THE SKIN LESIONS OF NEURAL LEPROSY V. OBSERVATIONS IN CEYLON

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In Ceylon, nonselective leprosy segregation has been carried on for many years without obligatory distinction on the basis of type of the disease. In consequence, among the 700 and more inmates of the Hendala asylum, near Colombo, there are many cases of the neural type, numbers of them of long duration and with old, extensive, skin lesions. The picture which, in total, they present is decidedly different from that seen in institutions where residence depends solely upon the patients' own desires in the matter, as for example in the Lady Willingdon Leper Settlement in Madras, where was obtained the material dealt with in the preceding report of this series. On the other hand, the leprosy survey that has been carried on in Ceylon since 1932 (1, 2) has brought to light many cases with much slighter lesions, which are being treated on a voluntary basis in clinics in Colombo and at several other places.

In view of these conditions it seemed advantageous to extend the study of the leprides to this country when an opportunity to do so arose early in 1936. The main purpose was, as before, to ascertain the nature of the lesions—whether or not they differed in any essential way from outwardly similar ones in the races that had been studied elsewhere and the relationships of clinically different varieties. The proposal having been approved we were enabled, through the active cooperation of the several authorities concerned, to secure useable material from a group of cases, of which 53 were of the neural type and are considered here. Specimens were taken in February, and were processed in India. In May the patients were re-examined, the clinical and histological appearances of the lesions compared, and

the clinical notes amplified. Multiple bacteriological smears were made from each case, and several of them were rebiopsied. Some of the new specimens were taken because the first ones had not been removed from the active parts of the lesions,¹ some because of changes that had taken place in the three-month interim.

MATERIAL STUDIED

In the selection of cases at Hendala all of the women and young children were looked over for representative lesions, and of the men the medical superintendent called up all that he believed to be of interest. The average age of the 39 neural-type cases selected there (21 males and 18 females) was unusually high, the distribution being: under 10 years, 3 cases; 10-19 years, 8 cases; 20-29 years, 9 cases; 30-39 years, 7 cases; 40 years or over, 12 cases, one of them claiming the age of 70. The cases studied in South India averaged much younger and much less advanced, the differences being due undoubtedly to the very different circumstances of hospitalization in the two places. The other 14 cases biopsied were found in the clinics; as a whole they were much younger and less advanced.

With regard to type-classification, our records in a few instances differ from the official ones, because of the practise in the hospital of classifying as "cutaneous" (previously as "B") any case found bacteriologically positive. As for the classification of the lesions, none of them fails to come within the scheme used in this study. As usual, there is much variation within the main classes; for present purposes they may be grouped as follows:

Variety	Cases	
Major tuberculoid, superficial	4	
Major tuberculoid, retrogressive	2	6
Minor tuberculoid, reaction cases	3	
Minor tuberculoid, band-lesion	1	
Minor tuberculoid, irregular lesions1	0	
Minor tuberculoid, papulate and spotty	4	
Minor tuberculoid, retrogressive	2 :	20
-	-	
Papulate (tuberculoid), various		4
Simple, active, elevated hyperemic	5	

¹The first specimens had been taken prior to adoption of the device of guiding the surgeon by marking with a skin pencil the exact area to be biopsied. Such marking prevents scrubbing in the surgical preparation of the area, but it insures removal of tissue from the right place and chemical antisepsis suffices to prevent untoward after-effects.

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Simple, elevated, irregular-surfaced	
Simple, slightly elevated, smooth 4	
Simple, nonelevated, smooth10	23
TOTAL	- 53

Though we found a fair number of clinically tuberculoid cases, especially of the minor grade, there was a conspicuous paucity of exuberant ones. Acute "reaction" major tuberculoid cases are not common in this country and none was seen. Those classed as of major grade were relatively mild and chronic, or had retrogressed so that they had to be classified on the history or other clinical considerations. Similar conditions apply, in general, to the minor tuberculoid group. As in Madras, advantage was taken of the opportunity offered here to pay more attention to the simple class of lesions than in the Philippines or China.

PRESENTATION OF FINDINGS

On the whole, in comparison with the other groups of cases dealt with in this study, the present group differs mainly as regards (a) the generally moderate or reduced grade of the tuberculoid lesions found, (b) on the other hand the extreme extent of the macules found in several cases of long duration, (c) the frequency of positive bacteriological findings, (d) the number of cases with evidence of reaction in the lesions, and (e) the progression of lesions and other changes that occurred in several cases in the interim between the two observation periods. With regard to the microscopic changes in the lesions, the findings are summarized in Table 1. The findings regarding nerve enlargement are indicated in Table 2.

MAJOR TUBERCULOID CASES

A feature of this group, which is not representative of this class in general, is the superficiality of the condition in the three cases that were at all active; to some extent the lesions were not unlike some of those seen in South Africa (4). They showed little of the usual tendency to the deep extension that is so often productive of greatly enlarged cutaneous nerves (see Table 2). The two with especially notable nerve involvement were more or less retrogressed.

The annular or "zone type" lesions of CASE 1 (Figs. 1 and 2) were most unusual as regards extent and chronicity. Though sections show changes that, so far as they go, are as marked as would be expected the condition both clinically and histologically, was essentially superficial, and there was not

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much palpable nerve involvement. The patient stated that, as is common in this variety, the patches had appeared in crops, never singly, but that all were at first flat.

Most of the lesions in CASES 2 and 3 might have been called marked minor but they are placed here because of other features, including, their histories. In Case 2 (Fig. 3; cf. Fig. 9) the lesions, many of which had retrogressed under treatment though frank major ones persisted on the face, had appeared in crops. Several recent ones, such as are often seen in major cases (two of which were removed for examination) are shown. In Case 3 there was a definitely major-degree lesion on the forehead, but it could not be biopsied. In the specimens from both cases the microscopic changes are rather slight for major lesions, and in keeping with the clinical appearance they are unusually superficial. There were only moderate cutaneous nerve changes.

Nerve involvement was more marked in CASE 4; it was noted "all enlarged and tender." The skin lesions, very widespread but of moderate degree at most, varied from active (as the biopsied one high on the back, Fig. 4), to residual; histological changes were not marked for the class.

