

## NECROTIZING REACTIONS IN LEPROMATOUS LEPROSY A CLINICAL AND HISTOLOGIC STUDY

M. F. R. WATERS, M.A., M.B., M.R.C.P.<sup>1</sup>

*The Research Unit, Sungei Buloh Leprosarium  
Selangor, Malaya*

AND D. S. RIDLEY, B.Sc., M.D.

*The Hospital for Tropical Diseases  
London, England*

The VIth International Congress of Leprosy divided reactions in lepromatous leprosy into two main groups: "lepra reaction" and erythema nodosum leprosum (ENL). Attention was drawn also to the Lucio phenomenon, but no decision was made as to whether it should form a subgroup or be considered as a third group of its own (19). The classification was left unmodified by the VIIth International Congress, but it was realized (3) that so much confusion existed clinically and terminologically that a separate Panel on Lepra Reaction would be required for the VIIIth Congress. The accounts of the differences between "lepra reaction" and ENL by Wolcott (23) and Jopling (7) define the classification of mild and moderate forms of lepromatous reaction. Severe reactions characterized by vesicles, pustules or necrosis remain a source of considerable difficulty. Thus recent papers have attributed such reactions to the Lucio phenomenon (11), bullous reaction (8), ENL (1,4), cutaneous allergic vasculitis (9), and lepra reaction modified by keratosis blenorrhagica (5). We have been impressed also by the different diagnoses made in our patients in severe reaction by visiting leprologists. In an attempt, therefore, to aid in the understanding of severe necrotizing reactions, we present a clinical and histologic account of six cases.

### MATERIALS AND METHODS

The six were from a total of approximately 100 lepromatous patients selected for special study by the Research Unit from routine admissions to Sungei Buloh Leprosarium between January 1959 and March 1962. All patients in the series except in Case 2 were born in Malaya, five being Chinese and one (Case 3) a Malay. Four had received no specific leprosy treatment, but in Case 5 the patient had been given two, and in Case 3 sixteen injections of dapsone before admission. The results of general clinical, urine, and chest x-ray examinations were normal.

Serial smears, taken from both ear lobes and from four active skin sites, were examined in the Research Unit, except in Case 2, in which smears (both ear lobes and one active skin site) were examined in the leprosarium's routine laboratory. The bacterial index (average of six sites) was assessed on Ridley's logarithmic scale (14), and the percentage (average of six sites) of bacilli staining uniformly by the Ziehl-Neelsen method was also recorded (22); hereafter these are referred to as "solid" bacilli as opposed to "fragmented" or "granular" forms.

Biopsy specimens were taken from two active skin sites (from one site only in Case 2). Subsequent serial biopsies were made from specimens taken from adjoining

<sup>1</sup>Present address: The National Institute for Medical Research, London, England.

sites<sup>(14)</sup>. One or more specimens of reacting lesions were taken in five cases (Nos. 2, 3, 4, 5 and 6). They were fixed in modified dilute Susa stain, and transferred to 70 per cent alcohol for dispatch by air to the Hospital for Tropical Diseases, London. Paraffin sections were stained by hematoxylin-eosin, Mallory's connective tissue stain, and phosphotungstic acid-hematoxylin. They were stained also for acid-fast bacilli.

All patients were tested with Dharmendra type lepromin, read at 2, 3, 7, 14, 21 and 28 days, and five were also retested at least once during their reactions. Tuberculin tests were carried out using 1 TU of RT 23 and read at 48 and 72 hours. Patients not reacting (readings of less than 5 mm.) were retested with 20 TU.

As a result of all investigations patients were classified by the system of Ridley and Jopling<sup>(17)</sup>.

Routine chemotherapy was by intramuscular dapsone twice weekly, 200 mgm. for 12 injections, and thereafter 300 mgm. The main treatment of the reactions was prednisolone given orally, except for two short periods in 1960 when prednisone was supplied. Ancillary treatment included intramuscular stibophen, intravenous calcium levulinate with vitamin B<sub>1</sub>, antihistamines, chloroquine, antibiotics, and also corticotrophin.

#### CASE HISTORIES

CASE 1 (No. 13576).—Male, 23 years, admitted May 1959. Lesions were stated to have developed on his thighs about two years before admission. On examination he was found to have widespread symmetric lepromatous infiltration. The skin of the face and ears was succulent. Macules were present on the trunk. There were atypical (borderline) lesions on both thighs, and there was slight symmetric nerve thickening.

The bacterial index was 5.0 and 53 per cent of bacilli were solid-staining. The biopsy index was 2.35, and the histologic classification was pure lepromatous (LL). The lepromin test was negative. The tuberculin test was negative with 1 TU, but positive (32 mm.) with 20 TU. Hemoglobin was 11.8 gm. per cent. White cell and differential counts were normal.

After six months' treatment with dapsone there was evidence of slight but definite clinical improvement. The biopsy index had fallen to 1.5. The bacterial index was 4.8, with 6 per cent solid bacilli. The lepromin test remained negative, but the tuberculin test (1 TU) showed a gross reaction with ulceration. Chest x-ray examination remained negative.

