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TUBERCULOSIS IN INFANCY *

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It is not my purpose in this paper to do more than discuss certain limited aspects of the subject of tuberculosis in the first two years of life. The literature of tuberculosis is so enormous, and appears so complete, that it is difficult to add anything really new to our knowledge of this subject. In looking over the literature I have been impressed with the fact that in many articles the conclusions drawn are not supported by the final proof afforded by postmortem examination. This is true especially in this country, where the difficulty of obtaining permission to make postmortems on infants is so great, that it has been difficult to record observations on even a small series of cases in which final proof was obtained. The new Memorial Building of the Infants' Hospital has been open for nineteen months. During the last nine months of this time the giving of written permission for autopsy in case of death has been a necessary requirement when babies are admitted to the hospital. The increase in the number of our post-mortems under this rule has been the impetus which caused me to reopen the much discussed subject of tuberculosis.

The importance of tuberculosis as a cause of death in the first two years of life is shown by the fact that in a series of sixty-two successive necropsies, tuberculosis was found in twenty-five, and was considered the direct cause in twenty-three cases, and as the contributing cause in the other two.

THE SOURCE AND MODE OF INFECTION

Of all the subjects of discussion in connection with tuberculosis in early life, the one which has occupied most space in the literature is the question of the source of the infection, and its portal of entry into the body. This question is still one about which extremely divergent views are held. One set of writers believes that milk infected with the bovine type of bacillus is the most common cause of the disease in infancy, and

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that the most common portal of entry is the intestinal tract, or the tonsils. Another group of writers believes that the human type of bacillus is the most common cause, and that the portal of entry is usually the lungs.

The evidence brought forward in support of these two views is of varying character. Such evidence as is based on statistics of the frequency of feeding with unsterilized milk, or of the frequency of known exposure to tuberculosis is only of confirmatory value. The two most important forms of evidence bearing on this question are, first, that derived from bacteriologic study of the bacilli obtained from infants by culture or animal inoculation, and second, that derived from a careful study of the lesions found postmortem.

Based on this evidence, the reports of various investigators remain extremely contradictory. So eminent an authority as von Pirquet¹ states in his article on tuberculosis in Feer's textbook, that the human bacillus, entering through the lungs, is the cause of tuberculosis in infancy, basing his conclusions on the 1,060 careful autopsies by Albrecht, in which a primary intestinal lesion was found in seven cases only, and on the 189 necropsies of Ghon, in which all but three showed what Ghon considered a primary lesion in the lung. On the other hand Mitchell's² studies in Edinburgh showed that in 90 per cent. of the cases the bacillus was one of the bovine type.

In general the reports of postmortem findings show a greater frequency of involvement of the peribronchial and mediastinal lymph nodes than of the mesenteric. Some prominent advocates of milk infection have endeavored to explain this on the theory that the bovine bacillus can pass without causing a lesion, not only through the intestinal mucous membrane, but even through the mesenteric lymph nodes, locating itself in the lymph nodes of the chest as the point of minimum resistance. This theory I believe to be inadequately supported, and entirely untenable. It may be possible that the tubercle bacillus can enter the body of the infant without a lesion at the portal of entry; this is still an open question. But that the bacillus can skip one set of lymph nodes to locate in another, is highly improbable.

The contradictory character of the evidence as to the source of infection and mode of invasion in infantile tuberculosis can only be explained on the ground of a variation according to locality. Such variation is probably largely dependent on the character of milk supplies, and the frequency of tuberculous disease in cattle in various parts of the world. I believe that infants can be infected either with human

1. Feer: *Lehrbuch der Kinderheilkunde*, 1914.

2. Mitchell: *Brit. Med. Jour.*, 1914, No. 2768, p. 125.

bacilli, usually entering through the lungs, or with bovine bacilli, usually entering through the intestine. The present study of postmortem material therefore bears only on conditions in Boston and its vicinity.

