

## TUBERCULOUS OSTEITIS FOLLOWING B.C.G. VACCINATION

By

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Complications of B.C.G. vaccination have been described by many Scandinavian authors. Most complications appear at the site of vaccination, and consist of specific reactions locally in the skin or regionally in the lymph nodes. Four fatal cases of generalized spread of the tuberculous process have been published, however, (1, 4, 8, 11). In all these 4 cases the main feature was generalized lymphadenitis. In 1 of the cases multiple foci in the skeleton were found (*Thrap-Meyer* 1954, *Waalder & Oeding* 1954).

A further 5 cases with generalized spread have been reported, and in 3 of them bone lesions were found. A short account of these cases is of interest in connection with the present observations.

One child, who was vaccinated 4 weeks after birth developed 6 months later a lupus-like lesion at the site of inoculation, with regional adenitis. Examination 2 years after vaccination showed multiple bone lesions in the metatarsus, the ulna, and the vertebral column (*Imerlund & Jensen* 1954). The patient was in poor general condition but survived the disease after surgical treatment and chemotherapy.

In a 7 month old child osteitis with sinus formation developed in the ulna 6 months after B.C.G. vaccination. The process healed after operation and chemotherapy (*Mørkbak* 1954).

A 2½ year old child, who was vaccinated at the age of 3 days and again, because of a negative tuberculin test, 4 months later, developed a fistulating tuberculous lesion in the talus, which healed after operation and chemotherapy (*Haraldsson* 1959).

*Horwitz & Meyer* (1957) have published a survey of the complications of B.C.G. vaccination, in which they mention all cases published up to the present. In all of them the diagnosis was verified by identification of bacterial type.

Thus, I have found 4 published cases of tuberculous osteitis in which bacilli of the B.C.G. type were demonstrated. In 2 of them the patient had a solitary lesion and in 2 multiple lesions.

#### PRESENT INVESTIGATION

Tuberculous infection in children has declined strikingly in Sweden during the last few decades. As from 1951, data on the age-distribution for newly discovered tuberculosis cases can be found in the annual report of the Central Tuberculosis Dispensaries, and it will be seen from Table 1 that there has been a marked decrease for children under 5 years of age in the 10-year period 1951–1960 as well. At the Orthopaedic Clinic, St. Görans Hospital, which is a special department for bone and joint tuberculosis, on an average 1 child per year has over the same period of time been treated for newly discovered tuberculosis. The causes of this striking decrease in the incidence of tuberculosis in children are of course many, and one of them is probably the B.C.G. vaccination scheme which to nearly 100 % covers all infants in the first few weeks of life.

TABLE 1  
*Cases of newly discovered tuberculosis in children under 5 years of age.*

|                                                                       | 1951 | 1952 | 1953 | 1954 | 1955 | 1956 | 1957 | 1958 | 1959 | 1960 |
|-----------------------------------------------------------------------|------|------|------|------|------|------|------|------|------|------|
| Number of registered tuberculosis cases in Sweden                     | 218  | 123  | 90   | 65   | 45   | 39   | 22   | 22   | 14   | 14   |
| Number of cases of bone and joint tuberculosis at St. Görans Hospital | 1    | 1    | 1    | 1    | 2    | 1    | 0    | 0    | 1    | 2    |

Even before the first cases of serious B.C.G. complications were published we had begun to consider the question whether the few cases of bone tuberculosis in children could be caused by B.C.G. In the 10-year period 1951–1960 we had seen 10 such cases in children under 5 years of age. All had been B.C.G. vaccinated in the first few weeks of life without any local complications. In none of them did X-ray of the chest show any pathological changes. All of the 7 children that were tuberculin tested were found positive. Further data on these 10 cases are set out in chronological order in Table 2. In cases 5, 6, and 9, in which the lesion was localized to the sternum and the radius, the symptoms ap-

