

CONGENITAL TUBERCULOSIS

BY

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Congenital tuberculosis may be defined as tuberculosis occurring in infants as a result of infection with *Myco. tuberculosis* during intra-uterine life.

The condition has been the subject of much controversy in the past; some have refused to accept it as a pathological entity, others, such as Baumgarten (1925), have ascribed many cases of tuberculosis occurring in young persons to a congenital origin. However, the present century has seen the establishment of the disease as a rare but well defined entity. It appears in two main forms: one in which the lesions are most prominent in the lungs and which is thought to be due to aspiration of infected amniotic fluid by the foetus, the other in which the earliest lesion is found in the liver and its regional lymph nodes. A third form, in which death of the foetus occurs before the development of macroscopic lesions, is known as tuberculous bacillaemia.

Two essential facts must be clearly established in every example of the disease. First, it must be proved to be a result of tuberculous infection: secondly, the infection must have occurred during intra-uterine life. A number of authors have laid down conditions which each reported case must satisfy, and of these Beitzke (1935) appears to have provided the most satisfactory criteria. He proposed that a case should not be accepted as congenital tuberculosis unless (1) the presence of *Myco. tuberculosis* in the infant was proved, and (2) either (a) a primary tuberculous complex was present in the liver, or (b) the tuberculous lesions were present at birth, or (c) extra-uterine infection could be excluded with certainty.

Using these criteria, Beitzke (1935) reviewed the literature and accepted 61 cases of congenital tuberculosis and 40 of tuberculous bacillaemia. Hughesdon (1946), using the same criteria as Beitzke, accepted a further six cases of congenital tuberculosis, one case of tuberculous bacillaemia and added four cases of congenital tuberculosis of her own.

Since then I have found 18 published cases for which a congenital origin was claimed, of which 10 satisfy the conditions required by Beitzke, Jordan and Spencer (1949), Hertzog, Chapman and Herring (1949), Ballabriga Aguado (1950), Germain, André and Marty (1950), Pagel and Hall (1946), Aufdermaur (1947), Daamen (1947), Danjou (1947), Wallgren (1948) and Debré, Furiet-Laforet and Royer (1948). To date 83 cases of congenital tuberculosis and 41 cases of tuberculous bacillaemia have been described. Of these, nine have occurred in the British Isles: those of Andrewes (1903), Morley (1929), Price (1937), Davin-Power (1941), Hughesdon (1946) and Jordan and Spencer (1949). A further case of congenital tuberculosis is presented here.

Case Report

The child, a girl, was born after 40 weeks' gestation and weighed 7 lb. at birth. She appeared well until just before death, having taken her feeds satisfactorily and almost regained her birth weight when, on the eighth day, attacks of cyanosis occurred and she died suddenly during one of them. There had been no clinical reason to suspect that she was suffering from tuberculosis. From birth she was isolated from her mother, and was not subsequently in contact with her.

Necropsy Report. The body was well nourished and without congenital abnormality. The skin was cyanotic.

HEART AND LUNGS. The heart was normal. Each pleural cavity contained 5 ml. of clear, yellow fluid. Grey-yellow tubercles measuring 1 to 3 mm. in diameter were present beneath the visceral pleura of all lobes of both lungs. In the substance of the lung were numerous tubercles of 1 to 5 mm. in diameter (Fig. 1). The tracheo-bronchial glands were not enlarged. The right lung weighed 62 g., the left 58 g.

ABDOMEN. There were 10 ml. of clear yellow fluid in the peritoneal cavity. White exudate was present on the peritoneal surface of the spleen, causing it to be matted to coils of small intestine. The mesenteric glands were not enlarged.

