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SELF-HEALING, OR ABORTIVE, AND RESIDUAL FORMS OF CHILDHOOD LEPROSY AND THEIR PROBABLE SIGNIFICANCE[1]

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Gomez, Avellana and Nicolas (2) studied early leprosy among Culion children and mentioned a few instances of disappearance, without treatment, of lesions that were either negative or positive bacteriologically. There is no subsequent record of those cases, and the period of their observations covered only about nine months. Lara and de Vera (3), in 1935, called attention to the occurrence in 7 out of 10 consecutive cases observed since 1927 among very young Culion children of a papular, bacteriologically-positive kind of leprotic lesion which showed marked tendency to subside, with or without treatment. Their observations likewise were not sufficiently extended to furnish information as to the permanence of the apparent healing of the lesions.

Souza Campos (12), of Brazil, was apparently the first to present a comprehensive clinical, immunological and histologic characterization of similar cases among breast-fed children of leprosy patients, after removal from the foci of infection. He placed great emphasis on the benign nature of "primary tuberculoid leprosy (lèpre cliniquement tuberculoïde)" in children. He described different clinical forms, included data on the histologic features, and remarked on the scarcity or absence of *Mycobacterium leprae*, a low sedimentation index, and positive Mitsuda reactions in most of his cases. He considered the lesions to be manifestations of allergy and immunity, attributed the benign course of the cases partly to the removal of the children from contact and partly to hygienic care, and theorized on congenital immunity—presumably maintained through breast-feeding—and disappearance of such immunity after the first year of life.

Fernandez (1), of Argentina, subsequently confirmed the observations of Souza Campos. He also mentioned abortive or latent infections among

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contact children, characterized by the appearance of activation in residual or even inapparent lesions after the subcutaneous or intramuscular injection of lepromin. He also considered such cases benign, unlikely to progress.

Lara, in 1948 (8), summarized the chief clinical, bacteriologic, histologic and immunologic features of 260 cases, among other things again confirming the essentially benign character of the papulonodular and other forms with discrete, thickened early lesions. He was probably the first to attempt definite appraisal of the extent and permanence of spontaneous healing in childhood leprosy, and the subsequent course in less favorable cases in relation to the morphology of the initial lesions. Nolasco and Lara (10, 11) further reported findings and observations indicating complete healing in most cases of apparent recovery, therefore a high degree of resistance. The children had remained throughout in a highly infected environment.

PRESENT STUDY

The present report deals with further observations on Culion-born children, along the same lines and employing the same procedures as those used in the earlier reports referred to, and is therefore largely an extension of them. After the lapse of eight years since the report made at the international congress at Havana in 1948 (8), the more recent observations have been analyzed and correlated, with a view to verifying or amplifying the earlier findings and conclusions. Special attention is given to the process of spontaneous healing in childhood leprosy. Emphasis is to be laid on the element of spontaneity by which so many of the cases aborted, for as in certain other institutions these children with initial lesions were given no treatment unless and until unfavorable developments became manifest. The observations on the small minority of cases that followed a less favorable course will be the subject of further studies.

MATERIAL

The data discussed here are based on observations of verified and probable cases of leprosy found in the course of frequent examinations of all Culion-born children, and also those brought still nonleprous from outside with their leprous mothers, since September 1932, who have been adequately studied for two years or longer following the onset of the disease up to March 1956. The cases number 287, out of the 347 cases detected during that period of nearly twenty-four years.

Not included are 50 younger children whose leprosy has been observed for less than two years, among them 23 with subsiding or newly-subsided early lesions. We have also excluded 2 apparently-healed cases because of some doubt about the nature of the suspected early lesions, which were reported 1+ for bacilli but were not confirmed in the histological examinations. Also excluded are 1 readmitted case with only apparent residual neural sequelae, and 7 others already with lepromatous changes on readmission—although one of them later apparently healed under treatment.

On the other hand, 2 that received some sulfone treatment are included among the healed cases. One, an apparently quiescent lepromatous case, upon showing slight signs of relapse that lasted six months, was given small doses of diasone and has remained negative for the last five years. The other, an early macular case with a solitary, bacteriologically-negative, indeterminate lesion received minimal diasone treatment at his parents' request and apparently healed in barely six months under that treatment.

OBSERVATIONS

The findings are summarized in four tables correlating the course of the disease with the clinical morphology of the initial lesions, the early bacteriology, the Mitsuda reaction, and the histologic structure. Discussed specially are the findings in two groups concerned in an experiment with repeated lepromin injections (i. e., Mitsuda tests). First, however, it is deemed necessary to define certain terms used in connection with the findings.

Early healing: All active lesions must have subsided for about six months or longer, within three years after the appearance of the initial lesion or lesions.

Late healing: Healing which occurs after three years from the appearance of the initial lesion or lesions.

Incomplete healing-relapsing: The tendency to heal is marked but not complete; it may be interrupted by recurring exacerbations alternating with periods of apparent subsidence, or incomplete subsidence, of lesions. A few cases of actual relapse are included in this category; the majority of them never attained the stage of apparent healing.