TABLE 2  
*Cases of tuberculous osteitis in children under 5 years of age during the period 1951-1960.*

| Case | Age<br>Year | Sex | Localization                        | Trauma    | Histological<br>examination | Tb-culture | Guinea-pig | Pre-operative<br>chemotherapy |
|------|-------------|-----|-------------------------------------|-----------|-----------------------------|------------|------------|-------------------------------|
| 1    | 1 1/12      | ♂   | Distal end of right fibula          | no        | tuberculosis                | negative   | negative   | -                             |
| 2    | 11/12       | ♂   | Proximal end of left tibia          | no        | tuberculosis                | -          | negative   | 2 days                        |
| 3    | 1           | ♂   | Distal end of left ulna             | no        | tuberculosis                | negative   | negative   | 4 weeks                       |
|      |             |     | Proximal end of left tibia          |           | tuberculosis                | negative   | negative   | 4 months                      |
| 4    | 9/12        | ♀   | Distal end of left femur            | yes       | tuberculosis                | negative   | negative   | 7 months                      |
| 5    | 4           | ♂   | Proximal end of left fibula         | yes       | tuberculosis                | negative   | -          | 7 days                        |
|      |             |     | Distal end of left radius           | fracture  | tuberculosis                | negative   | negative   | 4 months                      |
|      |             |     |                                     | suspected |                             |            |            |                               |
| 6    | 3 8/12      | ♀   | Distal part of sternum (substernal) | yes       | tuberculosis                | negative   | negative   | -                             |
| 7    | 1           | ♀   | Proximal end of right tibia         | yes       | tuberculosis                | -          | negative   | 3 weeks                       |
|      |             |     |                                     | fracture  |                             |            |            |                               |
|      |             |     |                                     | suspected |                             |            |            |                               |
| 8    | 1 4/12      | ♀   | Right cuboid bone                   | no        | tuberculosis                | negative   | negative   | 12 days                       |
| 9    | 3           | ♀   | Central part of sternum             | yes       | tuberculosis                | negative   | negative   | -                             |
| 10   | 1 2/12      | ♀   | Distal end of right femur           | no        | tuberculosis                | positive   | negative   | -                             |

peared at 3 to 4 years of age. In the other 7 children the disease ran a fairly similar course. The onset occurred about 1 year after vaccination and in one of the cases the bone lesion was localized to the cuboid bone but in the others it was seated around the epiphyseal line in the long bones.

In 5 of the cases one or several traumata were said to have been the factor that brought the symptoms into notice, but these statements must of course be viewed with great caution. In 2 cases, however, the trauma was so severe that a fracture was suspected at the hospital to which the child was first taken.

All the children were treated by operation and chemotherapy. The course was benign; all the lesions healed, and so far no disturbances in adjacent zones of growth have been noted. At operation specimens were taken for histological examination, cultivation of the tubercle bacillus, and guinea-pig tests. In all the cases the diagnosis could be verified by histological examination. Guinea-pig tests were made in 9 cases and all were negative. Tb cultures were made in 8 cases and were negative in all except for the last case, in which the examination was positive, and a strain with all the properties characteristic of the B.C.G. type was identified. A detailed description of the case will be given here.

#### CASE REPORT

A girl born on April 12, 1959, to healthy parents, was B.C.G. vaccinated on the left thigh 2 days after birth. The vaccine did not differ in strength or otherwise from the generally used Swedish B.C.G. vaccine. Nor have any complications been reported in other children who were vaccinated at the same time.

The girl developed no local reactions at the site of vaccination. She was breast-fed for 3 months and was in good health during the first year of life. There is no known heredity or exposure to tuberculosis.

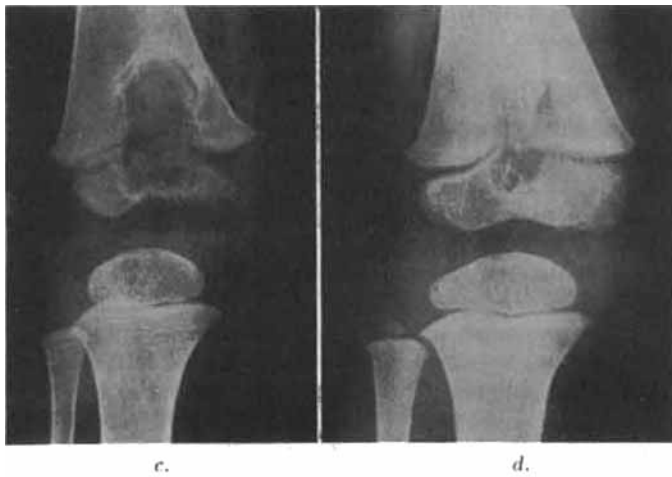
When she was 14 months old diffuse symptoms referable to the right knee-joint appeared, with increasing swelling in the next few months. At the age of 19 months she was admitted to a children's clinic. Her temperature was normal. E.S.R. was normal and X-ray of the chest showed no abnormalities. A tuberculin-test was positive. X-ray of the right knee-joint showed a destruction in the distal end of the femur. A proof-puncture at the level of the destruction was made and yielded a small amount of thick yellow pus; ordinary culture of the pus produced no bacterial growth.