There were also conspicuous nerve changes in CASES 5 and 6. The former was a typical major one, with many, generally distributed lesions, even involving the palms extensively but they were so much retrogressed that those of the hand cannot be distinguished in the photograph (Fig. 5), and those on the arm seem slight. In Case 6 there was only one lesion, a partially retrogressed one on the forearm (Fig. 6, A), but from it two conspicuously enlarged nerves led up (Fig. 6, B). No such large nerves were found in any other case. One of these nerves was removed with some of the corresponding area of skin; sections cut at intervals permit tracing the tuberculoid condition from the skin up through the small branches that join up to form the main one, which is caseous.

MINOR TUBERCULOID CASES

The relatively large group of this kind of lepride comprised a considerable variety, from the relatively smooth-edged, smoothsurfaced band-like lesion (interesting because of the uniform width of the raised margin) seen in several of the China cases but not in India, through the more superficially located, irregular-surfaced and -edged ones, to the most superficial and rough-surfaced ones which are more or less papulate in nature. There were also a couple of the kind which give an impression of, so to speak, frantic frustration, with sporadic efforts to produce new lesions with doubtful success in doing so. One case, especially interesting and uncertain of status because of peculiarities of appearance, was apparently in a reaction condition when first biopsied, and two others were probably in a more or less subsided stage of that condition.

Reaction cases.—One patient (CASE 7) had a few lesions of ordinary appearance but several were peculiar, among them two on the back, the lowermost of which was biopsied (Fig. 7).² Centrally more or less recovered, they had wide marginal zones that were considerably infiltrated and irregular of surface, but that otherwise suggested annular lepromata in that the surface was quite shiny, the edge sloped gradually off to the normal skin level, and to the contrary the inner edge, around the recovered center, was relatively sharp and abrupt. However, the diffused periphery was spotted with fine micropapulations. The two specimens taken (February and May) show rather marked tuberculoid changes, with certain differences between the two in the condition of the epithelioid cells that presumably resulted from reduced activity at the time of the second observation.

The other cases placed here (Nos. 8 and 9) were probably though not certainly in a reaction state; the principal lesions were very suggestive, and the histological findings are more so. In case 8 there was at the waist a large, very pale macule, considerably infiltrated and coarsely pebbled, with general erythema. The microscopic changes, chiefly superficial but of considerable degree, have the appearance of marked activity and a few of the tuberculoid foci show slight necrosis. The patient also had three small, recently erupted lesions elsewhere. In Case 9 the main lesion was on the whole evidently retrogressive and in part atrophic, but in part it was moderately infiltrated, irregular of surface and diffusely erythematous. Histologically the tuberculoid foci are peculiarly disturbed; there is much pyknosis and fragmentation of cells, and—a most unusual feature—some polymorphonuclear invasion. The patient denied having used any external medication other than chaulmoogra oil.

Band-lesion.—Only one case (No. 10) had a lesion of this kind (Fig. 8). Histologically it is rather slight and mostly deep in the dermis, in keeping with the outward appearance. In May it seemed to be more active than before and was rebiopsied; the microscopic changes are more marked but essentially similar.

Irregular-edged and -surfaced lesions.—A nice small lesion of this kind, really rough-surfaced, is shown in Fig. 9 (CASE 11). Histologically the changes are of moderate degree, with a narrow conglomerate zone of fairly active tuberculoid change sufficient to explain the surface appearance, but unexpectedly there is more in the deeper levels. The lesion had increased somewhat three months later (Fig. 10).

More advanced lesions of this variety are demonstrated in Figs. 11-14. In CASE 12 the largest lesions (shoulders, Fig. 13) were about four years old; the one biopsied was comparatively recent. Those of CASE 13 (Figs. 11 and 12) were similar but with histological changes in keeping with the moderate-degree, superficial appearance. In both cases the lesions had increased in May and were rebiopsied; the changes are somewhat more marked than in the first specimens. In Case 13 there was extension of the lesion around the biopsy scars.

² This photograph is one of several used here that do not show details satisfactorily. Ordinarily for work of this nature direct oblique sunlight is depended upon and moderate-speed films are used. Because of stormy weather the pictures referred to had to be taken indoors under unfamiliar conditions (with artificial light and supersensitive, coarse-grain film), and with contrast development the color differences were exaggerated and the finer surface details obscured.

The most extensive lesions of this kind were in CASE 14 of 20 years duration. Though those shown in Fig. 14 were not that old, they had been slowly progressive for years. Those of four other cases (Nos. 15 to 18) were of essentially similar nature, though varying greatly in number and extent. Another (No. 19) had very early and slight lesions of this kind; though apparently active, they were comparatively slight as regards elevation and surface irregularity, and the pathology is correspondingly slight.

In connection with the last case may be mentioned one (No. 20) with two lesions on the back. One was a very small hazy palish lichenoid area with several shiny papulations of fixed (not evanescent) appearance. The other was larger (2.5 cm.) and infiltrated, apparently a development from the lichenoid stage; it proved to be of more than slight degree tuberculoid, apparently active. What form it would have taken had it been allowed to progress cannot be said.

The considerable proportion of the cases with these irregular lesions that showed definite progression in the three months between the two examinations is of interest.

Minor tuberculoid lesions with papulate tendency.—Exaggeration of surface irregularity to the point of actual papulation, on an infiltrated base (i. e., not in a flat, simple macule), was observed in several cases. In some the papulation was more or less general, or at least dispersed over a broad lesion area, while in others it was more strictly peripheral.

The most striking one of the generally papulate group is shown in Fig. 15 (CASE 21). Many of the papulations were very coarse and full (active) in appearance though others were more or less retrogressed. The specimen shows correspondingly marked changes, apparently active, with superficial foci corresponding to the papules. This lesion was decidedly more active in May. A less striking one (CASE 22), also on the chest is seen in Fig. 16. In one part it had a wide margin studded with conspicuous, broad-topped papulations, largest and most numerous toward the edge. Microscopically there is more abnormality deep than superficially, but in the latter zone there are broad elevations which obviously represent the papulations described. A similar lesion was on the face of CASE 23 (Fig. 17); a small, less differentiated one on the buttock was biopsied and found to show the usual changes, though in slight degree.

Intermediate between this group and the one with only papulate lesions, CASE 24 had many large macules, obviously once minor tuberculoid but now more or less retrogressed, irregularly pale and diffused, some of which had more or less retrogressed papules, occurring both isolated and in groups (Fig. 18). Sections from the least retrogressed show more marked tuberculoid change than do ordinary simple lesions. The grouped areas were like that shown in Fig. 15 but undeveloped, overcome before they could progress much. Curiously, similar spots had occurred secondarily inside of certain much retrogressed, more or less residual macules.

