

HISTOLOGIC EXAMINATIONS OF TISSUES OF CHILDREN
WITH HEALED PRIMARY LESIONS OF LEPROSY
REPORT OF SEVEN CASES¹

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The object of this study was primarily to look for the possible presence of any lesions in the superficial lymph nodes and nerve trunks of children who had apparently recovered clinically from their primary leprosy skin lesions and who came to autopsy. It has been reported that *M. leprae* could still be demonstrated by lymph-node puncture in apparently cured, "quiescent" and "arrested" cases of leprosy in adults (⁶), or were found at autopsy to persist longest in the main nerve trunks, the regional lymph nodes of the extremities, and in the testes (²). Because of this earlier experience, the search for lesions in this study was confined mainly to these tissues of predilection, with particular attention to those tissues in anatomic relation to the sites of the lesions which had clinically resolved and disappeared.

In previous histologic studies, we have reported on active "primary" or initial skin lesions (^{3,4}) in children of leprosy parents. Also, in similar studies of scars left by such lesions (⁵), we have shown that most of the lesions had completely healed through spontaneous resolution.

MATERIAL AND METHODS

The present report is based on autopsy material obtained from 7 cases with apparently healed initial skin lesions, of children of leprosy parents varying in age from 9 years 11 months to 16 years 2 months and who had been born and reared at Culion, i.e., in a heavily leprosy environment. They had been under frequent and close observation by two of us (C.B.L. and J.L.I.) for the presence and development of leprosy lesions from the time of birth to death. Their clinical records served to determine the skin sites excised at autopsy, these being the previously positive and probable lesion sites that had been observed in life. Their last clinical observations had been made from 2 months to a few days before death, and recorded as "no trace of the previous lesion," or "no visible suspicious lesions." In other words, all 7 children at the time of death no longer showed signs or stigmata of the disease.

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Autopsy method.—The identified lesion scars, or, if these were unrecognizable, the approximate sites of the clinically healed lesions, were excised. Also, the principal nerve trunks of the extremities (the ulnars at the elbows and the peroneals in the popliteal fossae) and the regional lymph nodes (axillary, inguinal, and some epitrochlears) were saved for study. It may be noted here that none of the nerve trunks appeared even slightly enlarged; they all looked thin, pale and normal. No tissue of internal organs, such as the liver, spleen and kidneys, were saved, since these organs have been known to become involved mostly in advanced lepromatous leprosy (4). Some testes, however, were also saved. The individual tissue specimens, properly identified, were fixed in Zenker's fluid.

Histologic method.—All of the skin specimens, embedded in paraffin, were cut serially at 6-micron thickness, and mounted 3 to 4 sections to a slide. The 1st, 10th, 20th, 30th, 40th, 50th, etc., slides of each series (i.e., at 10-slide intervals) were stained with eosin and hematoxylin, to screen the lot for leprosy changes. With all specimens the effort was centered on the search for lepromatous, round-cell, or epithelioid lesions.

In the case of the nerve specimens, these were cross-sectioned at both ends and the remaining piece was sectioned longitudinally at about its center. Only one histologic section of each of these three portions was stained with eosin and hematoxylin for examination for the presence of leprosy lesions.

The regional lymph nodes were excised *en masse* and counted after fixation. Each was sectioned longitudinally for embedding. Only one slide of each node was examined histologically, but one slide of the largest of each regional group was also stained for acid-fast bacilli, using Wade's modification of the Fite-I technique (7).

REPORT OF CASES

In the following case reports only the salient pertinent clinical data are given, together with the histologic findings. A table prepared to summarize the data for each of the 7 cases is not included in this article, since all of the findings were negative.

CASE 1. L.P., male. Born September 5, 1937; died July 29, 1947, aged 9 years 11 months, due to crocodile bite, with avulsion of the two upper extremities and the left lower extremity. Only the right lower extremity was left when the body came to autopsy, and it supplied the only skin specimen obtained in this case.

Clinical observations.—On March 8, 1940, at age 2 years 6 months, there was seen medially above the left knee a reddish wheal-like area, 6.5 × 5.0 mm. in diameter, slightly shiny, with a faint pale halo, with slight desquamation at center, not vesiculated, negative for acid-fast bacilli in an ordinary smear. This lesion was biopsied. The microscopic findings were: tuberculoid lesion, extensive; 3 acid-fast bacilli found in two sections (J.O.N.). This lesion, definitely leprosy in nature, did not recur following its removal.