The Primary Lesion.—Von Pirquet, in his recent textbook article, adheres to the view of Ghon, that tuberculous infection always shows a primary lesion at the portal of entry. This view is very different from the one which has been most generally accepted, which holds that the tubercle bacillus in infancy can, and usually does, pass through the tissues at the portal of entry, and then, following the lymph channels, reaches the lymph nodes, where it produces the primary lesion. This widely taught view is based on the rarity in infancy of phthisis, the chronic process most characteristic of adults, on the prominence of lymph node tuberculosis as the chronic process most characteristic of early life, and on the fact that the most prominent tuberculous lesions found in the lungs of infants are of a secondary nature. I have been inclined toward this view of tuberculosis in infancy, and have been teaching it to my students year after year.

In the recent series of necropsies at the Infant's Hospital, I determined to investigate this question of the primary lesion, by making most careful and thorough examination of the lungs and intestine in each case. It seemed possible that the primary lesion in the lung as described by Ghon and Albrecht might have been overlooked. Frequently at postmortems the lungs are examined no more carefully than by making one or two incisions in each lobe, which disclose the secondary lesions, miliary tuberculosis, or tuberculous bronchopneumonia, so prominent in infancy. It is then easy to assume that the caseous bronchial lymph nodes represent the primary lesion. In my series the lungs were cut up into the smallest fragments in the search for the primary lesion, and all suspected areas were subjected to microscopic examination.

The question of interest in this investigation was how often there would be found a lesion at the portal of entry recognizable as the primary lesion described by Ghon and Albrecht, and differing from the well-known secondary lesions.

As a result a primary lesion was actually found at the portal of entry in twenty-two of the twenty-five postmortems. The three cases in which a primary lesion was not found at the portal of entry all showed chronic tuberculosis of the bronchial lymph nodes, but none of the mesenteric lymph nodes. The nature of the primary lesion found in the lung in some cases was such as to suggest that it might easily have been overlooked, and that in the three cases a still more inconspicuous primary lesion may, in fact, have escaped observation.

Wollstein and Bartlett,³ in a study of the tuberculous lesions found postmortem in 178 infants and young children, found tuberculous areas in the bronchial lymph nodes without pulmonary involvement in seven cases, and believe that this shows that it is possible for the tubercle bacillus to pass through the lungs without localizing there. They prefer this explanation to that of Ghon, who believes that in these cases the pulmonary lesion is overlooked. As a result of my observations I am inclined to revise my views on tuberculosis in infancy, to differ with Wollstein and Bartlett's explanation, and to believe with Ghon, that it is more probable that when a primary lesion is not found at the portal of entry it is overlooked.

The Location of the Primary Lesion.—The location of the primary lesion is important as evidence of the most frequent source of tuberculous infection in infants in Boston and its vicinity. The primary lesion was found in the lung in twenty cases, and in the intestine in two cases. If we add to the twenty cases the three in which the only chronic lesions were found in the bronchial lymph nodes we have a ratio of twenty-three cases of infection through the lung to two cases of infection through the intestine. This suggests that in Boston, at least, the most frequent mode of infection is by the inhalation of tubercle bacilli from a human source, but that infection through the ingestion of bovine bacilli in contaminated milk may occur.

The Primary Lesion in the Lung.—The lesion found in the lung seemed quite easily recognizable as a primary lesion, and distinguishable from the common widespread secondary lesions. In most cases it was a circular area, varying in size from that of a pea to that of a hazlenut. The center was caseous, but usually of a grayer color than the yellowish-white caseation seen in the secondary lesions. In some there was caseous softening, or small cavities; in one there was calcification. In a few cases the primary lesion was much larger, reaching to the pleura, where its situation was marked by firm fibrous adhesions. In two of these larger lesions there were large cavities, with irregular grayish walls. Around the periphery of some of the smaller lesions were numerous miliary tubercles, suggesting direct extension. In only one case was there more than one lesion of this description.

Microscopically the primary lesion differed from caseous tubercles and secondary caseous areas in this particular, that in the latter, even when the section showed wholly necrotic tissue, the lung structure, the outlines of bronchioles and alveoli, were faintly discernible. In the primary lesion the necrotic tissue always appeared uniform and the alveolar outlines could not be made out. In only one case was there evi-

3. Wollstein, M., and Bartlett, F.: AM. JOUR. DIS. CHILD., 1914, viii, 362.

dence of healing as shown by fibrous tissue formation in the primary lesions, but this is to be explained by the fact that all the cases were fatal ones in young infants in whom the resistance was probably very low.