During December 1959, deep red lesions of ENL were first noted, occurring principally on the limbs. From then on there were periodic eruptions of ENL nodules, associated with fever and malaise. The patient failed to respond to antihistamines and chloroquine, and prednisolone was therefore commenced in January 1960. At first a dose of 5 mgm. every 8 hours suppressed the reaction. But the periodic exacerbations became more severe, and at the end of March 1960, for no obvious reason, the character of the reaction lesions changed. They became more superficial, smaller (about 1 cm. in diameter), and lighter red in color; small vesicles developed in the centers of many about 24 to 48 hours after they had appeared. Sometimes the vesicles sub-



FIG. 1. Case 1. Back, showing numerous small papules and vesicles, and one larger lesion with a necrotic center.

sided at the same time as the surrounding erythema and induration. Usually, however, they became pustular, and some went on to necrosis, forming round ulcers penetrating deep into the dermis. These healed rapidly, leaving round, thin, hypopigmented scars about 5 to 8 mm. in diameter. Rarely, typical ENL lesions still occurred. The dose of prednisolone was raised to 10 mgm. every six hours, and occasional injections of 25 units of corticotrophin were given, but the reaction was only imperfectly suppressed (Fig. 1).

For the next two years there was little change in the precarious control of the reaction. No lowering of the prednisolone dosage proved possible, either following intercurrent courses of stibophen and calcium levulinate, by resting from dapsone, or by changing from dapsone to thiambutosine (Ciba 1906) (from November 1960 to January 1962). Nevertheless, throughout this time the lepromatous infiltration continued to decrease, and the biopsy and bacterial indices continued to fall. The steroid therapy resulted in a "Cushingoid appearance" and slight loss of weight and the patient also had recurrent widespread tinea, which responded to griseofulvin. In March 1962 the tuberculin skin test again gave a gross reaction, and about this time slight weakness of dorsiflexion of the left foot was noticed.

In June 1962 the patient appeared very well, with little residual lepromatous infiltration. He was rested from dapsone, and a successful attempt was made progressively to reduce the prednisolone. The drug was stopped in September 1962, and since then he has remained well and treatment with dapsone has been recommenced.

CASE 2 (No. 13664).—Male, 12 years, admitted August 1959. He was stated to have had leprosy for two years. On examination he had diffuse lepromatous infiltration; small nodules, 3-5 mm. in diameter were present on all four limbs, with fewer on the back but very many on the buttocks. The ears were enlarged, and the nerves slightly and symmetrically thickened. The bacterial index (average of three sites) was 5.3 and the biopsy index 4.2. No record was made of the bacterial morphology. The histologic classification was pure lepromatous (LL). The lepromin test was negative, and the tuberculin (1 TU) reading was positive.

Treatment with dapsone was commenced in September 1959, and for the next ten months he made slow but steady progress with flattening of most of the nodules. In July 1960, however, he had a sudden onset of fever, headache and pain below the left ear. His temperature was 103° F (39.4° C). There was multiple lymphadenopathy and mild right ulnar neuritis. The white blood count was raised, with a polymorphonuclear leucocytosis. He was treated with stibophen, calcium levulinate and short courses of prednisolone, and the dapsone was stopped. Nevertheless, after two months he remained in severe reaction, with high fever, persistent lymphadenopathy, mild conjunctivitis and loss of weight. The limbs were covered with superficial erythematous, slightly thickened lesions, 1 to 2 cm. in diameter, most of which had central vesicles or pustules. Many of the latter were ulcerating, especially on the lower limbs. The ulcers were circular in outline and varied in diameter from about 5 mm. to 2 cm. As his condition was steadily deteriorating, he was treated with prednisolone in high dosage, 10 mgm. every six hours being necessary to control the reaction (Figs. 2 and 3). The ulcers healed, leaving thin, round, hypopigmented scars.

From October 1960 to June 1962 precarious control of the reaction was maintained, and any attempt to lower the dosage of prednisolone resulted in fever, a fresh eruption of skin lesions, and on two occasions, mild orchitis. There was a persistent polymorphonuclear leucocytosis. Cultures of pus obtained from two nonulcerated pustules were sterile and a Ziehl-Neelsen-stained smear of the pus showed some fragmented acid-fast bacilli. The long continued steroid therapy resulted in development of "Cushingoid" features in the patient.

As resting from specific antileprosy treatment did not appear to lessen the reaction, active treatment was recommenced in October 1960 with thiambutosine, which was continued until November 1961 before changing back to dapsone. Throughout this time the lepromatous in-



FIG. 2. Case 2. Face. There is a necrotic lesion on the left cheek, and an edematous, vesiculating lesion of the left earlobe.

filtration decreased slowly but steadily. After two years' treatment the bacterial index had fallen to 4.3, and the biopsy index to 1.0.

During the second half of 1962 the patient's reaction began to settle, the dose of prednisolone was steadily reduced, and recently he was successfully taken off steroid treatment.