Exacerbating-advancing: There is an appreciable but not marked tendency to subside, but there is a stronger trend to progress to the advanced stages. This may be with or without associated nerve sequelae, and is usually with distinct phases of exacerbation or reaction, and accesses of erythema nodosum syndrome in lepromatous cases. This category and the last one above frequently precede or accompany transformation of a case to the lepromatous form.

Relapse: Reactivation of a case after at least six months of apparent healing or complete clinical subsidence of lesions.

Healing time: Total time from appearance of initial lesions to apparent complete healing. It includes intervening periods of relapse, if any.

Complete healing: Disappearance of all lesions leaving no trace whatsoever, or only ordinary-looking scars which may be nonanesthetic, or partially or totally anesthetic, with or without a halo or fringe of anesthesia. Anesthetic scars, either depressed or with crushed-tissue-paper surface, are indicative of former tuberculoid lesions.

Residual forms: Inconspicuous or inapparent cases, with known previous definite lesions that have apparently healed, but which on careful search show signs suggesting residual, active disease. There may be, for example, enlarged nerve trunks, tender or nontender, with or without

anesthesia; tender but not appreciably enlarged nerves; or minimal lichenoid or exaggerated follicular appearance at or near scars of healed lesions.

Fading hypochromic areas are difficult to evaluate, even if one could resort to extensive biopsy procedures.

We have deliberately not explored the possible provocative effect of lepromin injections in apparently healed cases, although one of us (C. B. L.) has suggested the possibility of such an effect in the appearance of early lesions in a large proportion of nonleprous but exposed children subjected to Mitsuda tests (4, 5). He has also seen rare instances of temporary activation in untreated adults with minimal suspected early or residual lesions. Permanent traces such as anesthetic healed scars and nonprogressive neurotrophic changes observed for at least three years are not to be confused with true residual lesions (possibly capable of reactivation) as here defined.

In characterizing the subsequent clinical course, we refer to the case as a whole, not to the initial lesions only. In the tables the different categories of healing or progress refer to the status of the cases as of last observation before discharge, death, transfer, or as of March 1956.

Morphology of initial lesions and subsequent course.—The different forms of initial lesions observed and the corresponding subsequent course of the 287 cases are correlated in Table 1. It will be noted that the papulonodular type of lesion was the most common one, seen in practically 30 per cent of all cases. Raised macules, wheal-like lesions, and flat macules were next in frequency, in that order, ranging down to 15 per cent. The scar-like-indurated and lichenoid forms and the infiltrations were all less than 5 per cent, the last-named less than 2 per cent.

It is readily apparent that all forms showed a distinct trend toward healing, but that those with definitely thickened and well-circumscribed lesions gave the highest proportions of healed cases, with the few that had more or less diffuse infiltrations giving the lowest proportion. The papulonodules, the discrete lichenoid, and the indurated, scar-like lesions were the most benign, as shown by the total proportions of healed *versus* the relapsing and advancing cases. The wheal-like forms, which frequently are more or less irregular in contour, and the raised and flat macules, followed in the order given. These findings in general confirm those reported eight years ago.

Apparent complete healing occurred in more than three-fourths (77.7%) of all cases. One-eighth (12.5%) showed incomplete healing, while the rest (9.7%) had a definite trend to progress. The tendency to persist and advance in the different forms was in reverse order to their tendency to heal.

The early-healing lesions in a few cases were so inconspicuous that they could not have been diagnosed if not subjected to biopsy. In one of the earlier reports (4) the occurrence of such benign and transitory lesions was already suggested, but not confirmed for lack of histopathologic

TABLE 1.—*Morphology of the initial lesion and subsequent course of the infection.*[a]

Initial lesion	Early healing		Late healing		Incomplete; relapsing		Exacerbating; advancing		Total cases	
	Cases	Percentages	Cases	Percentages	Cases	Percentages	Cases	Percentages	Cases	Percentages
Papulonodular	69	81.2 38.7	11	12.9 24.4	2	2.3 5.6	3	3.5 10.7	85	99.9 29.6
Scar-line indurated	12	85.7 6.7	0	0.0 0.0	2	14.3 5.6	0	0.0 0.0	14	100.0 4.9
Lichenoid	12	100.0 6.7	0	0.0 0.0	0	0.0 0.0	0	0.0 0.0	12	100.0 4.2
Wheal-like	38	63.3 21.4	8	13.3 17.8	9	15.0 25.0	5	8.3 17.9	60	99.9 20.9
Macular raised	31	45.6 17.4	14	20.6 31.1	14	20.6 38.9	9	13.2 32.1	68	100.0 23.7
Macular flat	16	37.2 9.0	11	25.6 24.4	8	18.6 22.2	8	18.6 28.6	43	100.0 15.0
Infiltration	0	0.0 0.0	1	20.0 2.2	1	20.0 2.8	3	60.0 10.7	5	100.0 1.7
TOTAL	178	62.0 99.9	45	15.7 99.9	36	12.5 100.1	28	9.7 100.0	287	99.9 100.0

a The percentages across the table (upper right) pertain to the proportions of healing (or otherwise) classes in each morphology group. Those reading vertically (lower left) are of the proportions of the lesion types in each healing group.

data. The frequent occurrence of common skin affections among our children tends to mask such lesions. We therefore think it not improbable that complete healing may occur in about 80 per cent of all childhood infections.