The situation of the primary lesion in the lung was as follows :

Left upper lobe	5 cases
Left lower lobe	0 cases
Right upper lobe	8 cases
Right lower lobe	5 cases
Right middle lobe	2 cases

The favorite situations were at the apex and near the hilus.

The Primary Lesion in the Intestine.—The lesion found in the intestine in two cases, and considered primary, was a tuberculous ulceration. In one case there was a single ulcer, while in the other case the ulcers were multiple. There was nothing about the appearance of these ulcerations differing from that seen in the secondary ulcerations found in several cases. My reasons for believing the intestinal ulceration to be a primary lesion in these two cases are, first, because in them the mesenteric lymph nodes *only* were tuberculous, and they were the only cases in which tuberculosis of the mesenteric lymph nodes was found without tuberculosis of the bronchial lymph nodes. As additional evidence, one of these cases was one of a series known to have occurred in a limited locality, and all having the same milk supply. Furthermore, animal inoculation from this case gave a bovine type of bacillus.

Involvement of the Lymph Nodes.—The bronchial lymph nodes were found tuberculous in the twenty cases having a primary lesion in the lung, and in three cases in which no primary lesion was found. They were involved alone in sixteen cases, including the three without evident pulmonary lesion. The mesenteric lymph nodes were tuberculous in addition to the bronchial lymph nodes in seven cases having a primary lesion in the lung, and were involved alone in the two cases having a primary lesion in the intestine.

Secondary Ulcers of the Intestine.—Tuberculous ulceration of the intestinal mucous membrane was found in seven cases beside the two in which this lesion was considered primary. In all cases the ulcers were multiple. My reasons for believing these lesions to be secondary are the following: 1. In all the seven cases a primary lesion was found in the lung. 2. In all of them there was tuberculosis of the bronchial lymph nodes, which in most cases appeared to represent a more advanced and older process than that in the mesenteric lymph nodes. 3. In all of them there was evident in the primary pulmonary lesion either caseous softening, or cavity formation, and conversely, in

no case in which such a condition was found in the primary lesion did I fail to find ulceration in the intestine. I believe it to be a probable conclusion that these tuberculous ulcerations of the intestine are secondary to swallowed tuberculous material coughed up from the softening of the primary lesion.

These seven cases with secondary tuberculous ulceration of the intestine were identical with the seven cases in which the mesenteric lymph nodes were involved in addition to the bronchial lymph nodes. This is a finding of the greatest importance in connection with the question of the ability of the tubercle bacillus to pass through the mucous membrane without causing a lesion at the portal of entry. In all there were nine cases in which the mesenteric lymph nodes were found to be tuberculous, and in all of them there was also found tuberculous ulceration of the mucous membrane of the intestine. There was no case in my series showing tuberculosis of the mesenteric lymph nodes without an intestinal lesion. In two cases the intestinal lesion was primary; in the other seven secondary to a primary lesion in the lung, from which tuberculous material was swallowed. I believe these findings to be evidence against the view of the ability of the tubercle bacillus to pass through the intestinal mucosa without leaving traces of its progress in the form of a definite lesion.

Other Secondary Lesions.—Chronic tuberculosis of the lymph nodes was found in every case. Most of the other secondary lesions were of an acute character. A more or less generalized miliary tuberculosis, or tuberculous meningitis was found in twenty-three cases. In two cases were chronic lesions only found. Tuberculous peritonitis was found in two cases. Solitary tubercle of the brain was found in one case.

The secondary lesions found in the lung were of two distinct kinds. One was a tuberculous bronchopneumonia characterized by exudate into the pulmonary alveoli, with more or less necrosis or caseation. This lesion was found in ten cases, and I believe it to represent an extension of the tuberculous process from the primary lesion to the lung through the bronchial channels. The other secondary lesion found in the lungs was a miliary tuberculosis, which both in macroscopic and microscopic appearance differed entirely from the tuberculous bronchopneumonia just described. The lesion consisted of numerous sharply defined miliary tubercles without any exudate into the surrounding alveoli. This was the sole secondary lesion found in the lung in thirteen cases. But such miliary tubercles were also found in a certain number of cases in which tuberculous bronchopneumonia was the most prominent lesion. This lesion probably represents extension of the tuberculous process from either the primary lesion or some sec-

ondary lesion through the medium of the general circulation, forming part of a general miliary tuberculosis. Twenty-three of the twenty-five cases showed miliary tubercles in various parts of the body.