Nonpapulate retrogressive lesions.—One of the two cases put here (No. 25) had lesions which seemed once to have been ordinary irregular minor

ones (Fig. 19); they were still hypochromic but had only a little remaining infiltration. Sections show an apparently retrogressed condition, with only a trace of tuberculoid left. The other one (CASE 26) had on the left scapular region a single macule of apparently similar nature, so far as could be told, it having been modified by local treatment. It was said to have been originally raised and erythematous, which suggests a major tuberculoid beginning. Sections show only slight tuberculoid changes.

CASES WITH PAPULATE LESIONS

Four cases fall here. One was of the frustrate kind which bring to mind sporadic guerilla warfare, unsuppressed but only temporarily successful. The others were simpler, flat macules that probably had never been elevated but which had developed (secondarily?) papulations that could be nothing but elevated tuberculoid foci.

Efforts to establish new lesions, by papulate and lichenoid initiation, with usually little progress before suppression of the process ("frustrate" lesions) were evident in CASE 27 (Fig. 25). There were also on the face several simple hazy diffuse spots of the kind that give so much trouble when seen alone in children examined for suspicious signs of leprosy infection. Specimens from two lesions, one of the larger macules (A) and a group of isolated papulate spots (B), both show slight tuberculoid changes—the latter with separate superficial foci that explain the papulation.

Three cases had more ordinary "simple" lesions in which definite papulations had developed. In CASE 28 there was on the abdomen a macule with a few small papules, sections of which show residual changes and a single tuberculoid papulate focus over which the epidermis is stretched; elsewhere the patient had a frank, minor tuberculoid lepride of moderate degree. In CASE 29 there was a single, small area on the arm with a few coarse papules in an area that may perhaps have been of more than simple grade originally. Sections (lesion removed entire) show a superficial tuberculoid focus that evidently represents a broad papulate elevation. In CASE 30 there were several small flat macules on the back (Fig. 21) in which the follicles appeared exaggerated, with a tendency to hyperkeratosis. Sections show slight-degree tuberculoid changes superficially, with notable concentration around some of the hair follicles.

Lichenoid follicular papulate lesions.—No specimen was obtained of this kind of lesion, of special interest as an early manifestation of leprosy and an early stage in the development of certain leprides. Such lesions were seen, however, in a few cases, including No. 27 mentioned shortly above, No. 20, in which a small minor tuberculoid macule was biopsied, and No. 50, from which a simple nonpapulate macule was removed. In the last of these there was, on the elbow, a group of well-separated papules, large, pale and conspicuous, with no change of color between them. On the buttock (Fig. 22) two areas in contact formed a bilobed one in which were numerous atrophic spots left by retrogression of such papules, several of which remained, especially in the zone of contact.

CASES WITH SIMPLE LESIONS

The twenty-three cases in this group presented about the greatest possible range of variations of this class of lesions, in appearance, extent and activity. A few of these macules showed the maximum degree of elevation and coarsening of texture that occurs in this class, still too slight to be called clinically tuber-culoid; these are exemplified in Figs. 25 and 26. As regards extent, there was a range from one or a very few small macules, especially in the clinic cases, to multiple extensive areas that involved most of the body (Figs. 23 and 24). Activity, so far as it could be determined, varied from relatively marked, with slight but definite erythema at the advancing edge, to obvious absence in retrogressed or residual lesions, in some of which the color had returned nearly to normal. In many instances hypochromia was marked, much more than in the lighter-skinned people in the Philippines and China.

Though the usual difficulty was experienced in estimating the status, as regards activity, of lesions intermediate between the frankly active and those that were obviously retrogressed or residual, the cases are arranged here according to the apparent condition in this respect. No attention is paid the duration of the case, the extent of the lesions or the presence of polyneuritic changes. The subdivisions are: (a) definitely active, with erythema; (b) doubtfully active or probably quiescent, and (c) evidently retrogressive or residual. The variations in the pathological findings in each subgroup are to be seen in Table 1.

Active, hyperemic lesions.—The most extreme involvement occurred in two of the five supposedly active cases with peripheral erythema. It is illustrated by CASE 31, (Figs. 23 and 24), duration 25 years, segregated for 22 years. A specimen from the point indicated on the back shows tuberculoid and infiltrative changes, apparently active, of the slight degree and superficial location usual in this variety of lepride. In the other extreme case (No. 32) the disease was supposed to be of only 10 years duration. Though the appearance was very similar the specimen shows only slight cellular infiltration, mostly in the plexus layer, with only very slight tuberculoid—a "trace," foci not present in all of the serial sections. In the case with the fewest and smallest lesions in this active subgroup (CASE 35), the specimen shows changes very similar to those in Case 31. CASES 33 and 34 were intermediate; the specimen from one of them shows only subtuberculoid changes.

Irregular-surfaced, slightly elevated lesions.-Irregularity of the surface (coarsening of the grain), with a very little elevation but without erythema,

	Histological fi	Tuberculoid, fairly	nostly superficial.	Tuberculoid, moderate.	Tuberculoid, moderate.	Tuberculoid, slight to	Moderate tuberculoid.	Tuberculoid, fairly mark aseous.		Tuberculoid, marked, trive appearance.	Tuberculoid, rather mar	very slight necrosis.	Tuberculoid, moderat	ourbed, (with polymorpho tot explained).
TABLE 1.—Summary of findings in lesions examined.	Clinical features with special reference to biopsied lesions	Major tuberculoid cases Extensive, moderate degree, superficial, slowly active.	(2 specimens) Ps (Figs. 1 & 2)	Moderately extensive, slight degree, superficial, active (4 specimens). B+ (Fig. 3)	Few lesions, slight degree, superficial active.	Extensive, slight degree, retrogressive; many nerves. (2 specimens) (Fig. 4)	Extensive, much retrogressed; many nerves. (Fig. 5)	Single retrogressive lesion; two nerves. (Nerve-skin specimen) (Fig. 6)	Minor tuberculoid cases	Marked, moderate extension, reaction? Lesion aty-	Rather marked, limited extent, recent reaction?		Few, large, some retrogressive; recent reaction?	
	Duration and residence	15	4	9 61	? Clinic	თო	63 63	1 Clinic		2?	. 10	6 mos.	3	8 mos.
-	Sex and age	F	50+	F 55	M 40?	M 60	M 41	36		H a	о н	18	Ę4	37
	Case No.	1	(12)	2 (1)	3 (52)	4 (45)	5 (29)	9 9		7	(or)	(11)	6	(10)