On the suspicion of tuberculosis she was transferred to this clinic on Nov. 19, 1960. On admission she had a normal temperature; E.S.R. by the micro-method was 68 mm. in an hour, and her general condition was good. On the left thigh there was a small mark after a Calmette vaccination, without any reactive phenomena. Around the lower part of the right thigh a diffuse swelling was seen, and the range of movement in the knee-joint was restricted by pain. X-ray showed a large cavity in



*Fig. 1a.* Radiograph before operation. A large bone lesion centrally in the distal end of the femur.

*Fig. 1b.* The healthy knee-joint.



*Fig. 1c.* 4 weeks after evacuation of the cavity. Ossification of the medial condyle of the femur has begun; this indicates that it was not destroyed initially, as possibly suggested by Fig. 1a, but only poorly developed because of the adjacent inflammatory process.

*Fig. 1d.* 16 months after operation. Bone structure is seen within the area of the old lesion, which has decreased in size. The medial condyle of the femur has now developed normally. The epiphyseal line and the condyles seem to be developing normally.

the end of the femur, extending across the epiphyseal line into the epiphysis, and in the centre of sequester-like formation was seen (Figs. 1 a and b).

Operation was performed on Nov. 24, 1960, when the child was 19½ months old, without previous chemotherapy. On the medial aspect of the knee a large para-articular abscess was found, which through a very narrow fistula at the level of the epiphyseal line communicated with the large bone cavity. The posterior cortical wall of the cavity was very thin, and there a hole was chiselled, through which the cavity could be emptied of its content of pus and granulation tissue. After local application of streptomycin the wound was closed by primary suture. The material obtained at operation was examined histologically and bacteriologically.

The histological examination showed epithelioid-cell granulomas with central areas of caseous necrosis and numerous giant-cells of Langhans type. At the periphery of the granulomas there were numerous plasma cells and a small amount of lymphocytes. Acid-fast rods were seen in the slides.

At the bacteriological examination ordinary culture produced no growth. Culture on Löwenstein medium yielded acid-fast rods. A guinea-pig test was negative. Identification of type was done at the Bacteriological Laboratory in Gothenburg, and the following answer was obtained: "The mycobacteria isolated from the patient are not virulent for guinea-pigs (3 animals inoculated). They do not grow at 20° C or 45° C and are sensitive to PAS, streptomycin and isoniazid. In contrast to tubercle bacilli of the human type but similarly to bovine tubercle bacilli, the bacteria are wholly sensitive in pentacyclic carbonic acid hydrazide. Since the isolated mycobacteria are avirulent for guinea-pigs and are of the bovine type, they cannot be distinguished from B.C.G. bacteria" (*Arne Lind*).

The postoperative course was uncomplicated. The operative wound healed by first intension. She was immobilized in plaster for 2 months and treated with chemotherapeutic agents (streptomycin and isoniazid) over 11 months. She was in hospital for 4½ months. The subsequent clinical course was also uncomplicated. The range of movement in the knee-joint became normal soon after the removal of the plaster and she has remained symptom-free. Radiologically, the cavity has gradually decreased and bony structure is visible (Figs. 1c and d). It will also be seen in the radiograph that the medial condyle of the femur, the ossification of which has been delayed, is developing normally, and up to the present there have been no signs indicating growth inhibition, despite the fact that part of the epiphyseal line has probably been destroyed.