The brain was not examined in three cases, and no lesion of the meninges was found in two cases. In nineteen cases a tuberculous meningitis was found, which was the immediate cause of death. In thirteen of these cases the meninges showed small miliary tubercles without evidence of exudate. In six cases, in addition to the miliary tubercles there was more or less cellular or fibrinous exudate along the course of the vessels.

Bacteriological Findings.—In only five cases in this series were animal inoculations made to determine whether the infection was with a human or with a bovine type of bacillus. The bovine type was found in one case, and the human type in four cases. The case in which the bovine type of bacillus was found was one of those having a primary lesion in the intestine and the one known to have been fed with contaminated milk. The four cases in which a human type of bacillus was found included one of the cases in which there was no apparent primary lesion. The cases in which the type of bacillus was tested by animal inoculation are too few to afford more than confirmatory evidence of the greater frequency of infection from a human source.

Previous Feeding.—The previous feeding of these patients was as follows: Fourteen babies had had milk of an unknown or doubtful character. Five babies had been fed exclusively on a milk considered to be of the best character. Six babies had been exclusively breast fed.

Exposure to Tuberculosis.—In four cases only was there a definite history of exposure to tuberculosis obtained. In a few others there was suspicion of such exposure.

THE DIAGNOSIS OF TUBERCULOSIS IN INFANCY

In this series of cases a diagnosis of the tuberculous nature of the disease was made during life in twenty-three out of twenty-five cases. This does not mean that the diagnosis of tuberculous infection in infancy is easy, or that it can be made in so large a number of cases. It must be remembered that these were all fatal cases, seen in the last stages of the disease. In fifteen of them a diagnosis was possible because they showed the definite clinical picture of tuberculous meningitis with characteristic cerebrospinal fluid. The two cases in which the diagnosis was not made were apparently cases of chronic nutritional disturbance with atrophy. One of them is particularly interesting. The child was treated in the hospital for some weeks as a feeding case and did very well, gaining weight steadily. At no time during its stay in hospital did it show any symptoms suggesting tuberculosis, nor did

it have any fever. Within twenty-four hours of its discharge from the hospital it had a series of convulsions followed by death. It was brought back for necropsy and showed extensive chronic tuberculosis of the bronchial lymph nodes with acute miliary tuberculosis of all the organs of the body, but none of the meninges. I am inclined to doubt if acute miliary tuberculosis can often be diagnosed in infancy unless the brain is involved.

The principal diagnostic feature in this series of cases was due to the existence of a tuberculous meningitis. The important question is, whether tuberculosis could have been recognized before the onset of this acute manifestation? For this is an important point in the treatment of the disease.

There are three important points beside the existence of such definite manifestations as tuberculous meningitis or tuberculous peritonitis, on which the diagnosis of tuberculosis in infancy is based. These are: 1. The finding of physical signs suggesting tuberculosis in the chest. 2. The evidence given by the tuberculin reaction. 3. The evidence by Roentgen-ray examination of the chest. An effort was made at the Infants' Hospital to carry out as thoroughly as possible these three methods of investigation, but owing to the fact that many babies were brought in in a moribund condition and died so soon after admission, the records have been very incomplete.

Physical Signs in the Lungs.—The physical examination of the lungs for signs suggesting tuberculosis gave the following results:

Positive	14 cases
Negative	11 cases

In four of the fourteen positive cases d'Espine's sign was the only one found. In the other ten cases evidences of consolidation in various parts of the lung were found which were of such a character as to suggest the possibility of tuberculosis, even if tuberculous meningitis had not also been present. In comparing the physical signs with the postmortem findings the following points were striking: 1. Acute miliary tuberculosis of the lung without tuberculous bronchopneumonia appears to give no recognizable physical signs in the lung. 2. Tuberculous bronchopneumonia usually does give recognizable physical signs in the lungs. In some cases only scattered râles are found; in others there are signs of consolidation in various parts of the chest. The infants may or may not show the appearance of bronchopneumonia with rapid breathing, etc. 3. The presence of d'Espine's sign in infancy usually means tuberculosis of the bronchial lymph nodes, but this sign may not be obtained in cases in which the glands are found enlarged at necropsy. 4. The primary lesion gives no recognizable physical signs in the chest,

unless very large, and in such a case the signs are only those of consolidation and are indistinguishable from tuberculous bronchopneumonia.