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Sex and are	Duration and residence	Clinical features with special reference to bionsied lesions	Histological findings	
M 63	25 8	Few, some large; band-like. (Activated) (Fig. 8)	Tuberculoid, rather slight; derate later.	mo
M 18	? Clinic	Few, small, marked degree. (Activated) (Figs. 9 & 10)	Tuberculoid, moderate, n zone, active.	narrow
F 17	4 2	Extensive, slight degree. (Activated) B+ (Fig. 13)	Tuberculoid, rather slight, parently active.	t, ap-
M 26	9	Few, moderate size, active. (Activated) (4 specimens) (Figs. 11 & 12)	Tuberculoid, moderate; marked later.	more
F 29	20 12	Several, extensive, active. (Fig. 14)	Tuberculoid, rather slight.	
F 25	10	Several, moderate size, active.	Tuberculoid, slight; quie	escent?
M 35	2	Few, one extensive, slight degree; inactive?	Tuberculoid, slight.	
M %	? Clinic	Few, moderate size, slight degree.	Tuberculoid, rather slight.	
M 58	15 Clinic	One; moderate size, retrogressive.	Tuberculoid, slight, retrogr	gressed.
 M 50?	× ×	Few, moderate size, slight, quiescent? (2 specimens)	Tuberculoid, slight; inact	tive?

TABLE 1.—Continued

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20	F F	- 73	Few, small, active? (2 specimens)	Tuberculoid, moderate, active?
21 (44)	28 M	- 05 00	Few; one large, coarsely papulate (3 specimens) (Fig. 15)	Tuberculoid, fairly marked.
22 (41)	M 64	5 22	Few; moderate size; papulate. (Fig. 16)	Tuberculoid, moderate.
23 (51)	M 13	1 Clinic	Few, papulate (Fig. 17)	Tuberculoid, slight.
24 (21)	30 F	2 1+	Many, extensive, retrogressive; some spotty. (Fig. 18)	Tuberculoid, rather slight.
25 (57)	M 19	2 Clinic	Several, large, markedly retrogressed. (Fig. 19)	Tuberculoid, trace; much retro- gressed.
26 (55)	M 36	5 Clinic	Single, moderate size, much retrogressed. Papulate lesions	Tuberculoid, trace; much retro- gressed.
27 (20)	M 7	; 1+	Several, slight, varied, macules and papules. (3 specimens) (Fig. 20)	Tuberculoid, slight, with papular foci.
28 (2)	F 12	1 6 mos.	Few, small macules with papules.	Mostly residual with a papular tuberculoid focus.
29 (7)	M 77	4 3	Few, small macules with papules.	Tuberculoid; a single papular focus.
30 (19)	¥∞ ¦	~ 6 .	Numerous, small, with follicular papulation. (Fig. 21) Simple lesions	Tuberculoid, slight, with folli- cular concentration.
31 (18)	45 45	52 52	Extremely extensive; erythema. (Figs. 23 & 24)	Tuberculoid, slight, not inactive.

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Sex and age	Duration and residence	Clinical features with special reference to biopsied lesions	Histological findings
F 35	10	Extremely extensive; erythema. (2 specimens)	Tuberculoid, trace only; retro-
F 25	8 8 mos.	Several, extensive, slight erythema (2 specimens)	Tuberculoid, slight.
F 50	2 8 mos.	Few, one extensive, slight erythema.	Moderate infiltration, subtuber- culoid only (?)
F 28	οŭ	Few, rather small, slight erythema.	Tuberculoid, very slight.
38 M	12 ?	Few, extensive, irregular. (Fig. 25)	Tuberculoid, very slight.
F 25	1 5	Few, moderate, irregular.	Tuberculoid, slight, retrogres- sive.
M 81	1? 1	Few, one large, irregular. (2 specimens)	Tuberculoid, trace only; largely residual.
M 30?	? Clinic	One, small, irregular, residual (not diagnosed positively).	Probably residual lepride.
M 21	11 10	Numerous, large, slightly elevated (2 specimens)	Tuberculoid, very slight.
45 45	6 4	Several, moderate size, slightly elevated. (Fig. 26)	Slight infiltration, slight subtu- berculoid; retrogressed.

TABLE 1.-Continued

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42 (32)	M 15	6 1	Few, small, slightly elevated (2 specimens)	Slight infiltration, not residual, subtuberculoid only.
43 54)	M 20	? Clinic	Several, moderate size, slightly elevated.	Slight infiltration only; inactive.
44 8)	M 13	5 %	Few, small, flat pale (Fig. 30)	Tuberculoid trace only; slight infiltration.
45 16)	F 18	2	Few, moderate size, flat, pale. (Fig. 27)	Subtuberculoid only; inactive.
46 40)	M 22	10 6 mos.	Several, large, flat, moderate, pale, inactive. (Fig. 28)	Tuberculoid trace; slight lesion, inactive.
47 35)	35 M	3	Several, large, flat, moderate, pale, inactive. (Fig. 29)	Very slight infiltration; practically residual.
48 47)	FI 9	2 Clinic	Few, small, slightly pale, retrogressive.	Tuberculoid, trace; almost residual.
49 48)	M 8	2+ Clinic	Few, small, slightly pale, retrogressive.	Almost negative; residual.
50 49)	£1 6	2 Clinic	Few, small, slightly pale (some papulate) (Fig. 22)	Residual only.
51	M 12	6 Clinic	Several, moderate size, slightly pale.	Slight infiltration, practically residual.
52 53)	M 25	3 Clinic	Few, small, faintly pale.	Almost negative.
53 25)	M 45	3 1	Few, small, faintly pale.	Very slight infiltration only.

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was present in four cases (Nos. 36 to 39). It is best shown in Fig. 25 (Case 36), the specimen from which shows "slight" tuberculoid changes—a few foci in every section. Slight surface irregularity was present in CASE 41 (Fig. 26); the biopsied lesion seemed retrogressive. In one instance (CASE 39) the coarsening was apparently residual; this lesion could not be diagnosed positively, and sections show only residual changes in the regions typically affected by the leprotic process.