LIVER. The liver (260 g.) contained a number of grey-yellow tubercles, measuring 1 to 3 mm. in diameter,

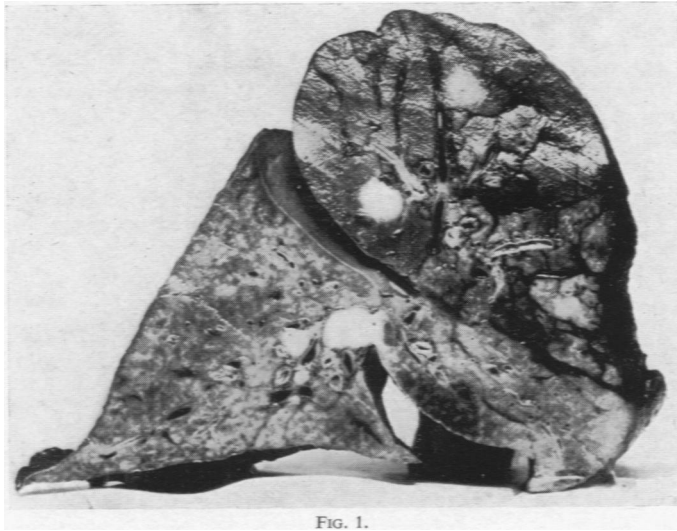


FIG. 1.

FIG. 1.—Cut section of lung.

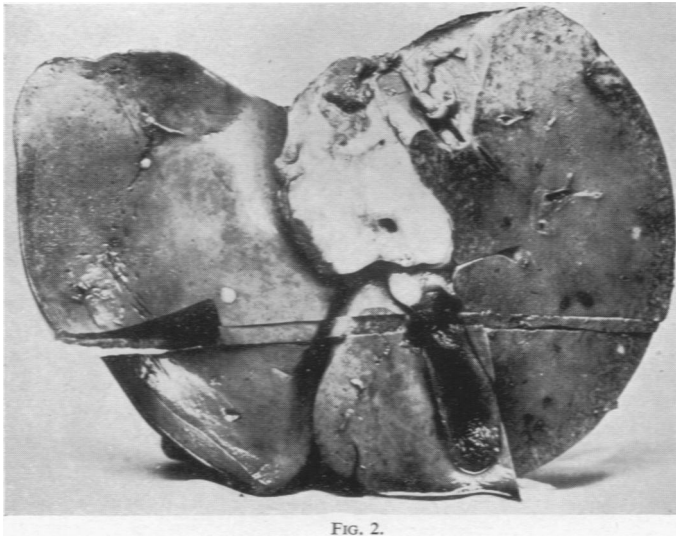


FIG. 2.

FIG. 2.—The liver showing at the porta hepatis the caseous tuberculous glands, part of which has been removed.

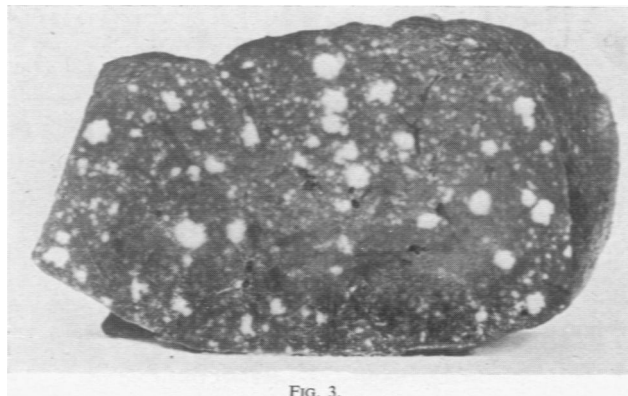


FIG. 3.

FIG. 3.—The spleen showing tubercles of various sizes.

beneath its peritoneal surface and also within its substance. A larger area of caseation, measuring 0.4 cm. \times 1 cm. was present in the right lobe. The glands of the porta hepatis were enlarged, measuring 3 cm. \times 2.5 cm. \times 1.5 cm. They were not attached directly to the liver and on section presented the appearance of caseous tuberculous glands (Fig. 2).

SPLEEN. The spleen (35 g.) was engorged and contained large numbers of grey-yellow tubercles of various sizes from 0.1 cm. to 0.5 cm. in diameter. The organ measured 7.5 cm. \times 4 cm. \times 3 cm. (Fig. 3).