Bacteriologic findings, Mitsuda reaction, and subsequent course.—Correlation of the bacteriologic findings in smears from scrapings, the Mitsuda reaction, the type of initial lesion, and the subsequent course was made in 255 of the 287 cases dealt with in this report. Refusal of the parents to permit lepromin testing is the main reason for not including the other 32. These cases comprised 72 with papulonodules, 55 with the wheal-like lesions, 63 with raised macules, 36 with flat macules, 12 each with scar-like and lichenoid lesions, and 5 with infiltrations. The data for the first four of these groups are shown in Table 2; the last three groups are omitted because of the relatively small numbers of cases.

Seventy per cent of the initial papulonodular lesions were bacterio-

logically positive, a majority of them graded 3+ or 4+, i. e., with few to many globi. Forty-seven per cent of the wheal-like lesions were also positive, most of them only 1+ or 2+, i. e., without globi. Nearly 32 per cent of those with raised macules but only 11 per cent with flat macules were found positive in smears, only 1+ or 2+ in most instances. The proportions of cases of all types with bacilli were somewhat lower than

TABLE 2.—*Clinical course of the four largest lesion-groups in relation to the bacteriology and lepromin reactivity (Mitsuda reaction).*

Bacteriological findings	Lepromin reaction (Mitsuda)	Character of healing or progression				
		No. of cases	Healed		Incomplete; relapsing	Advancing
			Early	Late		
Papulonodular lesions						
Negative	3+	18	17	1	0	0
	1+ or 2+	3	3	0	0	0
	0 or ±	0	0	0	0	0
	Total	21	20	1	0	0
1+ or 2+	3+	16	12	4	0	0
	1+ or 2+	3	2	0	0	1
	0 or ±	0	0	0	0	0
	Total	19	14	4	0	1
3+ or 4+	3+	25	23	2	0	0
	1+ or 2+	5	1	4	0	0
	0 or ±	2	0	0	0	2
	Total	32	24	6	0	2
Total cases		72	58	11	0	3
Percentages			80.5	15.3	0.0	4.1
Wheal-like lesions						
Negative	3+	19	14	2	3	0
	1+ or 2+	10	6	1	1	2
	0 or ±	0	0	0	0	0
	Total	29	20	3	4	2
1+ or 2+	3+	17	10	4	3	0
	1+ or 2+	2	1	0	0	1
	0 or ±	1	0	0	0	1
	Total	20	11	4	3	2
3+ or 4+	3+	3	2	1	0	0
	1+ or 2+	3	1	0	1	1
	0 or ±	0	0	0	0	0
	Total	6	3	1	1	1
Total cases		55	34	8	8	5
Percentages			61.8	14.5	14.5	9.1

those reported eight years ago, but the present findings refer only to the earliest visible lesions, while in the former report findings in post-initial—although early—lesions were also included.

Most of the cases with papulonodules, wheal-like lesions, and raised or flat macules were Mitsuda positive. There was, however, an interesting —and doubtless significant—decrease of strength of reactivity in these

TABLE 2 — Continued

Bacterio-logical findings	Lepromin reaction (Mitsuda)	Character of healing or progression				
		No. of cases	Healed		Incomplete; relapsing	Advancing
			Early	Late		
Raised macules						
Negative	3+	28	20	5	3	0
	1+ or 2+	14	6	3	5	0
	0 or ±	1	0	0	0	1
	Total	43	26	8	8	1
1+ or 2+	3+	2	0	2	0	0
	1+ or 2+	12	0	4	4	4
	0 or ±	3	0	0	0	3
	Total	17	0	6	4	7
3+ or 4+	3+	0	0	0	0	0
	1+ or 2+	2	0	0	2	0
	0 or ±	1	0	0	0	1
	Total	3	0	0	2	1
Total cases		63	26	14	14	9
Percentages			41.2	22.2	22.2	14.3
Flat macules						
Negative	3+	10	5	4	1	0
	1+ or 2+	21	7	4	5	5
	0 or ±	1	0	0	0	1
	Total	32	12	8	6	6
1+ or 2+	3+	1	1	0	0	0
	1+ or 2+	2	0	1	1	0
	0 or ±	1	0	0	0	1
	Total	4	1	1	1	1
Total cases		36	13	9	7	7
Percentages			36.1	25.0	19.4	19.4
All macular cases (raised and flat)						
Total cases		99	39	23	21	16
Percentages			39.4	23.2	21.2	16.1

groups, with 82, 71, 47, and 32 per cent, respectively, showing 3+ reactions. Most of those with papulonodules were 3+ irrespective of the bacillus content of the lesions. The same was true to a lesser extent of the wheal-like type graded 0 to 2+ bacteriologically, and of the raised macule type found negative for bacilli. About 50 per cent of the heavily bacillated cases with wheal-like lesions also gave 3+ Mitsuda reactions, but 87 per cent of such bacillus-positive cases with raised and flat macules together showed negative, weak, or at most 2+ reactions.