Slightly elevated smooth lesions.—In four cases (Nos. 40 to 43) very slight elevation was noted, without noteworthy change of texture. None of the photographs show enough detail to justify reproduction. In two instances the hypochromia was moderate, the lesions apparently quiescent; in one of the specimens slight tuberculoid is present and in the other only subtuberculoid changes. In the other two lesions the hypochromia was slight, the appearance indicative of retrogression, and histologically they are nontuberculoid, little more than residual.

Nonelevated macules.—There remains a group of ten lesions without definite elevation and with a considerable range of color change. In one case (No. 44) there were two or three inactive-looking small macules of which one, removed completely, shows around follicles and more superficially a few foci of infiltration with small tuberculoid centers. The biopsy scar as seen three months later is shown in Fig. 30 to demonstrate a peculiar pale halo that had developed around it. Another fairly similar though somewhat larger (Fig. 27, CASE 45) shows only subtuberculoid foci. Two (CASES 46 and 47) were moderately pale; the specimens from the former (Fig. 28) shows slight tuberculoid, but the one from the latter (Fig. 29) shows less than Case 45. The lesions of the last six cases (Nos. 48 to 53) were recorded as only slightly or faintly hypochromic; one of the more marked shows a trace of tuberculoid change, but the other five are more or less residual.

NERVE ENLARGEMENT

Involvement of the cutaneous nerves as a feature of neuraltype leprosy has been emphasized especially by workers at the Calcutta clinic, where great enlargement, often with caseation and occasionally cold abscess formation, is often seen, especially among their abundant major tuberculoid cases. Such enlargement is seldom encountered in Ceylon, and we do not know that an abscess has ever been diagnosed or operated upon here. However, we encountered one patient with enlargement of the great auricular so marked that it must have contained a large focus of caseation.

In the re-examination of our cases the nerves were noted particularly. The data collected (most of it by the junior authors) are indicated in Table 2. In the examinations it was the purpose to go thoroughly over each patient, but note was made only of the enlarged nerves found. We believe that no seriously affected ones escaped notice, though it cannot be said that all that had any

Case No.	Duration	Great auricular			Supra-orbital	Supra-	clavicular		Dorsal ulnar		Dorsal radial	Arm, any	nerves	Feet and legs,	any nerves		Inirapatellars	Ē	Cimars		Peroneal
		R	L	R	L	R	L	R	L	·R	L	R	L	R	L	R	L	R		R	L
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degree of enlargement were found, or, for that matter, that all which were palpated were necessarily abnormal.

The findings cannot be discussed in detail. A thorough study of the matter would involve detailed correlation of enlarged nerves with skin lesions, which we cannot make. The skin lesions which are most productive of palpable nerve enlargement—those on the hands, forearms, feet and legs—are often the most retrogressed and indefinite in cases of the chronicity of most of those dealt with, and so of least interest for the present study. Such lesions often disappear without trace, so that sometimes it is impossible to say whether an enlarged nerve on the hand, for example, resulted from a macule or arose independently of visible skin changes, which there is reason to believe sometimes happens.

Among the cases studied very few had nerves large enough to be evidently caseous, though it is realized that there is often slight necrosis with only moderate enlargement. One patient was brought from the country because of the obviously caseous nerves leading from the single (retrogressive) major tuberculoid macule (Fig. 6); this nerve specimen, a particularly interesting one, is the only one in our material.

In general, Table 2 shows that the frequency and degree of nerve enlargement decreases with decrease of severity of the leprides, though there are considerable variations. There was little of this involvement in three of the major tuberculoid cases, which is perhaps unusual but in keeping with the superficial nature of the skin lesions present. Duration of the disease may, on the whole, have had something to do with the frequency and extent of such changes, and of course the number and distribution of the lesions has a great deal to do with it. This matter of nerve enlargement, we would suggest, deserves careful investigation in different parts of the world.

BACTERIOLOGICALLY POSITIVE CASES

A surprising feature of our cases is the number of them that gave bacteriologically positive smears. It is not unexpected, if the examinations are thorough enough, to find an occasional positive case in any large group of neural ones, but the proportion of 15 out of 53, or 28 percent, is extraordinarily high. The findings are given in Table 3. In all instances but one the bacilli were very few.

The usual experience is that when ordinary neural cases

become bacteriologically positive it is in the nose, but among this group only two were positive in that site alone. Seven were positive only in the earlobes, though no evident lesions were present there, and five were positive in macules. Of the last group, one had been found bacteriologically positive on admission to the asylum three years before, in spite of which there was no indication whatever of the transformation to the cutaneous type.

Case No.	Duration years	Class of lesion biopsied	Positive regions
16	2	Minor, irregular	Nose, right side
42	?	Simple, inactive?	Nose, left side
41	6	Simple, inactive	Nose, both sides a earlobe, left
12	4	Minor, irregular	Earlobes, both
19	8	Minor, irregular	Earlobe, left
28	1	Papulate	Earlobe, left
32	10	Simple, active b	Earlobe, left
37	2	Simple, active?	Earlobes, both
40	11	Simple, inactive?	Earlobe, left
53	3	Simple, residual?	Earlobe, right
2	6	Major, slight	Macules biopsied, two
15	10	Minor, irregular	Macule biopsied. (See notes)
32	25	Simple, active b	Macules on back
45	2	Simple, flat	Macules on back, two
51	6	Simple (ex C?) c	Macule, near biopsy, scar; nose, right

TABLE 3.—Bacteriological findings in the positive cases.

"Ulcer of septum, right side, erythema, left. Bacilli very numerous.

^bThese cases were the active ones with extremely extensive lesions.

cThis patient had been in the Hendala asylum for three years as a supposed cutaneous-type case.

Positive findings in leprides are not uncommon in major tuberculoid lesions in a reaction state, but they are decidedly uncommon in the lesser kinds of leprides. One of our cases with positive lesions was slight major tuberculoid, not in reaction, one was minor, and three were simple. The latter included one of the two with especially extensive lesions, another (Case 45) was febrile at the time, though the lesions (Fig. 27) had undergone no discernable change; and in the third (Case 32) the positive lesion seemed entirely inactive. In the minor tuberculoid case (Case 15) the lesion concerned, and others, had a slightly shiny appearance, rather peculiar for the leprides, and faint erythema possibly a reaction condition. On the other hand a reaction case (No. 7, Fig. 8) that from its appearance was expected to

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6, 2

be positive was not. The two positive lesions in the major tuberculoid case (No. 2, Fig. 3) were rebiopsied, but no histological peculiarity was found.