BRAIN. The hemispheres appeared to be congested.

The other organs of the body revealed no macroscopic abnormality.

The placenta was not available for study. It weighed 1 lb. 12 oz., and was reported as having appeared normal.

On microscopic examination the pattern of the liver was normal. The liver cells showed marked cloudy swelling and some fatty degeneration. Scattered throughout the liver substance were areas of necrosis, complete at the centre and less complete at the periphery. In the outskirts of these were a few lymphocytes and plasma cells but they did not form complete rings. No giant cells were seen. Ziehl-Neelsen staining revealed many bacilli, having the morphological appearance of *Myc. tuberculosis*, within the necrotic areas (Figs. 4 and 5).

The microscopic picture confirmed the caseation seen macroscopically in the nodes of the porta hepatis. There were no giant cells. A direct smear from the cut surface of the node showed a mass of *Myc. tuberculosis* (Fig. 6).

The spleen contained necrotic areas in which were masses of *Myc. tuberculosis*.

The lungs were generally congested. Scattered throughout the substance were areas of necrosis similar to those in the liver.

The following details about the mother were kindly supplied by Dr. Mason:

Mrs. Irene W., aged 24, was well until November, 1949, when, during the fifth month of her second pregnancy, she developed a left pleural effusion. One pint of clear fluid containing only lymphocytes was aspirated on December 1 and on December 8.

On February 6, 1950, the patient was admitted to hospital for observation before her confinement. She was symptomless and apyrexial, with an erythrocyte sedimentation rate of 18 mm. in one hour (Westergren). She remained thus until April 17 when the evening temperature rose to 99° F. She went into labour on April 19, and during the next eight days the evening temperature varied between 99° and 101°. On April 29 she started a course of 1 g. of streptomycin and 15 g. of para-amino-salicylic acid daily. From June 15 the evening pyrexia ceased. She had completed a course of 120 g. of streptomycin by August 27 when she stated that she felt well. The erythrocyte sedimentation rate then was 4 mm. in one hour (Westergren).

A radiograph of the chest on April 27 showed a finely granular appearance of the lung fields which suggested early miliary tuberculosis. This mottling had cleared by June 29.

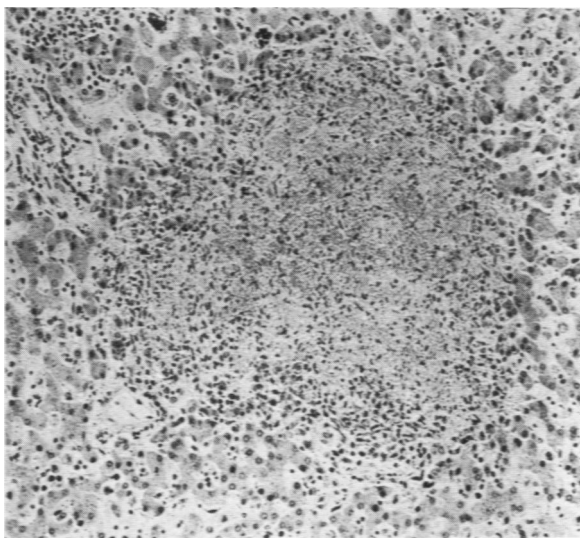


FIG. 4.—Section of liver \times 100 showing a necrotic tubercle (haematoxylin and eosin).

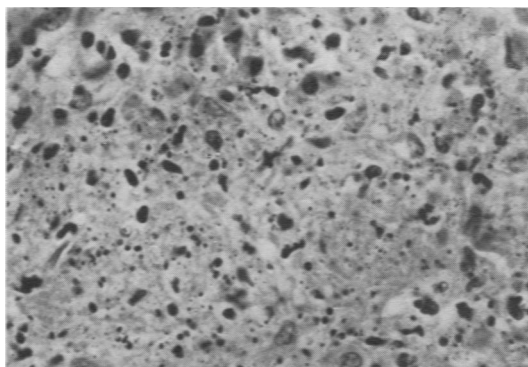


FIG. 5.—Higher power view of the centre of the necrotic area of Fig. 4 showing fragmentation of nuclei and absence of cell outlines (haematoxylin and eosin).

