

OBSERVATIONS ON THE PROGRESS OF INCIPIENT LESIONS OF LEPROSY

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INTRODUCTION

It has been affirmed repeatedly by numerous workers that there exist "abortive" cases of leprosy. Some of these never develop recognizable manifestations of the disease (nonprogressive "latent" infection), while others which become clinically positive do not progress beyond an early, "incipient" stage. In the latter class there are observed definite, characteristic lesions such as anesthetic macules, or localized insensitive areas of skin sometimes supplied by thickened nerves; all are usually negative bacteriologically. Without medication these lesions become stationary, or they retrogress and completely disappear and leave no trace of the infection, though occasionally an atrophic scar or a slight contracture of the fingers remains to show that the infection has existed. Unfortunately, so far as we are aware, such supposed abortive or self-limiting incipient cases have nowhere been followed up for a sufficient length of time after the disappearance of the lesions to give positive information as to their ultimate outcome. Moreover, as Manalang (1) rightly insists: "the so-called spontaneous improvement or disappearance of the disease which is common, should be confirmed histo-pathologically."

In 1924 the senior author (2) made a survey of all the children born at the Culion Colony who were living there at that time. The main purpose of this survey was to provide a basis for following the development of the incipient lesions from the earliest manifestations to the bacteriologically positive stage, or to their complete disappearance if that should occur.

In 1925-26 all of the Culion children above the age of two years were transferred to Welfareville, a government institution under the Public Welfare Commissioner, located in a suburb of Manila. At the same time the nursery in the non-leper settlement at Culion was remodelled, and every effort was made to have all children born in the colony brought there as early as possible, and this has been continued to the present day. Since that time all children born

at Culion who have not been taken over by nonleper relatives or guardians have been sent to Welfareville on reaching the age of two years.

The surviving children of the group studied by him in 1924 were re-examined by Rodriguez (3) at Welfareville in 1929, exactly five years after his first survey. It is hoped to repeat the examination of these same children, particularly those whose lesions have completely cleared up, every five years.

In 1931 Chiyuto (4) started to study intensively forty of the Welfareville children. Most of them had been born after 1924, and therefore are not included in the special group being studied by Rodriguez. Chiyuto lays particular emphasis on the correlation of the clinical and the pathological findings. He has found a pinkish papulo-vascular eruption and certain hazy depigmented areas to be "early leprotic manifestations as confirmed by the presence of perivascular round cell infiltration." With the cooperation of Manalang, Chiyuto's work at Welfareville may be expected to yield even more important results after a few more years of observation.

These observations on the Culion children have been outlined here for a definite reason. Since the practice of sending the older children to Welfareville was started in 1925, and the early removal of the infants was undertaken at Culion, there has been a marked reduction of the number becoming bacteriologically-positive lepers, both among the children transferred to Welfareville and among the younger ones remaining at Culion. Rodriguez (3) believes that the apparent reduction of "suspicious" cases and "clinical lepers" becoming positive among the Welfareville children studied by him was due to (a) fewer cases under observation because of discharge of many of the children, including some suspicious cases and clinical lepers; (b) intensive treatment of clinical lepers; and (c) most important of all, the much improved hygienic care and food given to them at Welfareville. The marked reduction of those becoming lepers at Culion was believed to be due to (a) the fact that there were very few of the older children left there, if any; (b) intensive treatment of clinical lepers; (c) improvement of the conditions as to care and food at the nursery; and especially (d) early removal of the newly born infants to the nursery. The great improvement both in the care and in the food of the children at Welfareville as well as at Culion is believed to have played a very important rôle in the reduction of the number becoming positive every year.

The point which it is desired to bring out in connection with this decrease of children becoming positive is that, in spite of such apparent diminution, Chiyuto has observed that the majority if not all of the lesions observed by him in the Welfareville children were

progressive. Moreover, he is inclined to believe that almost all of the more than 200 Culsion children at Welfareville have similar early progressing lesions. If so, few of them become positive, and since several of them are now 20 years old or are nearing that age many of the lesions observed by this investigator must either become stationary or disappear after progressing for some time. These findings suggest that although the proportion showing early lesions is about the same in both those who are properly fed and those poorly nourished and improperly cared for, proportionately more of the latter advance to the bacteriologically positive stage. In other words, arrested cases seem to be more common among the well fed and properly cared-for children. However, this matter can not be decided definitely until there have been many more years of clinical observation on the same children, and correlation of these observations with histopathological and bacteriological findings.