The Tuberculin Reaction.—Only the von Pirquet cutaneous reaction was employed. The results were as follows:

Positive	6 cases
Negative	12 cases
Not done	7 cases

The large number of negative reactions in cases proved to be tuberculosis is striking. It must be remembered, however, that many of the patients in the series were acutely ill, and that the reaction was observed very shortly before death, when resistance to the infection was probably at a minimum. It is possible that the results obtained in this series of cases has little bearing on the value of the reaction in cases not in the acute stage of the disease. Nevertheless, one of the chronic cases showed a persistently negative reaction, while in some of the most acute cases a positive reaction was observed within a very short time before death. On the whole, I am inclined to believe that the value of the cutaneous tuberculin reaction in infancy is not so great as many writers and statistical reports would lead us to suppose. A negative reaction seems to be a frequent finding in any stage of the disease, and gives no evidence at all. A positive reaction on the other hand, in infancy, means tuberculosis. For some time at the Infants' Hospital a routine von Pirquet test has been made on every case. We have yet to see a case in which a positive reaction has accompanied a negative post-mortem finding. There was no case in this series in which a positive von Pirquet would have been the only means of diagnosis, if found at a time preceding the acute stage of the disease. There was one case in which the diagnosis rested on a positive von Pirquet with a positive d'Espine's sign.

Roentgen Ray Examination of the Chest.—This was made in thirteen cases of the series, and was positive in every case. There were several cases in which it gave the only positive finding. In general there was a surprisingly close correspondence between the Roentgen-ray picture and the postmortem findings. The enlargement of the bronchial lymph nodes could be made out in most of the cases. Tuberculous bronchopneumonia was correctly diagnosed from the Roentgen-ray in several cases, but not in all those in which it was found postmortem. The primary lesion was not shown, when small, but was conspicuous when very large. Miliary tuberculosis of the lung without tuberculous bronchopneumonia was not shown.

There were two cases in the series in which before the acute stage the diagnosis could have been made from the Roentgen-ray picture

alone, and two cases in which d'Espine's sign was positive, but in which the diagnosis of the pulmonary condition rested chiefly on the roentgenogram.

The table shows the occurrence of the three forms of diagnostic evidence in the series:

CERTAIN DIAGNOSTIC SIGNS IN TWENTY-FIVE CASES OF TUBERCULOSIS IN INFANCY, COMING TO NECROPSY

Clinical Type	Roentgen Ray	Signs in Lung	Von Pirquet
1. Tb. peritonitis	?	0	?
2. Atrophy	?	0	?
3. Tb. meningitis.....	?	0	?
4. Tb. meningitis.....	?	0	?
5. Malnutrition	+	d'Espine only	0
6. Bronchopneumonia	+	+	0
7. Tb. meningitis.....	?	0	?
8. Tb. meningitis.....	?	0	0
9. Tb. meningitis.....	+	+	+
10. Tb. meningitis.....	?	+	+
11. Tb. meningitis.....	+	0	0
12. Tb. meningitis.....	+	0	0
13. Tb. meningitis.....	+	d'Espine only	?
14. Chronic tuberculosis of lung.....	+	+	0
15. Tb. meningitis.....	?	d'Espine only	+
16. Tb. meningitis.....	+	+	+
17. Tb. meningitis.....	?	0	0
18. Bronchopneumonia	+	+	0
19. Bronchopneumonia	?	0	?
20. Tb. meningitis.....	+	+	+
21. Chronic tuberculosis of lung.....	+	+	+
22. Tb. meningitis.....	+	+	0
23. Atrophy	?	0	0
24. Tb. peritonitis.....	+	+	0
25. Tb. meningitis.....	?	+	0