We cannot say—except to suggest a general parallel with the surprising frequency of activation of lesions seen in this group why so many of these cases should have been positive, and particularly why so many should have had positive macules. The clinical appearance, the subsequent course and the histological findings do not afford any indication that they were undergoing transformation to the cutaneous type.

CHANGES DURING THE OBSERVATION PERIOD

On the whole the present group of cases is, as has been said, unusual as regards changes that occurred within a short time after the surgical interference—and in some instances evidently as a result of it. On the Madras patients no similar changes were observed within two months or noted afterward by the clinicians concerned. Most of the Cebu cases were under continued clinical observation after they were biopsied, but showed nothing peculiar or in any way untoward. If any of the Chinese cases in Swatow showed any such changes no note was made of the fact by those who dealt with them. Of the Hendala patients, on the other hand, no less than twenty were noted to have undergone change in May, three months after the first biopsies.

Of these twenty cases two may be disregarded because the changes were retrogressive—decrease in the papulate condition shown in Fig. 16 (Case 22) and almost complete disappearance of follicular prominence ("hypertrophy") that had been present in several macules in another case (No. 29). To be mentioned briefly are eight cases in which the change consisted of a pale halo around the biopsy scar. Of most interest are the ten cases in which there was either more or less widespread activation of the leprotic condition as a whole or progression of the biopsied lesion at the site of the scar.

Activation of the disease.—Evidence that there had been more or less general activation of the disease, suggesting a condition of mild lepra reaction, was seen in seven cases. All of these were minor tuberculoid; no such changes were found in any case here classified as major tuberculoid or simple.

Case 10: Several lesions, first described as apparently retrogressive minor tuberculoid, were all definitely active in May, frankly raised and slightly erythematous at the margins; new ones were appearing. One of the old ones was somewhat suggestive of lepromatous change, an appearance that is not uncommon to leprides in a reaction state. A second specimen from the biopsied lesion (chest, Fig. 8), which shared the general exacerbation, shows somewhat more tuberculoid change than the first one, but especially more undifferentiated cellular infiltration. Smears were all negative, but a very few bacilli were found in sections of the second specimen, not from the first.

Case 12: The minor tuberculoid lesions in this case, apparently inactive at first, had become more infiltrated and had progressed somewhat (Fig. 13). The changes in a second specimen seem more active than in the first one; no bacilli found. The smear from one ear was found positive at this time.

Case 14: At first the large minor tuberculoid plaques were scurfy (Fig. 14); in May that condition was absent and there was, in parts, considerably more infiltration and probably more erythema. Smears all negative. Not rebiopsied.

Case 15: The several apparently active macules became more so, and especially more infiltrated. Some of them, including the one biopsied (found bacteriologically positive near the scar—all other smears negative) were somewhat shiny, suggesting subsiding reaction. Not rebiopsied.

Case 16: This patient had influenza three or four weeks before the second examination, and several of the lesions had become somewhat more infiltrated and active in appearance. Nose positive. Not rebiopsied.

Case 21: This strikingly papulate minor tuberculoid case showed reddening in limited portions of the lesions on the chest and scapula (Fig. 15), including the region of the first biopsy scar. However, a second specimen from there showed no increase in the pathological process. Smears and sections negative.

Case 23: The biopsied lesion showed no sign of activation (rather the contrary), but a papulate condition of the face was decidedly more marked (Fig. 17). In February there were evidences of application of trichloracetic acid there. We know of no evidence that that method of treatment stimulates such lesions.

In view of experience elsewhere the proportion of the entire group that these seven reactivated patients represent is too large for the findings to be a mere matter of chance. There was nothing to suggest that the surgical interference had had anything to do with the changes in them. The patients being old residents in the asylum, it is unlikely that anything to do with food or treatment can be invoked. This throws us back upon climatic influence. The first examinations were made early in the hot, dry season. The re-examinations were made just after the beginning of the southwest monsoon, when the climatic conditions had changed radically, with sunless days, torrential rains and sharp decline of temperature, especially at night.

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Local extension of lesions.—Extension of the biopsied lesions confined to the region of the scar was found in three cases. Though no such development is known to have occurred in patients elsewhere that were biopsied for this study, in the absence of any other likely explanation it can only be supposed that these changes were due to the surgical intervention and the subsequent healing process.

The best demonstration, though not the best actual example, of this change is shown in Figs. 19 and 10 (Case 11). The raised minor tuberculoid ring had become more prominent, and the process had spread beside the scar. A small recent lichenoid lesion a short distance above it had also increased. and a small patch on the face had become more reddish and infiltrated.

Activation and extension beyond the scar also occurred in a noninfiltrated, evidently inactive macule in Case 47. When re-examined there was a definitely infiltrated, faintly erythematous marginal zone along the whole upper edge from which the specimen had been taken (Fig. 29), and a zone of more pronounced infiltration surrounded the scar and extended 0.5 cm. beyond it. That the scar originally extended beyond the lesion is proved by the fact that the first specimen contains normal skin; the pathological changes are little more than residual. A second specimen, which included some of the scar, shows slight large round-cell accumulation in and above the plexus layer, with an apparent tendency to epithelioid change.

More marked progression had occurred in Case 13, around both of two biopsy scars. The lesions, on the shoulder and loin, had become much more erythematous and three bright red infiltrated areas had appeared on the face, obviously a reaction condition. On the shoulder, in an area measuring 2 x 3 cm. around the scar, the infiltration had increased markedly, with corresponding coarsening of the surface and erythema (Fig. 11). Sections show that the original specimen included normal skin, but in May, as seen in the photograph, the lesion had extended to the end of the scar. Beyond that, in skin that otherwise appeared normal, there were two concentric half-circles of color change. The first one, fairly well defined and 0.5 cm. or more wide, was darker than the lesion itself. The outer circle was an equally wide zone of slight hypochromia-a "pale halo." In the loin lesion there was an area 1.5 x 3 cm. of much increased infiltration and erythema around the scar, which was inside and parallel to the edge (Fig. 12). The affected areas in both lesions were rebiopsied. The specimen from the one on the shoulder shows a much more active, more cellular and less tuberculoid condition than the first one. That from the other area was removed from across the first scar and shows more keloidal change than leprotic condition.