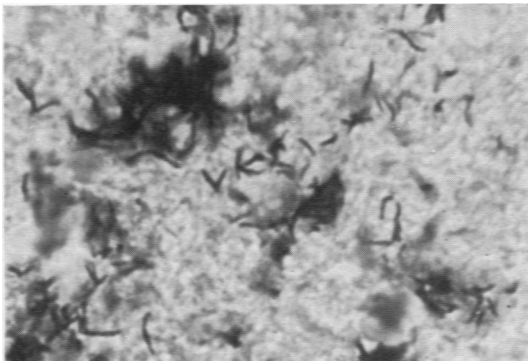


FIG. 6.—High power (\times 1200) view of gland of porta hepatis stained by Ziehl-Neelsen method showing numerous *Myc. tuberculosis*.

She was discharged symptomless on October 19, 1950, and has remained well.

Discussion

The case reported appears to be without doubt congenital. The presence of caseating tuberculous glands in the porta hepatis and a caseous area in the right lobe of the liver suggests that this was a primary liver complex from which a late miliary spread had taken place, as often in congenital tuberculosis the infant appears well at birth and subsequently dies rapidly with miliary dissemination.

The microscopic appearance of the lesions was similar to that described by Pagel and Price (1943) and Hughesdon (1946) and corresponded to the description of the 'soft tubercle' by Rich and McCordock (1929). It is noteworthy that the lesions showed local necrosis with very little tissue reaction; there were neither giant cell formation nor rings of epitheloid cells and lymphocytes. Such lesions have been described where the tissues have been overwhelmed by *Myco. tuberculosis*.

The mothers of infants suffering from congenital tuberculosis usually have advanced tuberculosis, often of the lungs, and the mothers frequently die soon after parturition. However, in some instances, such as the cases of Reichle and Wheelock (1939), Whitman and Greene (1922), Chiari (1932) and Hughesdon (1946), the mothers remained well, while in those of Morley (1929) and Söderström (1932) there appeared to be no evidence of maternal tuberculosis at all. In the case of Pagel and Hall (1946), although originally the mother was reported well, in a later publication (1948) the mother was reported as having subsequently developed fatal disseminated tuberculosis.

The present case is the first which I have been able to find where the mother was treated with streptomycin. It seems likely that maternal haematogenous spread occurred at or immediately following parturition and responded to antibiotic treatment.

Pathogenesis of Congenital Tuberculosis. Whitman and Greene (1922) were of the opinion that congenital tuberculosis was transmitted from the father by way of the spermatozoa, but there is now little support for this hypothesis. It is unlikely because genital tuberculosis in the male often leads to sterility, and because infection of the foetus at the time of conception would almost certainly lead to abortion. The latter contention is supported by the observation that tuberculosis of the placenta has never been found before the fourth month of pregnancy.

Calmette and Valtis (1930) tried to prove the existence of an ultra-virus as an alternative form of *Myco. tuberculosis*. It was suggested that in

such a form the bacillus might cross the placental barrier and infect the growing foetus. This hypothesis has now been firmly refuted by a number of workers and will not be discussed further.

Mothers of infants suffering from congenital tuberculosis usually have advanced tuberculosis. The maternal history may contain an incident which would have been likely to lead to bacillaemia, such as an acute flare-up of a quiescent tuberculous lesion, or the onset of miliary tuberculosis. Loewenstein (1935) found a positive tuberculous blood culture in 11 of 59 parturient women suffering from tuberculosis. Infection of the placenta, which is the first step in infecting the foetus, probably occurs during maternal tuberculous bacillaemia.