CASE 3 (No. 13703).—Male, 35 years, admitted September 1959. Three years earlier he had developed numbness of his right knee, and then redness of his right leg. One year before admission he noticed redness of his nose, face and ears. Shortly before admission he had received 16 dapsonc injections. On examination there was widespread infiltration, with numerous symmetric, hyperpigmented, thickened, lep-



FIG. 3. Case 2. Showing a number of scars from previous lesions present above the right elbow, as well as numerous fresh reaction plaques and papules.

romatous macules, a few small nodules on the face and extremities and a hyperpigmented plaque on the right leg. The right lateral popliteal nerve was considerably enlarged. Other nerves showed slight, symmetric thickening. Sensation was impaired over the right leg and there was slight edema of the right ankle. The bacterial index was 5.0 and, probably as a result of the previous sulfone treatment, only 5 per cent of bacilli were solid-staining. The biopsy index was 1.8. The histologic classification was pure lepromatous (LL). The lepromin and tuberculin tests were negative.

At the beginning of November 1959, just before treatment with dapsone was commenced, he was noticed to have one or two superficial ENL papules. Courses of stibophen and calcium levulinate failed to control the reaction, which became steadily worse, with high fever, malaise and numerous skin lesions. The latter appeared typical of ENL, frequently being of the large, deep variety, about 3 to 4 cm. in diameter, dark red, hot and edematous. Some lesions broke down to give pustules and ulcers, which healed leaving thin round scars.

Prednisolone was commenced in December 1959, but moderate dosage failed to control the reaction. By April 1960 he was receiving



FIG. 4. Case 3. Vesicles and ulcers of the right ankle.

10 mgm. every six hours; yet the eruption was still incompletely suppressed. About the end of July 1960, the skin lesions changed in character. Many were small, 5 to 8 mm. in diameter, with central vesicles and pustules, and resembled the superficial necrotizing lesions of Cases 1 and 2 (Fig. 4). Sometimes, however, large, superficial, red, raised areas developed, each with an outer erythematous ring encircling an edematous paler area containing tiny pustules in the center.

Since then control of the reaction has always been precarious. Sometimes the skin lesions have caused considerable pain and occasionally the vesicles contained extravasated blood. Two episodes of right lateral popliteal neuritis resulted in some weakness of dorsiflexion. There has been a persistent polymorphonuclear leucocytosis. The L.E. phenomenon, tested in May 1962, was negative. Concurrent courses of stibophen, rest periods from chemotherapy, and changing from dapsone to thiambutosine have not lessened his steroid requirements. He has received up to 50 mgm. prednisolone a day with occasional short courses of corticotrophin in addition. The patient now has marked "Cushingoid" features. Since March 1962 he has complained of lumbar backache. X-ray examination of the spine revealed osteoporosis, with compression of the bodies of vertebrae T 11 and 12, and L 1, 2 and 3. Although his underlying leprosy condition has shown continued slow clinical, histologic and bacteriologic improvement, for the past year he has had episodes of mild edema of the ankles, and he now has persistent albuminuria. It appears possible that he has developed amyloid disease and his prognosis is considered uncertain.

CASE 4 (No. 14360).—Male, 16 years, admitted August 1961. One year earlier he had noticed a patch on his right leg, and subsequently patches on the face and body. For seven to eight months his right leg had been numb. He had received some tablets from a private dispensary before being diagnosed and sent to the leprosarium.

On examination, there was infiltration and thickening of the face, ears, nipples, forearms and legs. Hyperpigmented macules were present on the trunk, face, arms and thighs. The nerves were slightly thickened symmetrically and appreciation of pin prick was impaired over the right knee and both legs and feet. The axillary, pectoral and supra-trochlear lymph glands were palpable. The bacterial index was 4.8 with 20 per cent solid bacilli (range 8 to 39 per cent). The lepromin test was negative, and the tuberculin test positive. The biopsy index was 1.6. The histologic classification was pure lepromatous (LL) and the hemoglobin 13.6 gm. per cent.

The patient claimed that he noticed one or two red spots on his skin just before commencing treatment on 9 October 1961. Eight days later he developed fever and a rash. His temperature was 103°F (39.7°). He had multiple lymphadenopathy. Skin lesions were scattered over much of the body, but especially on the face, chest, left buttock and

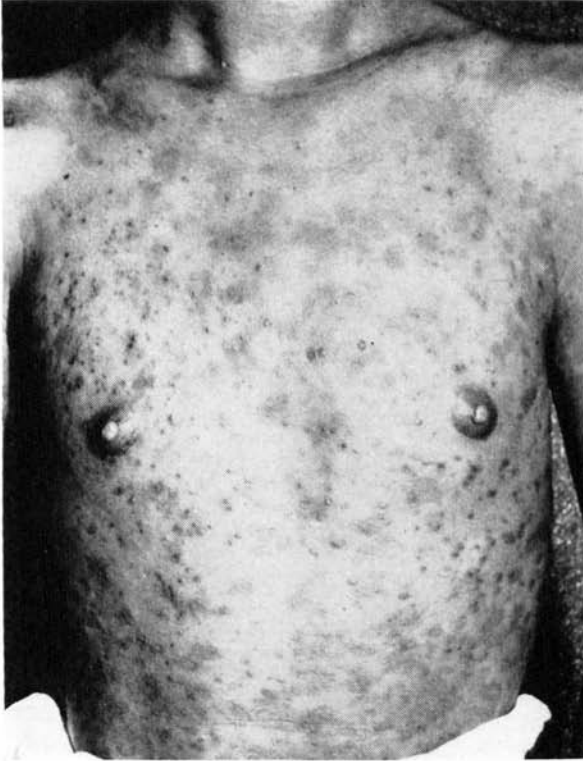


FIG. 5. Case 4. Tiny hemorrhagic papules are present on the sides of the chest, best seen in the right pectoral region.

thighs. On the upper part of the chest were erythematous plaques about 1.5 cm. in diameter, only slightly raised, which blanched on pressure. Elsewhere the lesions consisted of small macules and papules about 5 mm. in diameter. Some of the papules developed into vesicles, and especially on the sides of the chest extravasation of blood had taken place into the vesicles and into the base of some of the papules (Fig. 5).