Pale halos around scars.—The production of a pale halo around a biopsy scar, with no suggestion of infiltration, is another development that has not previously been observed in this work. Besides the case mentioned above two others (Nos. 39 and 41) had rather narrow halos barely perceptible in the photographs but persisting for months. In two cases (Nos. 17 and 33) were similar areas that, when seen a few months later by the junior authors, had increased decidedly. No further change is known to have occurred. A fairly conspicuous area occurred in Case 29 around the scar resulting from the complete removal of a small macule on the arm, which makes it seem unlikely that this change has any necessary significance as regards leprosy.

It may be, however, that in some instances apparently similar conditions may be of significance. In Case 41, the one with the highly positive nose, a small (1 cm.) pale area developed just above a biopsy scar. It seemed to be independent of the scar, but after a further three months the condition was noted (D.S. de S.) as an extension of the lesion around the scar. The lesion originally had seemed quite inactive, and microscopically it was of much retrogressed appearance, neither active nor residual with only subtuberculoid changes.

Two conspicuous halos were biopsied. One, shown in Fig. 30 (Case 44) was wider than usual (1.5 cm.), completely encircling a scar resulting from the removal of a very small, retrogressive macule. The specimen from the halo shows nothing to explain the color change unless that was related to an extremely slight accumulation of mononuclear cells around the plexus vessels. The other biopsied halo, a large ($4 \ge 5.5$ cm.) faint one in Case 20, also occurred after the complete removal of a small lesion. The specimen from it shows nothing more than the other one. Neither could be called definitely abnormal. In this second case another pale area was found surrounding a scar caused by application of some caustic substance to a small lesion.

These persistent pale zones or "halos" were interesting in that they had not been observed before in the course of this work, and naturally caused speculation as to their significance. The possibility was entertained that they might indicate the beginning of extension of the leprotic process beyond the original focus as a result of the surgical interference, but no evidence to support that idea has been seen.

SUMMARY AND DISCUSSION

In Ceylon 53 cases were selected for study as presenting lesions representative of the leprides as they occur in that country. On the whole they differed from those in other regions that have been studied in the present investigation as regards, among other things, the greater average age, the longer duration of the disease, and in some instances the extent of the lesions. Observations were made in two periods, in February and May, with a three-month interval.

Major tuberculoid cases were relatively few and none was found in the full-blown active stage or in reaction. Minor tuber-

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culoid cases of one form or another were fairly numerous but many of them, also, were of the lesser grades or more or less retrogressive. In a few of them, however, on the other hand, the lesions were in or recently had been in a state of reaction, which permitted comparison of the histological changes in that condition and in the ordinary more indolent and the retrogressive phases.

As in the preceding studies, all of the nonresidual lesions that could be classed clinically as tuberculoid of any form or degree showed histological changes of that nature. The variations of degree of these changes with the clinical features of the lesions serve to corroborate further the conclusion that there are neither clinical nor histological grounds for holding that the kind of lesion which is generally recognized as tuberculoid (the "major" variety) differs in its essential character from the less marked forms. Variations as regards the location of the principal lesionfoci in the depth of the skin go hand in hand with certain variations in appearance. Furthermore, the evident differences of tendency to penetrate deeply seem clearly to determine clinical differences as regards gross involvement of the regional nerves. It seems but reasonable to extend this factor to differences in sensory changes in the macules.

Nearly one-half of the cases biopsied had lesser (clinically "simple") lesions, varying in condition from frankly active to obviously residual. Though in some cases these lesions were few and small, in others they were numerous and extremely extensive, the influences to which they had been subjected having failed to halt the course of the disease over many years. With many of the nonerythematous, noninfiltrated lesions of this class the usual difficulty was encountered in estimating, in the absence of erythema, whether or not they were indolently active, or quiescent, or retrogressive. Hypochromia, which was in some cases relatively marked, is in general and within limits a useful indicator, particularly insofar as diminution of it occurs in retrogressive and residual lesions, but histological findings show it to be sometimes quite misleading; recovery of color is often delayed long after the pathological process has subsided apparently completely. Between the extremes of the obviously active and obviously retrogressed or residual simple lesions, precise criteria for evaluating by inspection the degree of the pathological changes that exist and the clinical prognosis are still to be established. Considerable variations were found in the pathological

condition of the lesions which were assigned to each subgroup of this variety.

With regard to the still moot question of the nature of the tissue changes in well-established macules of this ordinary simple class, none of them that seemed definitely active failed to show tuberculoid changes of slight degree, with at least a few foci of that nature in every section. Though intermediate lesions varied, this type of change was absent in the specimens from the more definitely residual ones. This series, like previous ones, affords no support to the widely held opinion that the essential change in the flat macules is banal chronic inflammation; to the contrary, it corroborates previous findings that the tuberculoid condition, of some degree, is the essential feature of all active leprides of whatever degree.

Special attention was paid to the condition of the cutaneous nerves, but the data permit only the observation that nerve enlargement does not occur constantly in major tuberculoid cases as they are seen in Ceylon, and that in general the frequency and degree of such nerve conditions decrease with decreased severity of the skin lesions. The number and distribution of the skin lesions obviously influences such changes, and the duration of the disease may do so.

Unexpectedly many of these cases (15, or 28 percent), were found bacteriologically positive in slight degree, in ordinary smears made during the second observation period. Only two of them were positive in the nose alone, though that is generally supposed to be the site most commonly positive in neural cases. There is no indication whatever that these positive cases were undergoing change to the cutaneous type.

Besides the cases in an apparently reaction state seen in February, certain others were observed in May. At that time no less than seven cases showed evidence of activation of the disease. All of them, it is interesting to note, were of the minor tuberculoid variety. These observations set this Ceylon group as a whole apart from the others dealt with in the present studies. No explanation for this activation is evident unless it lies with the climatic conditions, the only variable of which we are aware. The first observations were made early in the hot season, the later ones immediately after the beginning of the southwest monsoon.

In three other cases there was extension of the biopsied lesions, but only in the region of the scar. Though no such

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development is known to have occurred in other cases involved in this study, it seems probable that the local disturbance resulting from the surgical intervention was responsible for the stimulation of the lesion process. Another development seen in several cases and noted previously was the formation of a halo of hypopigmentation around the biopsy scar outside of the lesion area. This change, obviously due to the intervention, seems to have no significance as regards leprosy.

Appreciation is to be expressed for the interest taken in this work by Dr. R. Briercliffe, at that time Director of Medical and Sanitary Services, and by Dr. F. R. E. Bartholemeuz, Medical Superintendent of the Hendala Leper Asylum, and his staff, who participated actively in the collection of material there; also of the cooperation of members of the surgical and photographic departments of the Colombo General Hospital, and of the pathological department of the Medical College. Special thanks are due Mr. M. A. Mendis, photographer of the General Hospital, who under most difficult conditions, took many of the pictures used here.