However, there remain a few cases such as those of Morley (1929) and Söderström (1932), in which the mother was reported clinically and radiologically free from tuberculosis. It may well be that in such instances the mother was suffering from tuberculous endometritis from which direct spread to the placenta occurred. O'Brien and Lawlor (1947), amongst others, have shown that tuberculous endometritis may be discovered only by careful search of uterine curettings, and such a search was not undertaken in either of the two cases cited. The majority of women suffering from tuberculous endometritis are sterile, a fact which may explain the rarity of congenital tuberculosis where the mother is apparently healthy. According to Gofton (1937), tuberculous pyometritis is common in the dams of calves found to have congenital tuberculosis, and Reichle and Wheelock (1939) and Hertzog *et al.* (1949) all reported maternal tuberculous endometritis in their cases of congenital tuberculosis.

Vaccaro and Paredes (1947), from experimental studies on animals, believe that *Myco. tuberculosis* may cross the placental barrier without causing a lesion. However, this is not borne out by a study of human congenital tuberculosis. Since the condition is often unsuspected at birth the placenta has been carefully examined in a relatively small proportion of cases only; in those cases where it has been studied microscopically caseous tuberculosis has always been found.

Seigel and Singer (1935) have shown that placental infection begins as a thrombus containing *Myco. tuberculosis* in an intervillous space, and later develops into a necrotic tubercle. Often thrombosis of the foetal vessels draining the area occurs and no disease is transmitted to the foetus; this explains the fact that placental tuberculosis is much commoner than congenital tuberculosis. For instance, Schmorl and Geipel (1904) found tuberculous lesions in nine of 20 placentas belonging to tuberculous mothers.

Infection from the placenta to the foetus may occur theoretically in one or more of three ways: (1) by direct infection of the amniotic fluid which is then ingested or inhaled by the foetus; (2) by haematogenous spread; (3) by lymphatic spread.

INFECTION FROM AMNIOTIC FLUID. Foetal infection by aspiration of infected amniotic fluid probably occurs in a small number of cases. Schmorl and Geipel (1904) described tuberculosis of the placenta infecting the amniotic fluid by rupture of a caseous focus through the amniotic membrane. Since then, Reichle and Wheelock (1939) in a review of the literature accepted seven cases of the aspiration type of congenital tuberculosis and added one of their own. Often infection appears to have occurred during parturition when the infant became partially asphyxiated in the birth canal and began to breathe before delivery was complete.

Aspiration of amniotic fluid before parturition is also possible, since Snyder and Rosenfeld (1937) have shown that respiratory movements occur in foetal rabbits during intra-uterine life. Although this contention has been challenged by Whitehead *et al.* (1942), the work of Davis and Potter (1946) appears to have established without doubt the validity of intra-uterine respiratory movements.

Infants infected by aspiration of infected amniotic fluid are found on post-mortem examination to have miliary tuberculosis confined to the lungs. Often death occurs before the development of caseation in the regional nodes.

HAEMATOGENOUS SPREAD. In most of the reported cases congenital tuberculosis probably occurred as a result of haematogenous spread along the umbilical vein. Foetal tuberculous bacillaemia has been demonstrated by a number of workers. For example, Siegel and Singer (1935) cultured the cord blood of 15 infants born to mothers suffering from advanced tuberculosis; they obtained a positive result in one infant which died shortly afterwards and in which the heart blood also gave a positive culture. Warthin and Cowie (1904) demonstrated thrombi full of *Myc. tuberculosis* in the liver of an infant stillborn to a tuberculous mother.

In some instances, such as that of Whitman and Greene (1922), the tuberculous bacillaemia causes miliary tuberculosis without a primary complex, while in others a primary complex occurs, usually in the liver and sometimes in the liver and lungs. Siegel (1934), reviewing 30 cases of congenital tuberculosis, found that in 14 the lymph nodes of the lung were involved alone or predominantly, and in 13 the lymph nodes of the liver predominantly, suggesting a primary complex of the lung or liver respectively

Bertoye (1936) amongst others suggests that the liver is often the site of the primary complex because it is the first organ to come into contact with infected blood; he adds that in cases of primary infection of the liver and lungs simultaneously the sites are determined by the fact that each organ has a sluggish circulation. Most authors have been content to accept this explanation, but it does not explain why no primary complex has ever been described in any organ other than the liver or lung.