As regards the less frequent types: Of the 12 cases with scar-like lesions, 10 showed strong skin reactions; 5 were negative for bacilli and all of them healed later, 4 were graded 1+ or 2+ bacteriologically and one did not heal, 1 was 4+ but healed. Two of these cases gave only 2+ Mitsuda reactions; 1 was bacteriologically negative and healed, and the other which had 1+ to 2+ smears showed incomplete healing.

Of the 12 lichenoid type cases, all of them bacteriologically negative, 9 had 3+ and 3 had 2+ Mitsudas. All showed early healing.

Of the 5 cases with the infiltration-type lesions, one was bacteriologically negative, had a 3+ Mitsuda reaction, and late healing; and another, 2+ in both smears and skin reaction, showed incomplete healing. The other 3, all with weak or negative Mitsudas and smears graded 2+ or more, have progressed for the worse.

On the whole, with all types of lesions, there was fairly good correlation between low bacteriological grading, strong skin reactivity, and a high proportion of healed cases.

Healing and histologic features of initial lesions.—For various reasons, in barely 46 per cent of the total healed cases were biopsies made of their early lesions. The reasons included noncooperation of parents; the location of solitary lesions on inconvenient sites, such as the face, ear, or external genitalia; and heavy bacillus content and other features assuring the diagnosis. The correlated findings are shown in Table 3, which gives by type of lesion the duration of the active course of the disease in all healed cases, and the predominating early histology of initial or other early lesions in the biopsied cases.

Most of the biopsied papulonodules that were graded negative to 2+ for bacilli showed tuberculoid histology. On the other hand, most of this type that were graded 3+ or 4+ showed undifferentiated lesions consisting of round-cell or monocytic collections, with or without ill-defined epithelioid changes. Again, most of the wheal-like lesions, and a majority of the raised scar-like and raised macular lesions, graded negative to 2+ for bacilli also showed tuberculoid structure. One case with a wheal-like lesion with more numerous bacilli also showed tuberculoid histology; but another similar case that died two months after the appearance of the initial lesion and was autopsied showed lepromatous changes in the subsiding lesion, or scar (9).

Of the biopsied flat macules and the lichenoid type lesions, about equal proportions showed tuberculoid or undifferentiated structure.

As is to be seen in Table 3, the cases with the lichenoid, scar-like, and

papulonodular lesions had the shortest healing times; those with wheal-like lesions and raised macules were next, equal in time; while those with the flat macules took longest to heal.

Taking only the biopsied cases, however, those showing round-cell or monocytic collections had shorter healing times than those with tuber-

TABLE 3.—*Duration of active manifestations in healed cases, in years from onset to subsidence, with predominating early histology of the biopsied cases.*

Initial morphology	Average healing time of healed cases			
	Biopsied cases		Not biopsied (years)	Total cases (years)
	Round cells or monocytes (years)	Tuberculoid epithelioid (years)		
Papulonodular	2.0	1.7	2.4	2.2
Scar-like indurated	1.0	2.2	1.4	1.7
Lichenoid (pebbled)	1.1	1.6	1.3	1.3
Wheal-like	1.0	3.7	3.3	3.4
Raised macular	2.0	3.5	3.5	3.4
Flat macular	3.0	4.5	3.7	4.0

culoid lesions, except in the case of the papulonodules. The average healing time for all cases with undifferentiated histology was 2.0 years; for those with tuberculoid lesions it was 3.25 years.

It may also be noted that the healing time of cases with the different types of initial lesions roughly parallels their corresponding tendency to heal completely (cf Table 1).

Late healing of cases in the main resulted from: (*a*) a slow, torpid course, either without definite change in the character of the lesions or with transformation to another type following subsidence of the earlier lesions, for example, from papulonodules or wheals to hypopigmented areas; and (*b*) the occurrence of relapse in apparently healed cases, which we have found more frequently among those with tuberculoid histology (see below).

It appears from our observations that the oft-repeated assumption that cases of tuberculoid leprosy in children are benign and tend to heal spontaneously, thus manifesting the existence of a high degree of resistance, may be only relatively true. We feel that there is still need for further prolonged and careful study of observations and correlation, if we would have a better understanding of this phase of leprosy and its relationship to other phases or forms of the disease.

Permanence of healing.—The study of Culion children, commencing at birth, began in 1932. The oldest case now under observation has remained apparently healed, without any relapse, since early 1935. Of all healed

cases, as of March 1956 or the last observation at an earlier date, 82 per cent have been observed for 5-21 years (57.8% for 10-21 years and 18.4% for 15-21 years) since healing was first noted. Another 6.7 per cent have been observed for 3-5 years, and 11.2 per cent for less than 3 years, since subsidence of active manifestations.

Relapses.—Of the total of 223 healed cases, only 16, or 7.2 per cent, suffered true relapse. A very few cases of actual relapse at the time of the last observation were regrouped with the incompletely healed, relapsing cases.

There was only 1 relapse among the 24 biopsied, healed cases with undifferentiated early histology, while there were 10 relapses among 80 such cases with tuberculoid early histology. Relapse after apparent healing was therefore more common among those with lesions of tuberculoid structure than among those with lesions of undifferentiated nature, in a ratio of about 3:1.