Smears taken on 21 October gave a bacterial index of 4.7, with only 13 per cent solid bacilli (range 8 to 20 per cent). By October 30, the hemoglobin had fallen to 10.9 gm. per cent, and the patient had developed a mild polymorphonuclear leucocytosis. Treatment with prednisolone, 5 mgm. every six hours, was commenced on 20 October. The fever rapidly declined and the skin lesions began to subside. At first a maintenance dose of 5 mgm. every eight hours was sufficient, but in January 1962 the fever and papules recurred. In addition, the hyperpigmented area on the right leg developed into a red, round, hot, swollen reaction plaque, which tended to ulcerate, and there was edema of the right ankle. It proved necessary to raise the prednisolone dose to a total of 40 mgm. a day, and short courses of corticotrophin were also given.

Treatment with dapsone was continued. The lepromatous infiltration steadily improved and after six months the bacterial index had



fallen to 4.0, with 5 per cent of solid bacilli (range 0 to 9 per cent). Attempts to wean the patient from prednisolone have, however, so far (April 1963) proved unsuccessful.

CASE 5 (No. 14317).—Female, 18 years, admitted June 1961. More than a year earlier red patches had appeared on her arms and legs, and about six months before admission small nodules which “felt numb” had appeared on her arms. She had received two injections of dapsone before admission. On examination there was widespread infiltration of the arms and legs, with raised erythematous, hyperpigmented skin. An atypical annular lesion, anesthetic inside its margin, was present in the left scapular region. The face and ears were little affected. The radial nerves were slightly enlarged, the left more than the right, and the left ulnar and lateral popliteal nerves were also slightly thickened. The bacterial index was 1.4. The histologic classification was borderline-lepromatous (BL), near to pure lepromatous. The lepromin test was negative and the tuberculin test (1 TU) positive. Clinically and histologically the patient was considered to be in the transitional stage from borderline to pure lepromatous leprosy and already to have approached very close to the latter. The lesions on the limbs were nearly symmetric and lepromatous in appearance, with bacterial densities comparable to those of lepromatous leprosy. Although both ears appeared normal clinically, they were bacteriologically moderately positive.

Treatment with dapsone, and with ditophal (Etisul), 5 cc. by inunction three times a week, was commenced in July 1961. During the first three months progress was good, some flattening of the lesions occurred, and the bacterial index fell to 3.7 with only 3 per cent solid bacilli. During the fourth month, however, the patient developed left axillary lymphadenopathy, and four days later bright red papules appeared on the left thigh and the right arm. Most were 1 to 1.5 cm. in diameter and many had a small central pustule. One lesion, however, measuring approximately 3 cm. in diameter, had a large vesicle with a dark necrotic center. Daily injections of stibophen failed to suppress the reaction, fever developed and the large lesion ulcerated. A week later further lesions appeared. Some were small red papules, others were large irregular plaques, 2 to 3 cm. or more in diameter, which vesiculated and ulcerated (Fig. 6). Some of the vesicles contained a little extravasated blood. The test for the L.E. phenomenon was negative.

Prednisolone was commenced in November 1961, and it was found that 10 mgm. every six hours were required to control the fever and ulceration. Initial attempts to lower this dose proved unsuccessful and for a time in February 1962 corticotrophin was given daily in addition to the prednisolone. Treatment with dapsone and ditophal was not, however, interrupted; resolution of the lepromatous lesions continued



FIG. 6. Case 5 (borderline-lepromatous). Vesiculating and necrotizing lesions of the forearms, similar to those shown in Figs. 1 and 2.

and the bacterial index at six months had fallen to 3.5. During May and June the reaction appeared better controlled. An attempt was made once again steadily to reduce the dose of prednisolone and eventually, in October 1962, it proved possible to stop steroid treatment altogether. The patient had a small rebound reaction and several crops of spots during the next two months, but she has remained well in 1963. Moreover, the 18 months' biopsy, made in January 1963, showed a change in histologic classification to borderline leprosy (BB).

CASE 6 (No. 13871).—Male, 17 years, admitted February 1960. Two years earlier he had noticed several red spots on the abdomen and subsequently redness of both hands and feet. Redness of his face and ears developed two months before admission. On examination there was widespread, symmetric, mild lepromatous infiltration, involving most of the body but most marked on the face and limbs. Some lesions, especially on the face, were erythematous and those on the limbs were hyperpigmented. There was slight symmetric nerve thickening and both feet were anesthetic to cotton wool. Small soft lymph glands were palpable in the neck and the axillary and supratrochlear regions. Smears gave a bacterial index of 4.0 and the percentage of solid staining bacilli was 19 (range 6 to 30). The biopsy index was 2.7. The histologic classification was borderline-lepromatous (BL) in one biopsy

and pure lepromatous (LL) in the other. The lepromin test was negative and the tuberculin test was positive. Clinically the patient was considered to have pure lepromatous leprosy, although the biopsy suggested that tissue resistance had not yet been completely lost.