#### DISCUSSION

Out of the 10 children under 5 years of age, who in the past 10-year period were treated for bone and joint tuberculosis, 5 had bone lesions localized to the epiphyseal line of the knee-joint (cases 2, 3, 4, 7, and 10). In these children, as well as in 1 with a lesion in the distal end of the fibula (case 1), and in 1 with a lesion in the cuboid bone (case 8), *i.e.* 7 children in all, the disease ran a similar course, with onset at about 1 year after B.C.G. vaccination. In 1 of these 7 cases B.C.G. bacilli were demonstrated. In 3 the onset of the disease did not occur until 3 to 4 years after vaccination; 2 of these (cases 5 and 9) in which the

seat of the lesion was the distal end of the radius and the centre of the sternum, respectively, did not differ essentially in any other respect from the rest; one child (case 6), however, had a substernal abscess which at operation was interpreted as osteitis secondary to soft-tissue affection, possibly in a lymph-node.

The development of tuberculous bone lesions is a result of haematogenous spread. That such a spread of B.C.G. can occur has been shown by *Gormsen* (1956) in an interesting study, comprising histological examinations in connection with autopsies of B.C.G.-vaccinated human beings. He was able to demonstrate the presence of epithelioid-cell granulomas locally at the site of vaccination and in the regional lymph-nodes as well as in several internal organs, but not in bone-marrow. He does not state to what extent bone was examined, however. These granulomas did not show the picture typical of tuberculosis with formation of tubercle nodules, but had a strong resemblance to the histological picture that was found in the fatal cases after B.C.G. vaccination. *Gormsen* draws the conclusion that at least 2 to 3 years after vaccination, signs of generalized haematogenous spread can be found although there has been no manifest disease.

*Ustvedt* (1956), after an analysis of the 4 fatal cases, discusses the question of immunity and summarizes that the laboratory procedures could not throw any light on the question why generalized fatal disease should develop. He also points out that it is difficult to explain the atypical histological picture which to some extent resembles the findings in non-reactive generalized tuberculosis (*sepsis tuberculosis acutissima*).

In all my cases described here we are concerned with benign tuberculosis with, in one case, multiple and, in the others, solitary bone lesions, all of which healed after operative treatment combined with chemotherapy. The histological picture in the case in which B.C.G. was demonstrated was characterized by the presence of numerous plasma-cells diffusely without any very marked accumulation around the tuberculous foci. In view of this finding, which to some extent differs from what is usually observed in human tuberculosis, the histological findings in the other cases reported here were carefully examined. This analysis revealed in some cases a similar diffuse plasma-cell infiltration, in others a more or less marked accumulation around caseous lesions and epithelioid-cell tubercles.<sup>1</sup>

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<sup>1</sup> The histological examination was carried out by *Ake G. H. Lindgren*.

I cannot find any satisfactory explanation of the causation of the lesions. There were no local reactions at the site of vaccination. The information about traumata in 5 cases, and in some of them distinct injuries, is remarkable, however. Trauma and tuberculosis are an interesting constellation. The relationship is repudiated by several experimental workers, but some clinical observations are such that the importance of the trauma in the manifestation of a tuberculous lesion cannot be wholly denied (*Konshegg, Rich*). It is of course difficult to judge the significance of the trauma, when the patients are infants as in the cases under discussion, but since the symptoms appeared in close association with severe traumata we can hardly exclude the possibility that the trauma activated a latent lesion, which according to *Gormsen's* investigations is always present.

It is of course of the greatest interest that these B.C.G. infections should be established. Unfortunately, identification of the type is made difficult by the fact that B.C.G. is a bovine strain of low virulence, and is not easily differentiated from other bovine strains. In 6 of my cases the patients had been in some other hospital where chemotherapy had been given on the basis of the histological diagnosis before the cultures had been made (Table 2). It is possible that this is the reason why we obtained so many negative cultures. The chemotherapy had in some cases lasted for a short time only, but may nevertheless have been sufficient to enable the concentration in the specimens to inhibit bacterial growth. Our own routine is to avoid, if possible, chemotherapy before operations, in order to establish a confident bacteriological diagnosis. The main object is to be able to distinguish between septic and tuberculous infections before adequate therapy is instituted. If a B.C.G. infection, which is much more difficult to diagnose bacteriologically, is suspected, it is still more necessary to follow this routine.