In relation to clinical form of the initial lesion, the chances of relapse was approximately 1:25 for papulonodules, 1:10 for raised macules, and 1:8 for wheal-like and flat macular lesions. No case of true relapse has been observed, so far, among healed cases with scar-like indurated or lichenoid early lesions.

Most relapses occurred within the first three years after apparent healing. They seldom occurred after that period, rarely after five years, and none has been observed after 10 years of apparent healing.

The state of relapse was usually, but not always, shorter than the initial course. The second healing may occur within four years from the onset of initial lesions, but in three cases this was in the 11th, 12th and 13th years. In the majority of the cases second healing was noted after 5 years from the appearance of the initial lesions.

Residual forms.—These can be discussed chiefly in general terms. Conceivably, all apparently-healed cases may be potential residual ones. It would be impossible to deny this possibility and to prove that residual foci do not exist, even in a case apparently completely healed for a very long period of time and then finally becoming available for pathological studies. It would not be possible to search thoroughly all of the skin, nerves, lymph nodes and other structures that might afford lodgement for the last traces of the infection.

We are not here concerned with this purely academic concept of residual infection. Neither, on the other hand, shall we dwell on the common and readily recognizable, apparently inactive cases showing tell-tale damage to nerves and other organs and tissues associated with preexisting extensive leprous involvement. There is sufficient evidence that most cases of the latter kind still harbor deep-seated residual foci and bacilli long after all skin lesions have healed.

What is of greater practical importance, especially to the epidemiologist in field work, is the existence of inconspicuous residual lesions due to

incomplete spontaneous healing, or after active therapy, in early cases before gross tissue damage has occurred. In the present work, eight such cases were found after a more searching examination than we have usually employed in the routine examination of apparently healed cases. The findings were briefly as follows:

Five cases with chiefly tuberculoid early histology were found with an enlarged nerve trunk, usually the right common peroneal, with or without gross anesthesia in the region of distribution. Another case with a tuberculoid initial lesion showed a few micropapules, histologically residual tuberculoid, at the edge of the scar of the original lesion, this residual condition lasting several years before completely subsiding.

The other two cases began with flat, hypopigmented macules which were not biopsied early. In one of them a late biopsy of a fading macule showed only fibrous nerves; five years after all macules had faded the common peroneal and ulnar nerves were found tender but not enlarged, and there was no gross anesthesia. In the other, also five years after apparent healing, there was found an enlarged right common peroneal, and some anesthesia on the right leg and right elbow, both of these areas the sites of previous macules.

In six of these eight cases the first active phase underwent slow or late healing; in two there had been early healing. The Mitsuda reactions were 1+ in one case, 2+ in two cases, and 3+ in the other five. All had had initial cutaneous lesions, in common with all the other children studied. These residual cases will be watched for further developments.

OBSERVATIONS ON CHILDREN RECEIVING MULTIPLE LEPROMIN INJECTIONS

In 1940 (6) and 1946 (7), one of us reported observations on the development of lesions in a group of children who while very young had been given repeated intracutaneous injections of lepromin (Mitsuda) and were compared with a group similar in age and sex not so injected. Further observations of the status of the members of those groups who developed lesions are of special interest in connection with self-healing and the possibility of prophylactic immunization by such injections.

Each group consisted at the outset of 110 children without discernable lesions, aged from 2 weeks to 18 months, who had lived with their parents since birth and remained with them. The test group received, beginning in 1938, three lepromin injections at 4-month intervals. Losses for various reasons during the first observation period reduced the lepromin group to 104 and the control group to 105. In 1941 the children who were then non-leprous were transferred to Welfareville, in Manila. By the end of that year lesions had developed in 39 of the tested group and in 50 of the controls; and during the war period (1942-1945) 2 more known cases were added, 1 to each group, making 40 in the former and 51 in the latter.

Clinical observations.—In the 1946 report cited, a statistical analysis indicated that in the lepromin group there had been significant benefit—a higher age at the time lesions appeared and a lower rate of incidence—but only in the children who had been under the age of six months when the injections were given.

Now, ten years later, all but one of the 40 cases in the lepromin group (97.5%) are known to have undergone apparently complete spontaneous healing. The only one still active at last observation was a gradually-advancing macular case, a female child with an initial raised macule graded 1+ for bacilli who was taken from Culion by her parents, who returned home during the war, about 2 years after the onset of the disease. In this group 31 cases have been observed for 10 to nearly 18 years, 3 for 5-10 years, and 6—including the only still-active case mentioned—for less than 5 years. Six of the healed cases are young women who have had one or more childbirths as of last report, without showing any signs of relapse.

Of the 51 cases in the control group, 41 have healed (80%), including one apparently healing. This group also includes four young women who have had one or more children without signs of relapse. Nine were still with active lesions at last observation, as follows:

One subsiding case with a wheal-like initial lesion, 4+ bacteriologically, died 2 months from onset. The autopsy findings have already been cited (9).

One with an early raised macule, 1+, transferred with her parents to another leprosarium 9 years after onset. Still an active maculoanesthetic case.

Another active maculoanesthetic case, with an initial 2+ wheal-like area, was taken from Culion by absconding parents 4 years after the appearance of the first lesion.

One child died, still an active maculoanesthetic case, 4 years after the appearance of a 1+ raised macule.