On April 1, 1941, at age 3 years 7 months, a hypopigmented, pinkish, shiny, slightly raised area measuring 10.0 × 6.5 mm. was found on the posterior right leg, above the middle; a smear from this site was negative. On June 10, 1941, this lesion appeared as a faint, hypopigmented, slightly shiny and raised area, 14 × 10 mm.; and on October 6, 1941 it was faint pinkish, hypopigmented, 11 × 10 mm. It was still present as a purplish, slightly raised area, 15 × 10 mm., on March 8, 1942, but by September 10, 1943 it could no longer be recognized, nor could any scar be traced in the bimonthly clinical examinations from August 1945 to June 1947, one month before the child died. Two other similar lesions, one seen on the right knee on June 8, 1940, and another on the right mandible on August 12, 1941, had been recorded; these persisted at least 6 months and 7 months, respectively, before healing.

Mitsuda reaction: Positive 3+ at age 4 years, and again 5 years later, with all lesions apparently healed.

It was not possible to recognize the original site of the lesion at the time of autopsy, but a piece of skin from the probable site was excised for examination.

Histologic findings.—Skin, right leg posterior: No lesion found in any of the 9 slides examined.

Inguinal lymph nodes (13 nodes right, 11 nodes left): The sections of the largest node on each side were negative for acid-fast bacilli or lesions. Those of the other 22 nodes were also free from lesions.

Axillary lymph nodes (8 from each side): The examinations, done as with the inguinal nodes, gave equally negative results.

Common peroneal nerve, right: Three portions of this nerve were examined, lowermost, middle (at the popliteal fossa), and uppermost (from the thigh). Of each portion 2 cross sections and 1 longitudinal section were examined; none showed any lesion.

CASE 2. P.Y., male. Born January 20, 1938, died Jan. 21, 1949, aged 11 years.

Clinical observations.—This child was found 2+ for *M. leprae* in a shiny pinkish papule, 2 mm. in diameter, with pale halo, on the right ulnar surface above the wrist, on March 28, 1939, at age 14 months. On June 9, 1949, this lesion was almost imperceptible, indicated only by a small, brownish, slightly shiny spot. By October 7, 1939, it was again distinct, hypopigmented, pinkish, shiny, slightly raised, 3.5 × 2.5 mm. On December 8, 1939, it was hypopigmented, scar-like, 3 × 3 mm., with smaller-than-pinhead papular prominence on the lower border. A smear taken this date was negative. On April 4, 1940, the lesion was hypopigmented, slightly shiny and raised, 4.0 × 3.5 mm., practically not indurated; a smear was again negative. On October 2, 1940, the site was hypopigmented, slightly shiny, almost imperceptibly raised, not indurated, 6 × 5 mm. On June 11, 1941, it was a fading, hypopigmented, level, scar-like area 8 mm. in diameter; and on October 13, 1943 it could not be distinguished from any ordinary scar. From August 1945 until the death of the child no trace of the lesion was found in the 21 further reexaminations. No other definite lesion was ever found.

Mitsuda reaction: Positive 3+ at 3 years 8 months, with the active lesion present; also 3+ 5 years later, when the initial lesion had healed.

The child died of a malignant growth in the left buttock and abdomen. A biopsy of the mass in the buttock revealed carcinomatous tissue infiltrating the gluteal muscle fibers. The body was not autopsied; only sections of skin, nerves and lymph nodes were obtained for study.

Histologic findings.—Skin, right wrist, above ulnar: No lesion found in 4 slides examined.

Inguinal lymph nodes (10 nodes from each side): The sections of the largest node on each side were negative for acid-fast bacilli or lesions. Those of the other 18 nodes were also free from lesions.

Axillary lymph nodes (right, 12 nodes): Sections all negative for lesions; the largest node also negative for bacilli.

Epirochlear lymph nodes (2 right, 3 left; all small): Negative for lesions.

Testes (1 specimen from each): Negative for lesions.

Nerves, common peroneal (right and left), posterior tibial (right and left), median (cubital, proximal and distal, right; cubital and distal, left), and ulnar (at elbow and distal, both sides): Two cross sections and 1 longitudinal section of each specimen, all negative for lesions.