This report is intended as a contribution to the current discussion on the safety of B.C.G. vaccination and the question whether mass vaccination is still justified (*Wallgren* 1956). In most of these 10 cases of tuberculous osteitis the process can be suspected to be of the B.C.G. type, even though B.C.G. was demonstrated in only 1 case. In all the cases the course was benign. The localization close to and the partial destruction of the growth zones of the long bones in these infants may under unfavourable conditions lead to considerable growth disturbances. Fortunately, no such disturbances have so far occurred in the cases reported here.

## SUMMARY

Tuberculous osteitis in the lower end of the femur developed in a 14 month old child who had been B.C.G. vaccinated 2 days after birth. Tubercle bacilli identical with the B.C.G. strain were recovered.

Over the 10-year period 1951–1960 a further 9 children under 5 years of age were treated for tuberculous osteitis which was verified histologically. In most of these cases the course of the disease was fairly similar to that in the first-named case. All were B.C.G. vaccinated in the first few weeks of life, and in 6 of the children the symptoms appeared approximately 1 year after the vaccination. Identification of bacterial type could not be made, since the cultures were negative.

In all the cases the course was benign and the process healed after operation combined with chemotherapy. One of the patients had multiple, the others solitary bone lesions. Because of its localization to the proximity of the growth zones of the long bones, the disease must be regarded as serious despite its otherwise benign course. So far, however, no disturbances of the growth have occurred in the cases reported here.

The importance of trauma in the manifestation of the bone lesions is discussed.

## RESUME

Une ostéite tuberculeuse de la partie inférieure du fémur s'est développée chez un enfant âgé de 14 mois qui avait été vacciné par le B.C.G. deux jours après la naissance. Des bacilles tuberculeux identiques à la lignée du B.C.G. ont été recueillis.

Dans la période décennale 1951–1960, 9 autres enfants de moins de 5 ans ont été soignés pour une ostéite tuberculeuse assez similaire au premier cas mentionné. Tous avaient été vaccinés par le B.C.G. dans les premières semaines de la vie et chez 6 de ces enfants les symptômes se sont manifestés environ un an après la vaccination. L'identification du type bactérien n'a pu être faite, les cultures ayant été négatives.

Dans tous ces cas le cours de la maladie fut bénin et la guérison intervint après une opération combinée de chimiothérapie. Un des malades avait de multiples lésions osseuses, les autres une lésion solitaire. Par suite de sa localisation à proximité de la zone de croissance des os longs, la maladie doit être considérée comme étant grave malgré son cours bénin. Jusqu'ici, aucun trouble de la croissance ne s'est cependant manifesté dans les cas rapportés ici.

Il est discuté de l'importance que peut présenter un trauma dans la manifestation de lésions osseuses.

## ZUSAMMENFASSUNG

Tuberkulöse Osteitis entwickelte sich im unteren Ende des Femurs bei einem 14 Monate alten Kind, das 2 Tage nach der Geburt B.C.G. vakziniert worden war. Tuberkelbazillen, die identisch mit denen der B.C.G. Vakzine waren, wurden nachgewiesen.

Während der 10-Jahrsperiode 1951–1960 wurden weiterhin 9 Kinder unter 5 Jahren wegen tuberkulöser Osteitis, die derjenigen des ersterwähnten Falles ziemlich ähnlich war, behandelt. Alle waren während der ersten Lebenswochen B.C.G. vakziniert worden und bei 6 der Kinder traten Symptome ungefähr ein Jahr nach der Vakzinierung auf. Die Bakterientype konnte nicht festgestellt werden, da die Kulturen negativ waren.

In allen Fällen war der Verlauf gutartig und der Prozess heilte nach Operation, kombiniert mit Chemotherapie, aus. Einer der Patienten hatte vielfache, die anderen nur einen einzigen Knochenherd. Wegen des Sitzes in der Nähe der Wachstumszonen der langen Röhrenknochen muss die Erkrankung trotz ihres im übrigen gutartigen Verlaufes als ernsthaft angesehen werden. Vorläufig sind jedoch keine Wachstumsstörungen in den hier berichteten Fällen aufgetreten.

Die Bedeutung des Traumas in der Lokalisation der Knochenherde wird besprochen.

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