One, initially with a 2+ raised macule, died, a moderately-advanced lepromatous case, 5 years after onset.

Another advanced lepromatous case, with an initial 1+ raised macule, died after 17 years of active disease and two childbirths.

One absconded, a moderately-advanced lepromatous case, initial lesion wheal-like and bacteriologically negative, 17½ years after onset.

One active case under observation, the initial lesion a negative raised macule, but later with recurring bacteriologically-positive macules, is now an indeterminate case after nearly 17 years.

One moderately-advanced lepromatous case, now 8½ years after readmission with lepromatous features at that time.

The last four cases have been receiving nonintensive sulfone treatment.

Another slightly-advanced lepromatous case, with an initial bacteriologically-negative raised macule, has again become negative or quiescent under sulfone treatment after a brief relapse lasting six months. She has continued the treatment and has remained negative for the last 5 years.

Of the 41 apparently healed cases of this control group, 31 have been observed since onset of the lesions for from 10 to nearly 18 years, 1 for 5-10 years, and 9 for less than 5 years. One case was never seen by us after the development of leprosy; he was reported from Welfareville where he died during the war.

Lepromin reactivity.—The maximum Mitsuda reactions attained before and after the appearance of lesions in the lepromin group, and after the onset of the disease in the control group, are indicated in Table 4.

The only unhealed case in the lepromin group, a macular one, gave only 1+ Mitsuda reactions both before and after the appearance of lesions. In the majority of the lepromin-group cases there was intensification of the reaction after the lesions appeared, contrary to what might perhaps be expected.

In the control group, of the 35 cases with 3+ reactions healing occurred in 33, while 2 had the slowly-progressing maculoanesthetic type of the disease, one of them later with a lowering of the Mitsuda reaction to 1+.

TABLE 4.—*Mitsuda reactions (maximum) in the cases of the lepromin and control groups that developed lesions.*

Mitsuda reactions	Lepromin group		Control group (After onset)
	Before onset	After onset	
3+	9	34	35
2+	24	3	9
1+	7	1	0
0 or ±	0	0	2
Not tested	0	2	5
Total	40	40	51

Of the 9 cases with 2+ reactions, five healed. One of these was an early lepromatous (or borderline) case still under observation, which showed temporary depression of reactivity to 1+ and then a return to 2+ despite a brief, mild relapse before second healing. One active maculoanesthetic case that died also had a 2+ reaction; one living, active indeterminate case, and an active borderline or lepromatous case that died, were 2+ and later became 1+; and still another, an absconding active lepromatous case, showed loss of reactivity, becoming negative. One lepromatous case, a negative reactor, died five years from onset of lesions; finally, one case, still active and under observation, had a ± reaction.

The majority of the cases of both groups on the whole showed moderate to strong Mitsuda reactions, especially after the appearance of lesions. In the control group cases, after the onset of lesions, doubtful or negative reactions were seen in only two instances, both already with lepromatous changes. But in three other cases clinical features of lepromatous degeneration set in despite 2+ reactivity. On the other hand, the lepromin-group cases were not as good reactors before the appearance of their lesions as afterwards.

Histology and bacteriology.—As for the histologic and bacteriologic features of the cases, lesions from 22 in the lepromin group were biopsied. All were characterized as tuberculoid except one from a lichenoid-type lesion which showed uncharacteristic round-cell collections. Only 1 of

the 40 cases was graded 3+ for bacilli; 13 were 1+, and 26 were negative. The only unhealed case was 1+ for bacilli and was not biopsied.

In the control-group cases only 14 biopsies of early lesions were made, including the case that died two months after onset. The findings were: tuberculoid in 7 and round-cell infiltrations in 6, while the one that died had young lepromatous changes in the subsiding lesion. All cases with tuberculoid lesions healed. Of the 6 cases with undifferentiated lesions 5 likewise healed, apparently completely; the sixth case is still active, an indeterminate one with occasional exacerbations suggestive of a lepromatous trend.

Another striking feature of the control group was the occurrence of heavily bacillated (3+ to 4+) papulonodular initial lesions in 12 of the cases (against only 1 in the lepromin group). Complete healing has nevertheless occurred in all but one; in that case the lesion had receded clinically two months later, at the time of death, although histologic examination still showed active lepromatous changes. Of the lesser grades, 5 were 2+ and 17 only 1+ in smears from early lesions, while 12 were found negative. The initial lesions in 3 cases that were detected at Welfareville were not seen by us; 1 died during the war, 1 was readmitted to Culion already lepromatous, while the third, who was discharged from Welfareville, returned to Culion showing a large, atrophic anesthetic scar but no other sequelae. In two other healed cases the initial lesions had been biopsied immediately and found to have the tuberculoid structure, although one of them showed many bacilli in the sections.

Obviously, the lesions of the control-group cases were distinctly more bacilliferous than those of the lepromin group, even at the earliest stages. Yet the five in the former group that subsequently assumed lepromatous features were not among those with the most heavily bacillated early lesions.