Shortly after admission a few red spots were noticed on his face and slight desquamation on his legs, forearms and ear lobes. Despite the mild reaction, treatment was commenced in March 1960, with dapsone and Macrocydon. Three days later the reaction became worse. Small, red, warm papules about 5 mm. in diameter appeared on the face, arms, legs, chest, and abdomen. The temperature was 102°F (38.9°C). The spleen was tipped and the lymph glands showed further enlargement. He was treated with prednisolone, a total of 30 mgm. daily being required to suppress the fever and eruption. An early attempt to lower the dose was unsuccessful and from April to September he received 25 to 40 mgm. prednisolone daily, with occasional injections of corticotrophin. His face became rounded. The reaction was kept under rather precarious control, although a steady decrease in the lepromatous infiltration occurred. From the end of September onward, however, the reaction slowly settled. The dose of steroid was steadily lowered and eventually prednisolone was stopped, under corticotrophin cover, at the end of March 1961. The twelve months' biopsy, also taken in March 1961, gave a biopsy index of 0.6; moreover there was a change of histologic classification to borderline leprosy (BB). Since then there has been no recurrence of the reaction and the patient has made such good progress that few residual lesions are now visible.

#### HISTOLOGY

Histologically the five cases for which reaction biopsies were available could be classified in two groups before treatment, by some features of the reacting lesions, and by the outcome of the reaction.

The first group comprised Cases 2, 3 and 4, for which seven biopsies of reacting lesions were available, apart from routine biopsies of leprosy lesions. All showed the characteristic histology of pure lepromatous leprosy, before treatment and during and after the reaction. In all the reacting lesions there were quite large masses of lepromatous granuloma. In Cases 2 and 3 bacilli were relatively few; some were present in globi, but elsewhere were scanty and most were granular. In Case 4 bacilli were numerous in all parts of the granuloma and there were some solid-staining forms, but few large globi.

The reaction itself took place in the dermis, mainly in the superficial zone (Fig. 7). The subcutaneous tissue was seriously involved in only two out of the seven reaction biopsies. Edema was profuse. In the early stages of a reaction it was located in and around the granuloma; later it increased and was more readily apparent in the superficial zone of the dermis (Fig. 8). Infiltration with polymorphonuclear leucocytes was considerable, with some focalization at the center of many of the granulomatous masses and diffuse spread through other

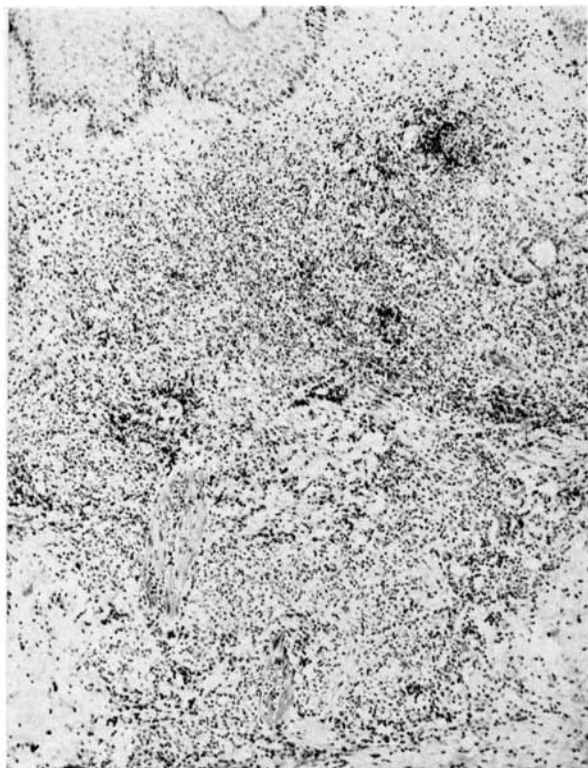


FIG. 7. Case 3. Extensive polymorphonuclear leucocyte infiltration in the superficial zone of the dermis.

parts of the granuloma. There was much karyorrhexis of polymorphonuclear leucocytes. Histiocytes infiltrated diffusely through the dermis. Lymphocytes were not numerous in most lesions, and plasma cells were very scanty. The endothelium of capillaries was swollen. Sometimes there was capillary necrosis with fibrinoid patches in or around the affected vessels (Fig. 9). Case 4 differed somewhat from the other two; there was much lepromatous infiltration of small blood vessels but no necrosis in them. There was a large patch of coagulation necrosis in one part of the granuloma, but no fibrinoid. Biopsies of reacting lesions at a later stage of the reaction were available from two cases; besides the more profuse edema already referred to, a micro-abscess had developed in Case 3, and in Case 2 there was liquefaction necrosis with ulceration. Plasma cells were present in appreciable numbers. Otherwise the later lesions were essentially similar to those observed in earlier biopsies. In many biopsies the epidermis was acanthotic.