CASE 3. J.S., male. Born May 4, 1938; died June 30, 1949, aged 11 years 2 months, due to an accident.

Clinical observations.—On June 3, 1939, at the age of 13 months, there was found a shiny pinkish wheal-like area on the right, cheek, 2+ positive for *M. leprae* in smears. In August 1939 the lesion was still pinkish, thickened and shiny, 3.5 × 5.0 mm., and in October 1939 it had grown to 8.5 × 7.0 mm. In February 1940 it appeared brownish, shiny, wrinkled, elevated, 12 × 8 mm., surrounded by a hypopigmented, pinkish halo; and in June 1940 it measured 15 × 13 mm., including the halo; the central purplish area was 10 × 8 mm. By August 1940 it had become a flat, slightly indurated area which gradually subsided; and from September 1943 it could no longer be clearly identified. Four other postinitial probable lesions appeared between the 6th and the 10th months after onset, all of which healed within 24 months following the onset, ahead of the initial lesion on the right cheek.

Mitsuda reaction, in October 1941 with the initial lesion apparently healing, was 3+. In 1946, when all lesions had been healed for several years, it was again 3+.

Histologic findings.—Skin, right cheek: No lesions found in 7 slides examined.

Inguinal lymph nodes, left (11 nodes): None showed any lesion, and the largest was negative for *M. leprae*.

Submaxillary lymph nodes, right (4 nodes, all small): No lesion found.

Anterior auricular, or parotid, lymph nodes, right (4 nodes): None showed any lesion, and the largest was negative for *M. leprae*.

CASE 4. R.F., male. Born March 17, 1938; died August 26, 1951, aged 13 years 5 months, due to jellyfish sting and drowning. Not autopsied; father refused further dissection after the site of the initial skin lesion above the right wrist was removed.

Clinical observations.—On October 4, 1939, at the age 16 months, there was found a purplish, shiny, flat papule, 3×2 mm., rather firm, the ulnar right wrist positive 1+ for acid-fast bacilli. On December 9, 1939, the lesion was pinkish, slightly raised and indurated; in February 1940 it was a reddish, shiny, elevated area, 5×3 mm. After April 1940, although slightly larger, it became less distinct and indurated and slightly wrinkled, and by February 1941 it was an almost unrecognizable, slightly depressed scar. From June 1941 it could not be distinguished from neighboring scars, and finally it was untraceable. Only one other probable lesion, a wheal-like area near the right angle of the mouth that persisted for only 8 months was observed (February 1941 to October 1941).

Mitsuda reaction: Positive 2+, 10 months before onset; then 3+ 2 years after onset, with all lesions nearly healed; and again 3+ 5 years later, with all lesions completely healed.

Histologic findings.—Skin, above right wrist: No lesion found in 7 slides examined.

CASE 5. B.T., male. Born February 6, 1940; died June 27, 1952, of tuberculous meningitis, aged 12 years 5 months.

Clinical observations.—A suspected leprotic lesion was first noticed on April 4, 1941, at age 14 months, on the midposterior surface of the right thigh. It was a pinkish, shiny, hypopigmented, slightly raised area, 3.0×3.5 mm., apparently formed by confluence of hypertrophied hair follicles; negative for *M. leprae*. On June 3, 1941, the area was still reddish, shiny, looking like hypertrophied follicles, about 4.5×4.0 mm. On October 4, 1941, the lesion had become purplish, pebbled, slightly indurated, 9×6 mm.; but on December 2, 1941, it was only slightly thickened, purplish, scar-like, 6×5 mm.; and in February 1942 the lesion site was a hypopigmented, scar-like area. From September 1943 to April 1952 no trace of any lesion was found in 42 reexaminations. Four other less probable lesions—reddish, minute, thickened areas which developed sealing—appeared 2 and 4 months after onset, disappearing in another 2 months.

Mitsuda reaction: In October 1941, 2+, while the lesion was still active. In 1946, with all lesions apparently healed, it was still 2+; but 3 months before the child died it had lessened to 1+.

The body was not autopsied, but specimens of the skin, lymph nodes and nerves were obtained.

Histologic findings.—Skin, right posterior thigh, middle: No lesion found in 8 slides examined.

Inguinal lymph nodes (9 right, 4 left): No lesion in any of the 13 nodes; the largest were negative for bacilli.