Thus it appears that the lepromin-group cases with lesions, as well as that group as a whole, enjoyed clinical and epidemiologic advantages over the control group. Is this apparent advantage to be attributed to mere chance, or did the early injections of lepromin exert a favorable influence? The answer cannot be given yet. There is hope that it will be forthcoming in a few years, when we know the fate of children who, in recent years, have been isolated at birth and, because of controlling circumstances, have been returned to their parents after developing moderate to strong Mitsuda reactivity induced by repeated lepromin testing.

DISCUSSION

Spontaneous healing in a large majority of cases of early childhood leprosy is a demonstrated fact. It has been observed in about three-fourths of all cases developing among exposed, Culion-born children since 1932. The healing is probably complete and permanent, without tell-tale stigmata, in about two-thirds of all cases, or about 88 per cent of the healed cases. 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. In a few healed cases observed for shorter periods that died from accidental or other causes and were autopsied, no evidence of the disease could be found in the skin or deep organs and tissues. With this evidence, and with nothing so far to refute it, we are not ready to subscribe to any nihilistic theory denying the possibility of complete recovery from leprosy.

What other significance may be deduced from the factual findings? Do the observations in Culion reflect the essential epidemiology of leprosy in the country generally, or in the world at large? For an adequate answer—affirmative, negative or qualified—further similar, truly intensive studies should be carried out in other places. Many persons would consider conditions at Culion exceptional except for other large leprosaria where the patients are not separated by sex but lead a normal community life and their offspring cannot all be protected by isolation at birth. There is, naturally, an extraordinary concentration of sources of infection in such places. Even so, wherever there exists in endemic regions a case of infectious leprosy in a family with children, the degree of exposure of the children would be high, if not as high as at Culion. In any case, the fundamental factors of transmission would be the same.

The 20-25 per cent of all cases representing the unhealed conditions—the torpid and creeping, the relapsing, and the advancing cases—will form the basis for future studies. It suffices to say here that it is our view that they mirror most of the cases among children and young adults admitted to and actually populating many leprosaria. And the existence of an undetermined, probably smaller, proportion of inapparent residual and quiescent cases among older children may serve as the source for the apparently new cases that appear among the adolescents and the adults in the general population, and as true foci for disseminating the infection.

The epidemiologic implication in all the above presentation is that the actual rate of infection may be, and probably is, at lease three times the observed apparent prevalence, where climatic, hygienic, economic and cultural conditions approach those obtaining at Culion. In epidemiologic surveys of large groups of the general population it would be well-nigh impossible to discover healed cases of childhood leprosy among the children, and especially so among the adult groups. Since healing occurs chiefly during the preschool and grade-school years, this fact may explain the low rates repeatedly found in surveys of school children in endemic regions.

A matter of scientific interest is the basic explanation of the facts observed. The great susceptibility of young children to infection is generally recognied. It creates a serious problem in every large institution where the patients live as at Culion, birth control is not practiced, and

separation of children at birth cannot be practiced. Together with and underlying the infant susceptibility, however, there must also exist a relatively high degree of resistance which is sufficient in most cases to overcome the infection, if not to avert it entirely. The self-healing tendency of childhood leprosy, even among those constantly exposed to reinfection, is beyond doubt; the evidence of it is adequate.

Is this a paradox, this complex situation of the susceptible-resistant child? We think not. However, we cannot follow the somewhat involved view of de Souza Campos that the newly-born child possesses congenital immunity (as is the fact with respect to many infectious diseases), maintained presumably through breast feeding, an immunity which disappears in a year whereupon he becomes susceptible—despite which there develop lesions which de Souza Campos believes are indicative of allergy and immunity.

We, for our part, conceive that the human organism is essentially resistant, unfavorable soil for leprosy; that in early childhood, the most susceptible period of development, it can still assert the ability of the species to resist the infection in an effective although not always conspicuous manner. Were this not the case there would develop and persist many more clinical cases among contact children, and also many definitely-proved cases—instead of only very occasional unproven ones—of adult infection among contact workers in leprosaria, as well as among members of the families and other household associates of unsegregated patients.

We think it further probable that individual and racial or ethnic characteristics, climatic environment, practices of hygiene, general material and cultural advancement, and even previous existence or nonexistence of the disease itself, besides other factors, may also influence prevalence and type of the disease among different peoples as well as among the same people at different periods of their history.

Our more recent observations again support the earlier findings which suggested a beneficial action of lepromin-test injections in very young exposed children. Decisive evidence can be obtained only through exposure of similarly-treated children who have been isolated at birth.

SUMMARY AND CONCLUSION

Practically continuous observations of Culion-born children of the patients over the past twenty-four years has revealed that many of them have developed unquestionable leprosy lesions. Approximately three-fourths of the cases of infection actually healed spontaneously, a majority of them apparently permanently, in spite of continued residence in the infected environment.

There was correlation between the process of healing and the clinical morphology of the initial or earliest recognizable lesions, as well as with bacteriologic, histologic and immunologic features. The papulonodular forms and other definitely circumscribed, thickened lesions were asso-

ciated with the highest proportions of subsequently healed cases, the infiltration-like, more or less diffusely thickened lesions, with the lowest proportion. The wheal-like and the raised and flat macular lesions occupied an intermediate position, in that order.