So much for some of the efforts which have been and are being made in the Philippines to follow the development of leprotic lesions in children of lepers cared for in institutions.

OBSERVATIONS REPORTED

Realizing the importance of making similar long-continued observations on adults and children who show similar incipient or early lesions but who are living in their own homes and carrying on their ordinary daily activities, we have attempted to re-examine at regular intervals patients having such lesions who have been seen at the Cebu Skin Dispensary. As was to be expected, however, the attendance of the majority of these patients was most irregular, and many were not seen again after the first visit. Furthermore, whenever any numbers of these cases are re-examined their attendance at the dispensary falls off at once.

It must be emphasized that only cases which were found to be "closed" or bacteriologically negative are included in this report; those found positive at the first examination are segregated at once and are not treated in the dispensary. Therefore, the cases dealt with in this report do not represent all, or even a cross-section of all, of the cases of leprosy found in Cebu.

There was a total of 563 closed cases of leprosy registered at the dispensary from January 1, 1928, to December 31, 1932, a period of 4 years. Diagnosis was based on the finding of one or more

characteristic changes, which include leprous macules (hypopigmented, red or hyperpigmented), localized anesthesia, paresthesias, contractures and atrophies, trophic ulcers, anesthetic ichthyosis, infiltrations, and urticaria-like rashes. For bacteriological diagnosis multiple smears were taken from the skin lesions, as well as from both sides of the nasal septum and from any suspicious portions of the nasal mucosa, and in some cases smears were also made from apparently normal looking skin of the ear-lobes, buttocks, and other sites of predilection. In all of the cases under discussion these were negative for acid-fast rods.

Only 225 of these 563 closed cases (40 per cent) continued attendance at the dispensary long enough to permit making at least two bacteriological and clinical re-examinations. Of these, 31 were found positive in one of these subsequent examinations, an incidence of 13.8 per cent. The shortest interval elapsing between the initial examination and the one which resulted positively was seven months, and the longest was four years. An analysis of the data on these cases is given in the following sections.

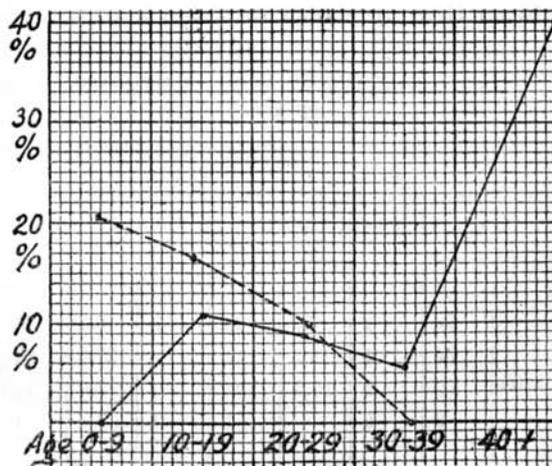
TABLE 1.—*Relation of age and sex to the incidence of progress to the bacteriologically positive stage.*

Age group, years	Males			Females			Total		
	No. in group	Positive	Per cent	No. in group	Positive	Per cent	No. in group	Positive	Per cent
0-9	11	0	—	14	3	21.43±10.94	25	3	12.00±6.50
10-19	52	6	11.55±4.43	47	8	17.07±5.47	99	14	14.14±3.50
20-29	34	3	8.82±4.86	20	2	10.00±6.70	54	5	9.26±3.95
30-39	15	1	6.66±6.43	3	0	—	18	1	5.55±5.40
40+	20	8	40.00±10.95	9	0	—	29	8	27.58±8.25
TOTAL	132	18	13.63±2.99	93	13	13.97±3.60	225	31	13.77±2.16

AGE AND SEX

The incidence of cases becoming bacteriologically positive, in relation to age and sex, is given in Table 1. From it one sees that of the 132 males followed up 18, or 13.6 per cent, became positive, while 13 out of 93 females, or 14.0 per cent, also turned positive. These proportions are almost identical.