The second histologic group, consisting of Cases 5 and 6, showed some evidence of a borderline tendency in the pretreatment biopsies, and were classified as borderline-lepromatous (<sup>17</sup>). In Case 5 there was a suggestion, but no more than that, of epithelioid cell development. The nerves were cuffed by lymphocytes. In Case 6, in one of two biopsies, some epithelioid cell tendency was seen and more lymphocytes

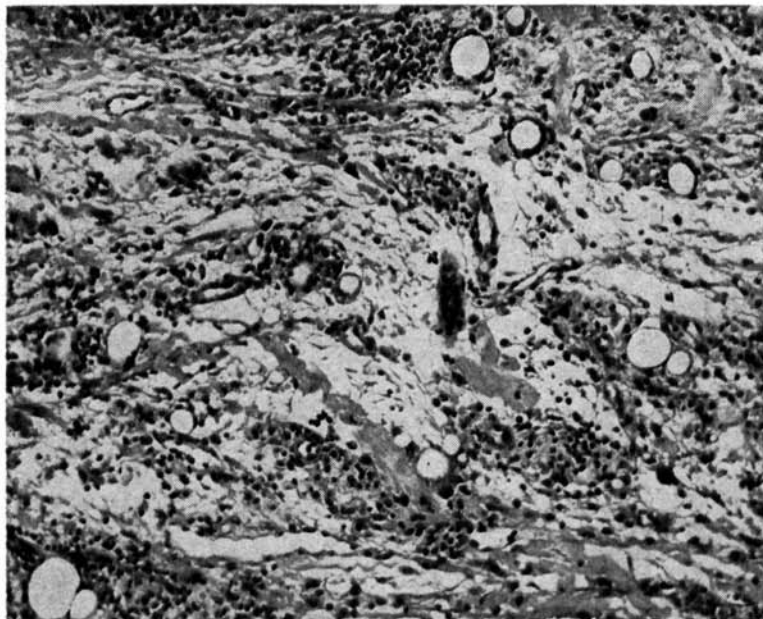


FIG. 8. Case 2. Copious edema in the superficial zone of the dermis. Late stage of reaction.

than are usually found in a leproma. The other biopsy specimen, however, appeared to be purely lepromatous. Bacilli were numerous in all.

In the pretreatment biopsies potential reactivity was already indicated by the degree of edema in and around the granuloma, although the patients were not at that time in reaction. Later biopsies of reacting lesions showed a reaction pattern similar to that of the first group. It differed, however, in the absence of capillary necrosis or fibrinoid change and in the rapid transformation into fibroblasts of the histiocytes that infiltrated the dermis.

During and after the reaction there was a progressive increase in the borderline features of both cases, histologically, though not clinically, and a diminution in the number of bacilli. At the last biopsy Case 5 showed definite epithelioid cells with early development of giant cells. Case 6 showed some tuberculoid features.

#### DISCUSSION

It is clear from clinical reports and from our own cases that reactions occur in lepromatous leprosy which do not fully conform to any of the accepted classifications. They may be characterized by vesiculation, pustule formation, hemorrhage or necrosis. The latter features are associated with some degree of capillary necrosis. Furthermore pustulation and ulceration commonly occur in severe "lepra reaction" and in "progressive reaction" as defined by Cochrane (<sup>2</sup>). Vesiculation and necrosis are considered part of the Lucio phenomenon (<sup>10</sup>). In

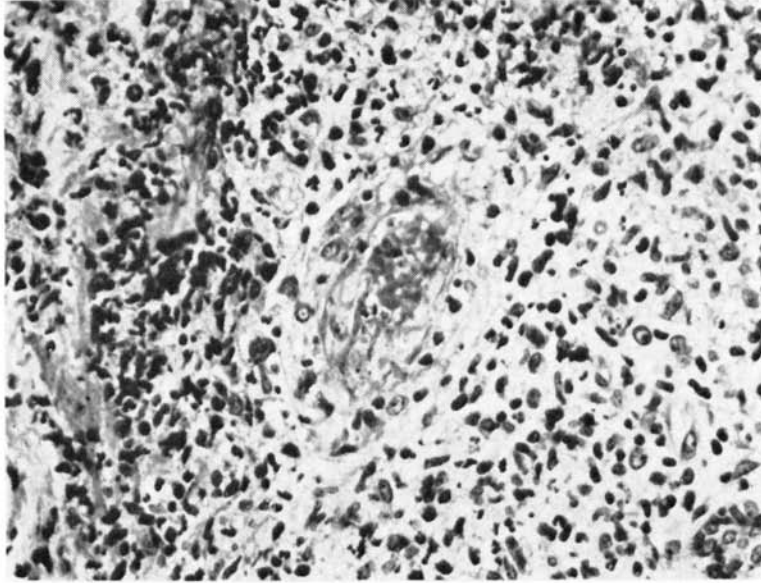


FIG. 9. Case 3. Capillary necrosis in the center of the area of reaction.

severe ENI, suppuration with or without ulceration has been reported by many authors including Murata (<sup>12</sup>), Wolcott (<sup>23</sup>), Pepler, *et al.* (<sup>13</sup>), Shuttleworth (<sup>18</sup>), Jopling (<sup>7</sup>), and Ridley (<sup>16</sup>). In any attempt, therefore, to classify such reactions, it is essential to consider all available evidence, including that of the outcome.

