlying disease to be tuberculosis.

Another difference between the young infant and the older child is that, in the former, pleural effusion is rarely seen and then not as an acute febrile illness. Indeed, at this age a tuberculous pleural effusion is usually discovered accidentally on routine radiography in a child who is not thriving; in the 313 children it occurred five times, only once as an acute illness. Complications due to bronchial involvement are more common. Bronchial stenosis often results: as many as 24 of the 251 survivors of the 313 children appear to have permanent structural damage in the lungs.

Tuberculous Meningitis

Tuberculous meningitis is due to the rupture of a sub-cortical or meningeal caseous nodule deposited there by the blood (Rich and McCordock, 1929) or as part of a miliary spread.

Treatment with streptomycin, and now isoniazid, has completely changed the prognosis. Although the treatment is prolonged and is still exacting for the child, the parents, and the doctor, there is the hope that it will become less so in the immediate future. Fifty per cent. of all cases and nearly 80% of early cases now survive. If relapse does not occur within two years the outlook seems good. Certainly the most important factor in prognosis is delay in treatment. This brings us to the need for early diagnosis.

Diagnosis is difficult because signs are not distinctive, and for the first few days of the illness there may be little change from normal. Furthermore, like many of the acute emergencies in childhood, tuberculous meningitis is not a common disease. The 30,000 children under 2 years of age on Tyneside yield about 20-30 cases a year, scattered in more than 200 practices. A doctor might practise years without seeing a case. Yet to wait until neurological signs are definite is to wait too long. Diagnosis must be based upon suspicion or knowledge of contact with tuberculosis, upon tuberculin-testing, upon alteration in the child's temperament as related by the mother, and upon the careful ascertainment of one important physical sign—neck stiffness. Of great importance are listlessness in a previously active child, irritability unusual for the child, interruption or alteration of consciousness without an obvious cause, or unexplained intermittent vomiting for more than three days. Neck stiffness is difficult to measure, for the conditions of examination may be unfavourable and it can be properly elicited only with the infant at rest. Detection is a matter of experience. The doctor's hand is slipped gently under the child's head, kept there until his attention is diverted and he is restful, then slowly raised so that the neck is flexed without the child offering voluntary resistance. In the healthy child the head will flex without resistance until the chin touches the chest wall. If neck stiffness is present, resistance is felt before full flexion is reached. Sometimes the child protests if the movement causes headache, yet resistance cannot be detected. Kernig's sign is unreliable in young children, and other neurological signs are merely indications of advanced disease.

Yet even neck stiffness may be absent for the first few days of the illness (it was noted in only half of our cases

at the first examination), and we may have to rely upon alteration of behaviour, listlessness, abdominal pain, crying, and vomiting. The great step is to suspect the illness and to take the necessary steps to exclude it.

Superficial Tuberculous Lymphadenitis

We were surprised that as many as 10% of young children should have presented with visible superficial tuberculous lymphadenitis, and that as many as 37 of the 313 had superficial tuberculous lymphadenitis at some stage while under observation; in 27 it was in cervical glands, and in the remainder in auricular or inguinal glands. Four primary foci were demonstrated on the skin, two were visible on a tonsil, and in the conjunctiva (Miller, 1953); three others were presumed to be in the middle ear associated with tuberculous mastoiditis and post-auricular glands. In the remainder the primary lesion could not be found, but presumably it existed somewhere in the throat or nasopharynx. On radiographic examination 12 showed definite and three probable evidence of a primary lung lesion. We think, therefore, that simultaneous primary infection of the upper respiratory tract and the lungs is not very uncommon, and that in the great majority of cases the infection is human in origin. Often the swollen gland is found accidentally when the mother is nursing or washing the child; it is painless and hard, and, if watched carefully, slow progressive enlargement is seen to occur over some weeks, until in most cases softening leads to redness of the skin. Sometimes the child reacts much more sharply with fever, local tenderness, and periadenitis, so that it is quite impossible to determine the infecting organism by clinical examination alone. A tuberculin test is always necessary as part of the examination. Although a negative tuberculin reaction eliminates tuberculosis as a cause of the lymphadenitis, it must be remembered that a positive reaction does not prove that the lymphadenitis is tuberculous. Five of the 313 children had pyococcal cervical abscesses after becoming tuberculin-positive.

Skeletal Tuberculosis

Though only 10 of our 150 ill infants presented with bone tuberculosis as an initial sign of illness, 26 of the 313 children developed such lesions during the time of observation; two others had foci apparently limited to synovial membrane. Three children had more than one bone lesion. There were seven cases of tuberculous mastoiditis, probably caused by local extension from the middle ear. The mastoid process excluded, bone or joint lesions are caused by spread from a distant primary complex. The spine or bones of the legs are most commonly affected. The lesions all appeared within two years of primary infection, and 21 of the 26 children had symptoms before their second birthday. The diagnosis of tuberculous disease of bone is possible at all ages before the development of gross physical signs; the first indication is limitation of function and involuntary guarding of the affected limb. Young children do not complain of localized pain; they become fretful, are less active, go off their feet, walk with a limp when they are moved. Any of these complaints requires both a tuberculin test and radiography. A diagnosis of tuberculous osteitis cannot be sustained in the presence of a negative tuberculin reaction.

One new experience is the development of bone lesions sometimes as long as two years after miliary tuberculosis or tuberculous meningitis has been cured (two cases in this series). In another series 4 out of 16 bone lesions were in such children (Cammock and Miller, 1953).