The curves of incidence with relation to age are shown in Text-figure 1. That for males is roughly saddle-back shaped, starting at zero in the first decade, rising sharply to a first summit in the second decade, followed by a descent through the second and third decades and a rise after forty. On the other hand, among the females the age-incidence curve shows a descending slope from the first to the third decades, with no more cases becoming positive after that period. The differences shown by this figure are very interesting, but a much larger group of cases must be observed, before any definite conclusions can be drawn with regard to them.



TEXT-FIG. 1. Curves showing incidence with relation to age in cases becoming bacteriologically positive. Solid line, males; broken line, females.

If the males are subdivided into two main groups, namely (a) those below 30 years, and (b) those above this age, there are among the former 112 patients with 10 becoming positive (an incidence of 8.92 ± 1.82 per cent), and among the latter 20 patients with 8 positive (40.00 ± 7.38 per cent). The difference in rates between the groups would be 31.08 ± 7.60 per cent; this difference is significant. Were the females similarly divided it would be found that 13 out of 81 in the younger group (16.05 per cent) became positive, while none of the 12 cases above 30 years of age did.

These observations are quite unique, and if they are confirmed by subsequent studies with a larger number of cases they may prove important, inasmuch as it is the common experience in most coun-

tries, in contrast with our findings, that a large proportion of males are admitted to leper hospitals in the second and third decades of life. It is possible that, especially among young females, there are large numbers of frustrate forms which never reach the hospitals.

TYPE OF LESION FIRST OBSERVED

At the first examination of the 225 patients under discussion a variety of undoubted lesions of leprosy were noted, as has been indicated. It has seemed worth while to ascertain the frequency with which cases showing the different varieties of lesions became positive. The data on this are shown in Table 2.

TABLE 2.—Relation of type of original lesion to incidence of positive change, by sex.

Type of lesion first seen	Males			Females			Total		
	No. of type	Positive	Per cent	No. of type	Positive	Per cent	No. of type	Positive	Per cent
Hypopigmented macule	55	4	7.3	44	3	6.8	99	7	7.1
Red macule	35	5	14.3	39	8	27.6	64	13	20.3
Localized anesthesia	29	3	10.3	13	1	7.6	42	4	9.5
Trophic ulcer	3	0	—	3	1	3.3	6	1	16.7
Contracture and atrophy	3	1	33.3	2	0	—	5	1	20.0
Hyperpigmented macule	2	1	50.0	0	0	—	2	1	50.0
Urticaria-like rash	1	1	100.0	1	0	—	2	1	50.0
Infiltration	2	2	100.0	0	0	—	2	2	100.0
Paresthesia	2	1	50.0	0	0	—	2	1	50.0
Ichthyosis (anesthetic)	0	0	—	1	0	—	1	0	—
TOTAL	132	18	13.6	93	13	14.0	225	31	13.8

With regard to the macules, it is to be understood that their classification into hypopigmented, red, and hyperpigmented varieties is arbitrary, inasmuch as a pale or hypopigmented macule may become red, or vice versa, and either variety may become hyperpigmented

in part or all over. However, some such classification is useful to those who wish to follow the progress of these macules.

Several clinical varieties of the pale or depigmented macule are seen among our dispensary patients. The most frequent type is a smooth, hairless, nonscaly area of variable size, the borders of which may show pin-head elevations. Similar small papules may also be scattered just outside the borders. This lesion is usually anesthetic, and it has a decided tendency to progress; it ordinarily starts as a papule or a group of papules. Histologically this type usually has a "tuberculoid" structure.