At the onset of their reactions none of our patients showed spread of lepromatous infiltration or nodulation, or increase in bacillary density, but rather the opposite. Moreover, because of the successful steroid therapy, it was possible to continue antileprosy treatment in every case. During the period of observation, despite the severe reactions, the lepromatous infiltration continued to decrease and the biopsy and bacterial indices to fall steadily. We do not consider, therefore, that "lepra reaction" enters the differential diagnosis.

The distinction from the Lucio phenomenon would at first appear less definite. Recently, however, Harter and Kim (<sup>4</sup>) have suggested fourteen points to be considered in the diagnosis of this type of reaction. Not all fourteen are applicable to our patients, as we did not take nasal smears, and the high doses of steroids given were sufficient both to affect the severity and scarring of the lesions, and possibly to suppress eye complications. Nevertheless, none of our six patients had pure, primary, diffuse, lepromatous leprosy. In all cases the lesions were painful and in five they occurred on the face. The five tested with lepromin during their reactions were Medina-Ramirez-negative. (Lapapí (<sup>10</sup>) records that in the Lucio phenomenon, a positive result will still be obtained at 48 hours, even with bacillary lepromin.) In none

was the reaction helped by antileprosy treatment. Nerve lesions occurred in two of the six patients. At the time of the onset of the reactions the proportion of solid bacilli was below 20 per cent in all the five cases for which results were available, including the two untreated cases, and in three it was below 6 per cent. The condition of the bacilli therefore corresponded to that before the onset of ENL (<sup>16</sup>). For these reasons we do not believe that our patients were showing the Lucio phenomenon.

Study of our six cases has revealed that they fall into two groups which differ essentially in their outcome. The first group, consisting of Cases 1, 2, 3 and 4, had undoubted lepromatous leprosy (LL), clinically, bacteriologically, histologically, and in the rate of response to treatment. This group, which from general experience is without doubt the larger, belongs to ENL with respect to the following features: leprosy classification, the relatively small number of bacilli in the reaction lesions and their granularity at the time of onset, the predominant location of reactions outside the leprosy lesions, the large number of polymorphonuclears, the relationship to specific chemotherapy, the response to steroids, and the prognostic effect of the reaction. Moreover, three of the four had typical ENL lesions at the same time as their necrotizing reactions or immediately before their onset.

Histologically they differ from the common forms of ENL in their severity and the extensiveness of the reacting lesions, the copious edema, the more diffuse spread of the infiltrate, the superficial situation of the reaction and the vascular necrosis. The affected vessels are much smaller than those in the Lucio phenomenon and the whole reaction is more superficial. Not all the points of difference from ENL are apparent in every biopsy, and they are differences of degree rather than of fundamentals. For the reasons already mentioned we are content to include this group of cases in the ENL phenomenon. In this we are in agreement with Harter and Kim (<sup>4</sup>), whose 11 cases appear essentially similar to our Cases 1, 2 and 3 if allowance is made for differences in treatment.

The two cases comprising the second group, Nos. 5 and 6, are unique in our experience. Histologically (and Case 5 clinically and bacteriologically), these patients were not quite pure lepromatous (LL), yet nearer than the average borderline-lepromatous (BL) case. The reaction itself was very similar to that of the first group, and did not resemble the pseudoexacerbation of de Souza Lima and Rath de Souza (<sup>20</sup>) or the acute infiltration reaction of Tajiri (<sup>21</sup>). But the outcome of the reaction histologically was a very marked shift toward the tuberculoid type of leprosy, and clinically and bacteriologically there was a beneficial effect on the course of the infection. It is concluded that cases very close to lepromatous (LL) may undergo what

is in essence a reversal reaction, but which presents the appearance of a severe type of ENL. It is possible that failure to distinguish this type of reaction may have been responsible for some earlier favorable reports on the prognosis of ENL. The distinction can be made only by accurate histologic classification of the type of leprosy.

If our conclusions are correct, viz., that some unusually complicated reactions are essentially similar to ENL, while other almost indistinguishable reactions have quite different significance, they emphasize that there is a limited number of ways in which the tissues can react, and that appearances alone in reactions are not a good basis for their classification.

All our patients received prednisolone and we are in general uncertain of the outcome in the absence of steroid therapy. But patients showing small hemorrhages similar to those seen in Case 4, have in our experience a very serious prognosis. Such reactions are rare. Molesworth (personal communication) recalls having seen only three during 11 years at Sungei Buloh Leprosarium. Nevertheless, during 1959 we observed two of these patients. Both had lepromatous leprosy and both began reacting before commencing treatment, possibly as a result of vaccination. In both, the reaction consisted of crops of many tiny papules, in the majority of which tiny petechiae or hemorrhages appeared. Both had high intermittent fever for several weeks and both died suddenly, slight jaundice being noticed in the last 24 hours of life. Postmortem examination was unhelpful, beyond confirming the presence of widespread lepromatous leprosy. The morphology of the bacilli in the skin was not noted in one case, but in the other the bacilli were almost entirely fragmented (<sup>14</sup>) (Cases 2 and 3). One of the two patients received no corticosteroids and the other was only given doses insufficient to suppress the reaction. Therefore, when the present patient developed similar lesions, he was immediately given prednisolone in high dosage, and it was with relief that we observed rapid suppression of the reaction.