Confirmation of Diagnosis

So far we have considered the way in which tuberculosis presents and when it should be suspected. How can it be confirmed? Ultimate *proof* must be the recovery of the tubercle bacillus, but diagnosis is usually made by a combination of tuberculin-testing and radiography.

The importance of the tuberculin test in paediatrics cannot be overestimated. It is part of any complete examination.

and it is necessary in order to help to assess the significance of radiological changes found in the chest or bones. As in everything else, experience of the relative advantages of different methods is required.

The test gives a positive result four to six weeks after primary infection, and thereafter a positive reaction means simply that a child has undergone primary infection. It does not mean that any particular illness is tuberculous in origin, but it emphasizes the possibility, or indeed with a young child the probability, that it is so.

A negative reaction is important, for the presence of tuberculosis is practically dismissed unless the child is very ill, when other physical signs are almost certainly present.

Two tests are in general use—the percutaneous (jelly) and intradermal (Mantoux). In the jelly test the skin is carefully cleaned with acetone or ether, and a petroleum jelly ointment containing Old Tuberculin is placed on the skin; usually the child's initial or a "v" mark is outlined with the jelly, to the length of about 1 in. (2.5 cm.). This is covered with a piece of strapping without any intervening lint. After 48 hours the strapping is removed and the skin examined 72 hours later—that is, after five days. This interval allows any strapping reaction to fade and gives a delayed tuberculin reaction time to appear. The result is not often in doubt. There is either no reaction whatsoever or, if positive, a reddish-brown slightly raised area; or sometimes a line of papules, not indurated or oedematous, will show on the skin in contact with the jelly. It is best to regard any reaction as positive until proved otherwise, but sometimes if only two or three papules are present the intradermal test will be necessary. We do not recommend the use of flourpaper (very fine sandpaper) in testing children under 5 years of age. The jelly test is roughly equivalent to 0.1 ml. of 1:1,000 Old Tuberculin by intradermal injection. It is most useful in clinic work where repeated tests are necessary and time is not important. Avoiding a prick, the doctor retains the child's confidence. But it takes five days, and occasionally an intradermal tuberculin test is necessary afterwards. So if there is any urgency, if the child is ill and tuberculosis seems likely, an intradermal (Mantoux) test should be used. The intradermal test consists of the intradermal injection of 0.1 ml. of 1:1,000 Old Tuberculin; 48 hours later a weal or area of induration more than 5 mm. in diameter indicates a positive reaction. Redness without induration is ignored, and redness surrounding a weal is not included in measurement.

The reactions of the tests are therefore very different and should not be compared. That of the jelly is on the skin—a series of small spots, papules, or vesicles which sometimes coalesce; that of the intradermal test is oedema in the skin at the site of injection. Every child with a positive reaction should be known to his family doctor, and it is most important that the results of tuberculin tests done in clinics or elsewhere should be communicated to him. It is also important that he should recognize the significance of the information and its value if the child becomes ill.

Why is this Urgency Necessary?

Almost all deaths from tuberculosis in infancy are the result of tuberculous meningitis or miliary tuberculosis. Both conditions are now treatable. In the early stages of tuberculous meningitis (uncomplicated by radiological miliary spread) there is a 75% chance of survival and a 50% chance of complete recovery; in the later stages 30% survival and only 10% complete recovery (Lorber, 1954). In meningitis alone the results are better than if miliary is also present. Relapse may occur, but it is unlikely after two years: the results depend almost entirely upon the stage at which diagnosis is made and treatment started. In the great majority of cases the first person to see the ill child is the family doctor, and his is the most difficult role of all. He must suspect and seek confirmation of his suspicions: early diagnosis depends upon the use of the tuberculin test, radiology, lumbar puncture, and bacteriological proof.

Summary

In this paper we have dealt with the recognition of tuberculosis in young children, arguing that diagnosis by clinical signs is outmoded and that early recognition requires above all suspicion, followed by tuberculin-testing, radiology, or other investigation.

One-third of 150 ill children presented with illnesses caused by lung primary lesions or miliary tuberculosis; one-third with tuberculous meningitis; one-fifth with superficial lymphadenitis. Bone lesions are relatively uncommon and sensitivity phenomena quite uncommon at this age.

The techniques and relative roles of the tuberculin jelly test and Mantoux test are considered.

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HISTOPLASMIN SENSITIVITY IN UGANDA

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Histoplasmosis was first known as a rare severe generalized infection, but during the past ten years American workers have shown that there is also a benign and usually symptomless form producing pulmonary infiltration followed by calcification. It is commonest in the United States, between the Mississippi and the Arkansas Rivers, where incidences of up to 80% of positive reactions to the intradermal injection of histoplasmin have been recorded. The geographical distribution of cases of proved histoplasmosis and of histoplasmin sensitivity have been ably reviewed by Mochi and Edwards (1952).

A few cases of the generalized disease have been diagnosed in Africa. In the Union of South Africa Simson and Barnettson (1942) encountered one, Lurie (1949) two, Murray and Brandt (1951) three, and B. A. Dormer one (Mochi and Edwards, 1952); in French and Anglo-Egyptian Sudan Catanei and Kervran (1945), Kervran and Aretas (1947), and Jelliffe (1949) found other cases, while one has been reported from Senegal by Friess and Delvoye (1947) and from Belgian Congo by Dubois *et al.* (1952). *Histoplasma capsulatum* in Africa may be a different and unusually large form, as in the cases of cutaneous disease seen by Duncan (1947) in a man who had been in West Africa. In another British case the patient had been in Sudan, as well as in