Another fairly common variety has the same general appearance when viewed from a distance, but on closer examination it shows a smooth, atrophic-looking surface and there are no papules at the border. The sensibility may or may not be impaired. The borders may simply shade off into apparently normal skin, or there may be a peculiar zig-zag or whorl-like accentuation of the depigmentation at the borders. After reaching a certain size this lesion shows no tendency to progress further. It gradually fades by the return of normal pigmentation, this usually starting at the center. Histologically, this type is characterized by simple round-cell infiltration.

A type of depigmented macule that is rather rare in the Philippines is a raised, uniformly hypopigmented area showing a rough surface. On close examination the apparent roughness is found to be due to an exaggeration of the normal ridges and furrows of the skin.

The red macule may be merely a more advanced stage of the depigmented macule, reached when a pinkish or reddish color appears either at the border or at the center. This change is usually accompanied by a rapid increase in the size and possibly also the number of the macules. Occasionally, however, such a lesion may be reddish at the start; usually such macules do not remain single for long.

We have called "hyperpigmented" those macules which were pigmented at the very start. This type, which is rare in Filipinos, seems to be more common in people with fair skin.

Of the 99 cases which had hypopigmented macules at the first examination 7, or 7.1 per cent, became positive, while of 64 cases with reddish macules 13, or 20.3 per cent, became positive. Of the 42 cases with localized anesthesia without any other manifestation 4, or 9.5 per cent, became positive. From this it appears that the reddish type of macule is the one most likely to turn bacteriologically positive.

Such lesions as trophic ulcers, atrophies, and contractures, although they may be the first symptom observed by the patient or the physician, indicate a fairly advanced stage of the neural type of the disease, and such cases rarely become positive in the skin. On the other hand such manifestations as urticarial rashes, infiltrations,

etc., are associated with the cutaneous type, and patients showing them are especially liable to become positive.

It is shown in Table 2 that the rarer symptoms first noticed by the patient at the outset of leprosy, such as urticaria-like rashes, infiltrations, etc., which usually occur among adults, were less frequent in women than in men in this group. This may explain why fewer women became positive after the thirtieth year than men. If this observation should be confirmed in a larger group of closed cases it may partly explain the preponderance of male over female lepers among adults.

It is not possible in this article to describe case by case the development of the lesions from the bacteriologically negative "closed" stage to the positive or "open" stage. In summary, it is to be said that among the 7 patients with only depigmented macules when first observed who became positive, the lesions first seen underwent this change in only one instance. In 3 cases new macules appeared suddenly, and those were the ones found positive; while in the other 3 cases the ears, cheeks, and chin gradually became infiltrated and red, the original pale macule either retrogressing or becoming stationary. It is worth mentioning that in all these cases the pale macules were multiple, except in one case where there was only one lesion which, however, was very extensive.

Among the 13 cases first seen with reddish or pinkish macules, the original lesions became positive in only 3 cases. New lesions which became positive appeared in 4 cases. In 4 others the original lesions either became stationary or improved markedly, but the earlobes, cheeks, and nose subsequently became thickened. In the remaining 2 cases urticaria-like eruptions appeared.

One of the last two was a girl with reddish macules on the buttocks which practically disappeared after about one year of regular treatment. She then got married against advice, moved to another island, and stopped treatment altogether. Just before her first delivery she had an evanescent urticaria-like rash accompanied by a slight fever. She came to Cebu for examination but when we saw her the eruptions had disappeared, and smears taken from their sites as well as from the nasal septum were found negative. She received a few injections but soon left to rejoin her husband. About a year later she had gonorrhoea, and an acute lepra reaction again appeared. Another pregnancy followed about six months later, and just after delivery another exacerbation occurred. This time the rash did not disappear and on bacteriological examination, numerous acid-fast rods were present.

Of the 4 positive cases that at first showed nothing but localized anesthetic areas of the skin, one developed an ichthyosis-like condition over the anesthetic area and this region was later found to be bacteriologically positive. Another developed a reddish macule over the insensitive area on the right knee, followed by the appearance of similar macules on the buttocks; after a few months, the macules became raised and were found positive. In a third patient the anesthesia disappeared completely after about four months treatment, but in spite of the fact that she continued to receive injections quite regularly (though only 2 cc. per week) numerous bacteriologically positive macules appeared all over the body about one year later. In the last of these cases an extensive anesthetic area on the right thigh became reduced to isolated patches of anesthesia after fourteen months of treatment, but six months after she had stopped reporting for treatment pinkish macules appeared on the buttocks, and five months later the ears, cheeks and the glabella became infiltrated.