Axillary lymph nodes (13 right, 12 left): Findings negative, as with the inguinal nodes.

Peroneal nerves: One specimen from each side examined and found negative for lesion.

Ulnar nerve: One specimen from each side examined and found negative for lesion.

Testis, right: No lesion.

CASE 6. C.P., male. Born January 22, 1940; died May 20, 1953, aged 13 years 4 months, due to jellyfish sting.

Clinical observations.—On April 4, 1941, at age 14 months, a purplish, raised, scar-like area, 2.5×2.0 mm., very slightly indurated, was seen 2 cm. below the medial left cubital area. On April 21, 1941, this lesion was reddish-brown, wrinkled, shiny, scar-like, 3.0×2.5 mm., not distinctly indurated, but 2+ positive for *M. leprae*; two months later it looked about the same and was still positive (1+) bacteriologically. By December 1941 it had become a purplish, level scar which was negative for bacilli and in February 1942 it was not distinguishable from an ordinary scar. From September 1943 the lesion

site could not be definitely located. No other suspicious or probable lesion was observed.

Mitsuda reaction: Six months after onset, with healing lesion, it was 3+ positive. Five years later it was again 3+, and also 10½ years later, with the initial lesion completely healed.

Histologic findings.—Skin, medial left cubital: No lesion found in the 4 slides examined.

Axillary lymph nodes, left (18 nodes): No lesions; the largest was also negative for *M. leprae*.

Ulnar nerve, left (elbow level): No lesion in either cross or longitudinal section.

Testis, right (2 pieces): Both without lesion.

CASE 7. A.B., male. Born December 25, 1938; died of an accidental fall on February 11, 1955, aged 16 years 1 month. Autopsy revealed extensive contusion of the brain.

Clinical observations.—On April 17, 1941, age 2 years 4 months, there was seen, 2 cm. below the middle of the left popliteal space, a reddish area measuring 9 mm. On May 13, 1941, the lesion was a fading hypopigmented area, 10 mm. diameter, not raised or pinkish, but on June 5, 1941, it was again pinkish, hypopigmented, 10 × 12 mm., very slightly raised. Negative for *M. leprae*.

The upper half of the lesion was excised on June 5, 1941, the lower half being left for further observation. Histologic findings: Very young epithelioid foci (subtuberculoïd) and round-cell collections; positive (1+) for acid-fast bacilli. One bacillus was found in a small nerve trunk close to the subcutis, and one in the superficial corium (J.O.N.).

On August 12, 1941, the biopsy site was a slightly raised, shiny scar, and subsequently only the scar remained without any trace of the original lesion. A second probable lesion, a hypopigmented, pinkish, raised area below the right groin, 13 × 12 mm., bacteriologically negative, was seen on October 4, 1941; this had persisted for about 5 months when a small satellite was seen just below it. At the next observation, 1 year 7 months later, only a hazy hypopigmented area, 23 × 11 mm., remained.

Mitsuda reaction: This was 2+ positive 6 months after onset, while the lesion was still active. Again 2+ five years later, all lesions healed.

Because only the upper half of the original lesion had been removed for biopsy, the skin saved at autopsy included specimens from both above and below the biopsy scar.

Histologic findings.—Skin, left popliteal, below biopsy scar: No lesion found in the 11 slides examined.

Skin, left popliteal, above biopsy scar: Only the healed scar of the excision was seen in the first 5 serial slides; no lesion in the other nine slides examined.

Inguinal lymph nodes, left (14 nodes): No lesion in any of the slides examined; the sections of the largest node were negative for bacilli.

Peribronchial lymph nodes (16 nodes): No lesion in any of the 16 nodes; the largest were negative for bacilli.

Ulnar nerves, elbow (2 specimens, 1 right and 1 left): No lesion.

Common peroneal nerves (1 specimen right, 1 left): No lesion.

Popliteal lymph nodes (2, small) and blood vessels (including perivascular tissue): No lesion.