The treatment of these severe reactions remains a source of considerable anxiety. Although it is possible that the continuation of antileprosy treatment enhanced the reaction in some cases, undoubtedly the very severe evolution of the reaction in Case 2 was not prevented by stopping dapsone at its onset. Moreover, changing from dapsone to thiambutosine did not affect the severity of the reactions, and short rest periods from active therapy failed to permit any decrease in the doses of prednisolone required for control. In our experience hormone therapy is alone able to suppress the fever and prevent successive eruptions of skin lesions. It may even be lifesaving in some cases. When, however, long-term corticosteroid treatment proves essential, we agree with Jopling and Cochrane (<sup>8</sup>) that full antileprosy treatment should also be continued under the steroid cover. Prolonged rest periods from



specific chemotherapy can but allow viable bacilli to multiply and the total bacillary load to rise. The risk of further leprosy complications is increased, the total treatment time is lengthened, and it is possible that the total period of reaction is also prolonged. Our finding that patients may be successfully weaned from prednisolone after as long as three years of treatment supports the long-term use of corticosteroid drugs in very carefully selected patients.

#### SUMMARY

The VIth International Congress of Leprosy divided reactions in lepromatous leprosy into "lepra reaction" and erythema nodosum leprosum; the status of the Lucio phenomenon was left undecided. Little difficulty is experienced in classifying the milder reactions, but severe reactions, especially those showing pustulation and necrosis, remain a source of confusion. A clinical and histologic account is given of six such patients, including four lepromatous, and two lepromatous with slight borderline features, who developed severe reactions, five of them with pustulation and ulceration.

It is thought that the reactions in the pure lepromatous cases were a severe form of ENL. The other two patients underwent a histologic change in classification toward tuberculoid as their reaction progressed. The two groups presented with almost identical reactions which were, however, different in nature.

The second type of reaction had a beneficial effect on the course of infection. The prognosis of the first type probably would have been poor but for treatment. Corticosteroids enabled antileprosy treatment to be maintained in all cases with good results. It is possible, however, that one patient has developed amyloid disease.

#### RESUMEN

El VI Congreso Internacional de Leprología dividió las reacciones de la lepra lepromatosa en "reacción lepra" y eritema nudoso leproso; el estado del fenómeno Lucio fue dejado indeciso. Poca dificultad se encuentra en clasificar las reacciones medianas, pero las reacciones severas, especialmente aquellas que muestran pústulas y necrosis, siguen siendo una fuente de confusión. Se relatan hallazgos clínicos e histológicos en 6 pacientes de ese tipo, incluyendo cuatro lepromatosos, y dos lepromatosos con rasgos ligeramente limítrofes (borderline) que han desarrollado reacciones severas, cinco de ellas con pústulas y ulceraciones.

Se ha pensado que las reacciones en los casos puros lepromatosos fueron formas severas de ENL. Los otros dos pacientes evolucionaron en su clasificación con cambios histológicos hacia tuberculóide al progresar sus reacciones. Los dos grupos se presentaron con casi idénticas reacciones, las cuales, de cualquier manera, eran diferentes en naturaleza.

El segundo tipo de reacción tuvo un efecto benéfico en el curso de la infección. El pronóstico del primer tipo probablemente hubiera sido pobre, sino fuera por el tratamiento. Los corticoesteroides permitieron mantener el tratamiento antileproso en todos los casos, con buen resultado. Es posible, de cualquier manera, que uno de los pacientes haya desarrollado la enfermedad amiloidea.

## RESUMÉ

Lors du Sixième Congrès International de Léprologie, les réactions de la lèpre lépromateuse avaient été classées en "réaction lépreuse" et "érythème nouveaux lépreux"; la place exacte du phénomène de Lucio n'avait pas été décidée. S'il n'est guère difficile de classer les réactions légères, les réactions sévères, et particulièrement celles accompagnées de pustules et de phénomènes nécrotiques, demeurent par contre une source de confusion. Sont ici rapportées les données cliniques et histologiques ayant trait à six malades, quatre lépromateux, et deux lépromateux présentant des caractéristiques légères de border-line, qui avaient développé des réactions graves, avec formation de pustules et ulcérations chez cinq d'entre eux.

Les auteurs considèrent que les réactions survenues dans les cas lépromateux purs étaient une forme sévère d'erythema nodosum leprosum. Les deux autres malades ont subi au cours de la réaction une transformation histologique vers le type tuberculoïde. Les deux groupes ont présenté des réactions presque identiques, mais différentes toutefois quant à leur nature.

Le second type de réaction a eu un effet bénéfique sur le cours de l'infection. Le pronostic du premier type aurait probablement été mauvais sans traitement. Les corticostéroïdes ont permis dans tous les cas de poursuivre le traitement anti-lépreux avec de bons résultats. Il est cependant possible qu'un des malades ait développé une amyloïdose.

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