TREATMENT

The treatment consisted of weekly intramuscular injections of *Hydnocarpus wightiana* ethyl esters with 0.5 per cent iodine. No "plancha" (local intradermal) injections were given, these being outpatients. The dose varied from 1 to 5 cc. according to age and the general physical condition. The importance of cleanliness, regular health habits and proper diet was emphasized at each visit to the dispensary, and after a few weeks a gain in weight as well as a cleaner appearance, both in body and in clothing, was generally the result.

In analyzing the positive cases with respect to treatment received they were arbitrarily divided into two groups: (a) the irregular group, composed of those receiving 60 per cent or less of the expected number of injections, and (b) the regular group consisting of those who had received more than 60 per cent of their weekly treatments. Table 3 shows the relation between the duration and regularity of treatment and the percentages becoming positive.

It is seen from the figures shown that there were 173 cases in the irregular group, among which 28, or 16.18 ± 1.88 per cent, became positive. Of the 52 cases receiving more than 60 per cent of their expected number of injections only 3, or 5.77 ± 2.18 per cent, became positive. Therefore the proportion becoming positive was

2.8 times higher in the irregular than in the regular group, and this difference is found to be significant, being 10.41 ± 2.88 per cent.

The figures given below would seem to show that the chaulmoogra treatment was quite effective in preventing the development of bacteriologically positive cutaneous lesions in many of the cases in the dispensary group. This result is at variance with the experience of Rodriguez among the Culion children (3), in which group the chaulmoogra treatment did not prevent closed cases from developing into open or bacteriologically positive cutaneous-type cases. One possible explanation for this difference is the common observation of many leprosy workers that leper children as a rule react less favorably to the chaulmoogra treatment than do adults.

TABLE 3.—Relation of regularity of treatment to the incidence of positive changes.

Duration of treatment	Irregular treatment *			Regular treatment *			Total		
	No. of cases	Positive	Per cent	No. of cases	Positive	Per cent	No. of cases	Positive	Per cent
0-12 mo.	23	3	13.0	19	0	—	42	3	7.1 ± 3.96
13-24 mo.	40	4	10.0	10	1	10.0	50	5	10.0 ± 4.24
25-36 mo.	45	6	13.3	9	0	—	54	6	11.1 ± 4.27
37-48 mo.	60	14	23.3	14	2	14.2	74	16	21.5 ± 4.78
Over 48 mo.	5	1	20.0	0	0	—	5	1	20.0 ± 17.97
TOTAL	173	28	16.2	52	3	5.8	225	31	13.7 ± 2.16

* "Irregular treatment," 60 per cent or less of the number of injections that the patient should have received in the period under treatment; "regular treatment," over 60 per cent.

Further reference to Table 3 shows that there is no correlation between the duration of the treatment and the number becoming positive, even among those receiving treatment regularly. In other words, it did not follow that the longer the treatment the less the proportion turning positive. The figures tend to show that the longer these closed cases are followed the more may be expected to become positive, regardless of the treatment. Of course, our experience so far is limited to a maximum of only seven years. We agree entirely with Mitsuda (6) that neural cases, to which type most of these closed cases belong, should be observed for at least 10 to 20 years in order to ascertain the course of the disease in this type of leprosy.

When the two groups shown in Table 3 are combined, so that the regularity of the treatment is not taken into account, the incidence

seems to increase with the duration of the treatment. This is to be expected, as there were three times more patients in the irregular group among whom the proportion becoming positive was higher than in the regular group.