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DESCRIPTION OF PLATES

(Concerning the photographic quality of some of these pictures, see footnote on p. 203.)

PLATE 17

FIGS. 1 and 2. Extensive, multiple, slowly spreading, annular tuberculoid lesions of great chronicity, but of moderate degree as regards elevation and of relatively superficial location in the skin and consequently without much involvement of the superficial nerves. Case 1.

FIG. 3. Major tuberculoid lesions of rather slight degree and unusually superficial location. The marginal zone of the large one is very narrow, irregular and broken, more "minor" than "major" in character (cf. Fig. 9), but frankly major lesions were present elsewhere and the more recent small ones here shown have the characteristics of that variety, becoming modified as they grow older and begin to spread. Case 2.

FIG. 4. Extensive major tuberculoid leprides of varying degrees. The most prominent one is at A (biopsied); while similarly prominent parts of a very extensive area are seen at B. The rest of the latter, and most of the one indicated by C, are markedly retrogressed. Case 4.

FIG. 5. Hand and forearm of a patient with many, widely distributed, much retrogressed major tuberculoid lesions. High on the arm are some relatively conspicuous ones, but lower down they are progressively more resolved and the residual changes of those that had existed on the hands are indistinguishable in the photograph. Polyneuritic changes (atrophy and contracture). Case 5.

FIG. 6. Partly retrogressed solitary major tuberculoid lesion on the forearm (A) with conspicuously enlarged nerves leading from it (B). Case 6. (No such enlarged nerves found in any other case of this Ceylon group.)

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PLATE 17

FIG. 7. A typical minor tuberculoid case in reaction at the time of biopsy (three months before the rather unsatisfactory photograph was taken). In the larger lesions the outer edge of the infiltrated marginal zone diffused off whereas the inner edge was more abrupt, but smears were negative and sections (two specimens, February and May, from point indicated by scar) show no suggestion of lepromatous change. Case 7.

FIG. 8. Minor tuberculoid lesion on chest with unusual, uniform bandlike marginal zone (cf. China cases). Histologically rather slight tuberculoid, mostly deep seated, in keeping with the fairly smooth surface. Somewhat more active in appearance three months later, with somewhat more marked microscopic changes. Case 10.

FIGS. 9 and 10. A small minor tuberculoid lesion, very irregular of surface and outline, histologically marked superficially but also with considerable deep change. Progression after three months (Fig. 10), with notable extension around the biopsy scar and increase in the papulate follicular ("lichenoid") focus above. Case 11.

FIGS. 11 and 12. Larger lesions of similar nature, on shoulder and loin. In both photographs (taken in May) extension of the process and the biopsy scars is evident. Case 13. WADE, DE SIMON, FERNANDO]



PLATE 18

FIG. 13. Another example of irregular minor tuberculoid lesions. Progression in this case, also, occurred in the three-month observation period. Case 12.

- FIG. 14. Extensive lesions of the same general kind, in a case of long duration; the lesions shown had been extending slowly for years. Case 14.

FIG. 15. Minor tuberculoid lesion with marked tendency to papulation on a moderately infiltrated, relatively slightly raised based—a modification of the "irregular-surfaced" form due to the wide separation of the superficial lesion-foci. Case 21.

FIG. 16. Similar to the preceding case in location and nature except that the papulations were smaller and less conspicuous. Some retrogression of them occurred in the interval before the photograph was taken. Case 22.

FIG. 17. An essentially similar condition on the face, the underlying infiltration not evident, as is frequently the case with lesions of the face. Case 23.

FIG. 18. Case intermediate between the more ordinary minor tuberculoid ones and those with papulation but without underlying infiltration observable clinically. Such infiltration actually present in the larger lesions here, but obviously retrogressed. Case 24.

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PLATE 19

FIG. 19. Retrogressive minor tuberculoid macules on the arm, subsiding uniformly without the focal development that determined the papulation in the following cases. Case 25.

FIG. 20. "Frustrate" papulate macules---otherwise simple ones in which retrogression is irregular, papulations develop, irregular extension occurs, and new ones appear to undergo similarly inconclusive progress. Case 27.

FIG. 21. Multiple macules with fine papulations (almost indistinguishable in the original photograph) which were of the follicular kind prominence of the follicles with a tendency to hyperkeratosis. Microscopically there is a notable concentration of slight-degree tuberculoid changes around the follicle. Case 30.

FIG. 22. A bilobed area on the buttock containing shiny atrophic areas, undoubtedly resulting from previous papulations, in a case in which such lesions seemed to originate in the lichenoid follicular condition. Case 50.

FIGS. 23 and 24. A patient, disease of 25 years duration, showing multiple simple macules of extreme extension and still progressing, with hyperemia on the edges in places. Anteriorly the mid-zone of the chest is as yet unaffected but the neck, most of the face, and much of the arms have been covered by the process, hypochromia (actually less marked than it seems) persisting remarkably over much of these areas. Posteriorly there are only a few small areas that have not been invaded. Histologically (site of specimen indicated) slight tuberculoid and infiltrative changes, superficial and apparently active. Case 31.

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Plate 20

FIG. 25. A large simple macule on the back with slight elevation at the edge (the maximum degree for "simple" lesions) and rather conspicuous coarsening of the grain of the skin. Very slight tuberculoid changes found. Case 36.

FIG. 26. Lesions (A, B) similar to the preceding but less marked, possibly retrogressive. Case 37.

FIG. 27. Two small, flat simple macules on the back, the specimen from one of which (X, taken by mistake in rather than across the edge) shows only subtuberculoid foci. The large area on the arm is quite similar to Fig. 19 in appearance. In May, when photographed, the patient was febrile and a skin smear was positive. Case 45.

FIG. 28. Moderately pale, flat simple macules, specimens from which (X) show slight tuberculoid changes. Case 46.

FIG. 29. Similar lesions, some with central recovery of color. Specimen (X) shows only slight changes, subtuberculoid. The lesion had become reactivated locally when the photograph was taken, having extended around and beyond the scar. Case 47.

FIG. 30. An unusually large slightly pale "halo" around the scar resulting from the complete removal of a very small, inactive-looking simple macule that showed only slight histological changes. Case 44. WADE, DE SIMON, FERNANDO]

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