DISCUSSION

Histologic examination of the sites of the definite or probable initial or postinitial skin lesions did not reveal the presence of even residual leprous lesions, which we had previously encountered⁽⁵⁾ in 3 out of 13 apparently healed skin lesions of the type here reported. Because the children in the present study were older—an average of approximately 10 years from discovery of the first lesion to the time of death—a shifting of the position of the original lesion sites relative to the surface landmarks may have taken place, so that the exact sites, unless indicated by definite natural scars, or biopsy scars, might have been missed at the autopsy table. This possibility cannot be ruled out. However,

considering the clinical disappearance and nonrecurrence of the initial skin lesions, and our finding⁽⁵⁾ of their complete resolution in most of the cases in a slightly larger series of somewhat younger children, we feel that the present observations constitute sufficient evidence that the lesions had in fact completely healed and disappeared. So, for the purpose of this report, the original skin sites can be considered as of secondary importance, and the search for possible findings in other tissues or organs as of greater importance.

In a study of 287 cases Lara and Nolasco⁽¹⁾ stated that spontaneous healing in a large majority of cases of early childhood leprosy is a demonstrated fact. It had been observed in about three-fourths of all cases that "a majority of the healed cases have remained without apparent relapse for upwards of 10, even up to 21, years despite the stresses of adolescence and, in an increasing number of them, even through the period of greatest reproductive activity and attendant child-bearing and nurturing of offspring." The 7 children in this report originated from the same group of children reported on in that study.

Concerning the tissues examined, the present effort likewise failed to demonstrate leprosy lesions, or bacilli, in any of the larger main nerve trunks or regional lymph nodes of the extremities, or in the testes examined, sites which had previously been shown to harbor them longest in apparently cured adult cases⁽²⁾.

The frequent, regular clinical examinations of these children up to the time of their deaths by two of us (C.B.L. and J.L.L.) had likewise failed to show any manifest clinical reactivation of the infection after the skin lesions had apparently disappeared and completely healed. The negative clinical, bacteriologic and histologic findings, both before and after death, may therefore be considered as evidence that the cases had completely overcome their initial leprosy infection.

However, because of the impracticability of searching all of the skin, nerves, lymph nodes and other structures which might still afford lodgment for latent residual infection, if there was any, we cannot positively claim that these healed cases in children could never again have become reactivated or serve as possible sources of infection.

SUMMARY AND CONCLUSIONS

1. This report records wholly negative histologic findings in the healed skin lesion sites, regional lymph nodes, peripheral trunk nerves, and testes examined, in 7 children born at Culion of leprosy parents who died at an average age of 12 years 5 months (range 9 years 11 months to 16 years 2 months), or after an average interval of 10 years 9 months from the appearance of lesions to the time of death, and an average interval of 8 years 4 months after the apparent healing of all skin lesions. The average age at onset was 1 year 6 months.

2. The negative clinical picture as regards signs of leprosy for an average of more than 8 years before the time of death was confirmed

postmortem by the negative histologic and bacteriologic findings in the tissues examined.

3. Comment is made on the impracticability of searching all of the skin, lymph nodes and other structures which might still afford lodgment for any lurking latent infection.

4. Nevertheless, we consider that the method of study, together with the regular clinical observations and concurrent laboratory findings, sufficiently justifies the opinion that the first leprosy infection in these children had been completely overcome.

RESUMEN Y CONCLUSIONES

1. Expónense en esta comunicación los hallazgos histológicos absolutamente negativos en los sitios de lesiones cutáneas curadas, ganglios linfáticos regionales, nervios de los troncos periféricos y testículos examinados, en 7 niños nacidos en Culión de padres leprosos, que fallecieron a una edad media de 12 años y 5 meses (límites, 9 años y 11 meses a 16 años y 2 meses) o al cabo de un plazo medio de 10 años y 9 meses desde la aparición de lesiones hasta la fecha de la muerte y un promedio de 8 años y 4 meses desde la aparente curación de todas las lesiones cutáneas. La edad media a la iniciación era de 1 año y 6 meses.

2. El cuadro clínico negativo en cuanto a signos de lepra durante un promedio de más de 8 años antes de la muerte quedó confirmado en la autopsia por los negativos hallazgos histológicos y bacteriológicos en los exámenes ejecutados.

3. Se comenta lo impracticable que es buscar todos los tejidos cutáneos, linfáticos y de otro género, que podrían todavía ofrecer abrigo a cualquier infección latente en acecho.

4. No obstante, considérase que el método de estudio, junto con las observaciones clínicas de rigot y los concomitantes hallazgos de laboratorio justifican ampliamente la opinión de que se había subyugado totalmente la primera infección leprosa en estos niños.

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