There was found fairly good correlation between low bacterial content of the lesion, strong Mitsuda reactivity, and a high proportion of healed cases. The correlation between clinical morphology and healing seemed to be even more consistent. Also, the correlation with respect to the healing time showed definite advantage for the circumscribed, thickened lesions.

As regards the histologic correlation, healing occurred earlier in the case with lesions with undifferentiated, round-cell or monocytic infiltrates than in those with lesions showing the tuberculoid structure, except with the papulonodules.

Knowledge of the clinical morphology of the early lesions and the pattern of their corresponding subsequent course, therefore, is usually of greater value than reliance on uncorrelated histologic, bacteriologic or immunologic observations.

Relapses, when they occurred, were chiefly noted within less than three years of apparent healing, gradually becoming more rare after longer periods, and practically not seen at all after 10 years. Relapses occurred more frequently in cases whose early lesions were of tuberculoid histology than in those with undifferentiated lesions. They were also more frequently seen among the cases with wheal-like and macular types of early lesions than among those with papulonodules, lichenoid, or scar-like indurated lesions.

Attention is called to the existence of a small but not insignificant number of apparently healed cases which show inconspicuous, minimal, definite or suspicious signs of active disease, such as enlarged or tender nerve trunks with or without anesthesia, and micropapulate or follicular residules at or near anesthestic atrophic scars. These residual cases are likely to be overlooked in ordinary surveys, especially without the aid of previous records or history. It is probable that most of them are benign, but there is always the possibility that they and other undetected forms of apparently healed, or latent, primary infections may serve as the sources for at least some apparently new infections occurring in older children and adults, besides being unrecognized foci for further dissemination.

A second progress check-up of the status of cases occurring in two experimental exposed groups of children previously reported on in 1940 and 1946, one group receiving repeated intracutaneous injections of lepromin and the other serving as a control, revealed indications of an apparent advantage for those that had received the injections before the appearance of leprous lesions. The more recent findings give further support to the earlier suggestion that such injections, through Mitsuda

testing, may have protective value, especially when given to very young children. The evidence, however, is inconclusive; a more crucial test would be the exposure to infection of lepromin-tested, Mitsuda-positive children who had been isolated at birth, and such an observation—necessitated by circumstances—is under way at Culion.

RESUMEN

Esta comunicación, derivada de 24 años de estudio de niños nacidos en Culión, que en su mayor parte residieron continuamente en el ambiente infectado, versa sobre las alteraciones que ocurrieron espontáneamente, sin tratamiento antileproso. De 347 niños que manifestaron lesiones cutáneas tempranas, se mencionan aquí 287, excluyénse a los otros 60 por haber sido observados menos de dos años (50 casos) o por otras razones. Los desenvolvimientos se correlacionan con la morfología clínica de las lesiones más tempranas observadas y con las caracterísiticas bacteriológicas, inmunológicas e histológicas.

En más de tres cuartas partes (7.7 por ciento) de los casos, las lesiones habían cicatrizado, al parecer en la mayor parte permanentemente. la mayoría de los demás mostraba cicatrización incompleta, no siendo más que 10 por ciento del total definitivamente evolutivos. La curación fué más frecuente—y también más rápida—en los casos con lesiones engrosadas, circunscritas. Los coeficientes de curación fueron: lesiones pápulonodulares, 94%; induradas escaroideas, 86%; y liquenoideas, 100%; total, 100%. En el orden de la frecuencia de la curación, siguieron: las lesiones urticaroideas, 76.6%; las máculas elevadas, 66.2%; y las máculas planas, 62.6%; total, 69.0%. Las pocas infiltraciones formaban una clase por sí solas, sin que cicatrizara espontáneamente más que 1 de 5, mientras que 3 se volvieron evolutivas.

Se observó bastante buena correlación de la cicatrización con los coeficientes bajos de las lesiones en cuanto a bacilos y con la intensa reactividad del enfermo a la lepromina, aunque con más excepciones que las notadas con el factor de la morfología clínica.

La correlación con las histopatología demuestra que, con excepción de los pápulonódulos, los casos cuyas lesiones revestían la naturaleza de infiltrados no diferenciados globocelulares o monocíticos sanaban generalmente antes que los que tenían lesiones de estructura tuberculoidea.

Las recidivas, cuando las hubo, se presentaron, en su mayor parte, en término de menos de tres años de la curación aparente, volviéndose gradualmente más raras a partir de entonces. Fueron menos frecuentes en los casos que tenían lesiones no diferenciadas más bien que tuberculoideas, y menos frecuentes de todo en los que tenían las tres clases de lesiones engrosadas, circunscritas.

Discútese la existencia de una pequeña proporción de casos aparentemente curados con lesiones residuales de los nervios o de la piel, señalándose que son en particular susceptibles de pasarse por alto en las encuestas corrientes.

Una partede esta comunicación trata de la observación continua de un grupo de 103 niños que, en 1938, sin lesiones entonces, recibieron tres inyecciones intradérmicas de lepromin (prueba de Mitsuda) a plazos de cuatro meses, y de otro grupo comparable mantenido en observación como testigo. Los hallazgos indican una ventaja aparente para los que recibieron las inyecciones, sobre todo si tenían menos de seis meses de edad. Se halla en camino una observación ulterior de esta naturaleza.

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