Most of the blood returning along the umbilical vein is shunted past the liver by way of the ductus venosus, and this fact, combined with the knowledge that foetal tuberculous bacillaemia occurs, makes it likely that all the foetal organs come into contact with *Myc. tuberculosis*. Further, Brickner (1927) has shown that the arrest of particulate matter is best achieved by the liver, spleen, bone marrow and lungs and next best by the renal cortex and adrenal, while Rich and McCordock (1929) state that experimentally *Myc. tuberculosis* behaves in a manner similar to particulate matter when injected intravenously. It would appear likely, therefore, that following haematogenous spread, the foetal organs are infected with *Myc. tuberculosis* in proportion to their ability to remove circulating organisms from the blood stream. Subsequently, other factors must operate to achieve the disease pattern observed whenever a primary complex has been described. The following explanation is offered.

It can be shown experimentally in animals that after haematogenous spread infection with *Myc. tuberculosis* some clumps of organisms multiply and form a lesion, while others are killed and absorbed (Rich and Follis, 1942). This appears to be due to the varying abilities of different tissues to support the growth of the organism. It seems probable that the mechanism must be similar in congenital tuberculosis, and it is suggested that the infecting organism usually dies out in all the organs except the liver and sometimes the lung. Siegel (1934) states that the lung and not the liver is the organ most often infected, but he does not distinguish between primary and miliary lesions, a point of obvious importance.

It is interesting to speculate why primary liver infection occurs in the foetus, in view of the rarity of progressive tuberculosis (other than miliary) in the adult liver. Thus Ashton (1946) was able to find in the literature of the 10 years before publication of his paper, only one example other than his own of massive tuberculosis of the liver.

The importance of adequate oxygen supply to the growing *Myc. tuberculosis* has been stressed

by a number of workers, such as Rich and Follis (1942). Since the foetal liver receives blood direct from the umbilical vein before it has mixed with the blood of the inferior vena cava, the oxygen tension in the blood supplying it must be high compared with that of the rest of the foetal body, the opposite of what is found in the adult. Rich (1946) has suggested that in cases of primary infection of the liver and lungs at birth the lesions in the lungs develop more rapidly than those in the liver, because the former are exposed to a higher oxygen tension; thus at the time of death the two lesions are equal in size whereas at birth the liver complex exceeded that of the lung. Following primary infection, the regional nodes become invaded by *Myc. tuberculosis*. The terminal miliary spread, which occurs in nearly all cases, probably originates from these nodes which infect the blood stream, either directly or by way of the thoracic duct.

LYMPHATIC SPREAD. Since the placenta is embryologically part of the foetal body, it is possible that infection of that organ could act as a primary lesion. In that case the regional nodes in the porta hepatis would become involved (i.e. the first to be encountered along the path of the vein draining the part). The lymphatic drainage of the placenta does not appear to have been studied adequately, and no reliable data could be found on this subject; an attempt is being made to investigate the matter. Until more information is available the possibility of lymphatic spread along the umbilical cord must remain *sub judice*.

Summary

The literature concerning congenital tuberculosis is reviewed to date and the most recent cases evaluated, using the same criteria as Beitzke (1935) and Hughesdon (1946). A new case is put on record, and the pathogenesis of the condition is discussed in detail.

I should like to thank Mr. Riddell for permission to publish details of a case under his care. I am grateful to Dr. Wordley for his help and encouragement; to Dr. Mason for clinical data; and to Dr. Thomas and Dr. Ulrich for help in the Spanish and German translations. Mr. Dallan kindly photographed the specimens.

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