It must be emphasized that the injections were all given intramuscularly and that the "plancha" or local infiltration method was not employed. It is the opinion of many experienced leprologists, among them Lara (5) of Cullion, that the latter method is much more effective than the intramuscular, and it may be that the results would have been different had it been used. This method takes more time than our very limited personnel can afford to give to this work, but we are now employing it in view of the results here described.

DURATION OF DISEASE AT OUTSET OF TREATMENT

In Table 4 the incidence of positive cases in relation to the duration of the disease and the regularity of treatment is given.

TABLE 4.—*Relation of duration of disease and regularity of treatment to incidence of positive changes.*

Duration of the disease	Irregular treatment *			Regular treatment *			Total		
	No. of cases	Positive	Per cent	No. of cases	Positive	Per cent	No. of cases	Positive	Per cent
Under 1 year	80	15	18.7	25	0	—	105	15	14.2
1 to 5 years	67	8	11.9	21	3	14.2	88	11	12.5
Over 5 years	26	5	19.2	6	0	—	32	5	15.6
TOTAL	173	28	16.1	52	3	5.6	225	31	13.7

* "Irregular treatment," 60 per cent or less of the number of injections that the patient should have received in the period under treatment; "regular treatment," over 60 per cent.

Considering only the total cases, there is evidently no advantage in favor of those who were placed under treatment within a year after the onset of the disease over those who had had it for a longer period. Here again the results are influenced by the preponderance of those receiving the treatment irregularly. Of those receiving treatment regularly, none of the 25 early cases of less than one year duration became positive, while among the 21 cases of 1 to 5 years duration 3, or 14.2 per cent, became positive. Again, none of the six cases who had the disease over 5 years became positive. It may

be that, irrespective of treatment, the disease shows the greatest activity during the period from the first to the fifth year and that many cases extending beyond the period tend to become arrested spontaneously.

SUMMARY

Some leprosy workers believe that there are many frustrated cases of the disease which never develop marked cutaneous or neural manifestations and therefore are seldom seen in treatment centers and never in hospitals. To obtain direct evidence on this matter is difficult, as it needs periodic examination of many such cases, together with their contacts, carried on systematically over a long time—at least from ten to twenty years.

We have had the opportunity of examining repeatedly two distinct groups of patients showing the earliest, bacteriologically negative lesions of leprosy, along with others who have been in contact with the disease but as yet show no manifestation of infection. However, the maximum period that any of these cases has been studied is only seven years, so that our observations must be considered as merely preliminary.

The first group, observed for seven years, consists of 336 children born of leper parents at the Culion Leper Colony, previous to 1924. They had been exposed to the disease for varying periods of time. We have also taken into consideration the studies by Chiyuto and Manalang on younger Culion children born after 1924 and now taken care of in Manila. In these children at Culion the chaulmoogra preparations, administered intramuscularly, did not prevent the development of bacteriologically positive lesions. Transfer of Culion-born children to Manila when two years of age has apparently diminished greatly the number becoming positive. Nevertheless, Manalang and Chiyuto have found that almost all these young transferred children show lesions which they consider early manifestations of leprosy. These findings suggest that good hygienic care and proper food do not prevent the appearance of clinical symptoms, but do tend to prevent the infection from progressing to the bacteriologically positive stage—in other words, under these conditions many cases are "frustrated." However, final conclusions must await several more years of study of these cases.

The other group consists of 225 "closed" cases of leprosy treated at the Cebu Skin Dispensary (out of a total of 563 cases seen there) who have been re-examined clinically and bacteriologically at least twice. The period of study varied from seven months to four years, the average about two years. Of these cases, 31 or 13.8 per cent had become bacteriologically positive during the period of observation.

The sex incidence of those becoming positive is practically equal, 13.6 per cent among the males and 14.0 per cent among the females, but interesting differences between the two sexes in the age distribution were noted.

With regard to the type of lesion, the red macule was the one most apt to become positive. A sudden change in the area of localized anesthesia independent of macules, either a rapid increase or decrease, was found to be of ominous import.

The proportion becoming positive in the small group which had received treatment regularly was significantly less than in the larger group treated irregularly, although in some cases even prolonged intensive treatment did not prevent them from becoming positive.

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