

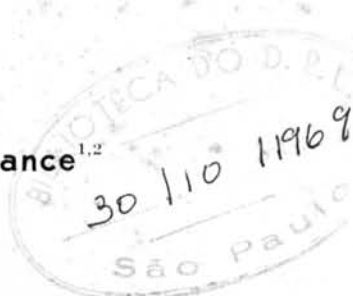
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The Histoid Leproma Its Characteristics and Significance^{1,2}

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The first published reference to the existence of histoid lesions in leprosy was a report by Wade on "histoid leproma," read in the author's absence by Rees, at a conference held by the International Academy of Pathologists in London (⁸). Even before this meeting, however, Wade had demonstrated sections of this unique form of leprotic lesion to several leprologists and subsequently distributed sets of his sections to some of them working in different countries.

The publication of his authoritative article in 1963 (⁹), in which was included clinical material describing what he termed the "histoid variety of lepromatous type," invited widespread attention to this subject.

Melamed *et al.* (²) in 1964, reported a case previously rendered negative by sul-

fone drugs, which developed eruptive relapsing lesions of the borderline type (interpolar and dimorphic), some of them with lepromatous histoid histology.

Jonquières (¹) found histoid lesions in one relapsed and five "nonrelapsed" cases. He considered the histoid leproma of Wade as a young leproma in a special reactional field.

Sanchez (⁷), after reviewing the files of the Instituto de Dermatología de Guadalajara (Mexico) for the period from 1948 to 1956, in which more than 5,000 slides from cases of leprosy were screened, found seven of them that fulfilled the requirements for the diagnosis of lepromatous leprosy resembling "nodular subepidermal fibrosis."

An important contribution to the study of the histoid leproma was made in an article by Pettit *et al.* (³) in 1966, which stated that the histology of the lesions of four patients in whom they had established direct proof for the existence of DDS-resistant strains of *Mycobacterium leprae* had much in common with histoid lesions, thereby linking this variety of leproma in some way with drug resistance.

In 1966 Price and Fitzherbert (⁴) reported on 10 patients with lepromatous leprosy

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of histoid nature in Ethiopia. The characteristic features of these patients included gross nodulations, mainly on the face, deep involvement of the dermis, and resistance to treatment by sulfones and thiambutosine. However, only one out of three cases biopsied corresponded histologically to Wade's histoid leproma.

The purposes of the study here reported were as follows: (1) identification of different forms and stages of the histoid leproma by clinical, pathologic, and bacteriologic methods, and (2) investigation of any possible bearing that this unique leprotic lesion may have on such problems as drug resistance, classification, and the natural course of leprosy.

METHODS AND MATERIALS

The methods of study used were as follows: (1) Follow-up of individual histoid lesions and other concomitant manifestations of leprosy in the same patients. (2) Ensurance of good anamnesis and review of hospital records since first admission. (3) Investigation of patients' past and current antileprosy treatment. (4) Supplementary laboratory examinations. The first phase of the investigation lasted from June 1965 through May 1968.

Sources of material. In the course of a general examination of all 524 patients residing at the Eversley Childs Sanitarium, Cebu, Philippines, in June 1965, it was found that eight of them presented nodular lesions that were later confirmed clinically and histologically as histoid lesions. Of these eight patients, six were readmitted relapsed cases, and two were newly admitted patients who had not received antileprosy treatment previously and therefore had had no opportunity to relapse. Not one among the rest of the patients in the sanitarium showed this distinctive lesion. Thereafter, without neglect of the follow-up reexamination of the latter, the two former groups were considered as the best sources of material, and were therefore more intensively studied.

It became apparent soon after the study was started that the clinical features of the histoid lepromas and associated leprotic lesions differed markedly between patients

who had relapsed after sulfone treatment and those whose leprosy had not so relapsed; the longer these patients were followed-up, the more apparent the differences became. For this reason, the results in the two groups are here reported separately.

RELAPSED CASES

Of 72 relapsed patients readmitted to the Eversley Childs Sanitarium, 28 or 39 per cent developed histoid lesions after relapse. Twenty among these (71%) had been rendered clinically and bacteriologically negative (disease arrested) and eight were improved to the extent that they neglected their treatment thereafter. The ages of those who developed histoid lepromata ranged from 26 to 56 years, the average being 38 years; there were 16 males and 12 females among them. Among those who had been disease-arrested, the "negative" period lasted from two to 12 years, the average being seven years. The observation period during which their histoid and other leprotic lesions had been followed up, ranged from four months to three years, with an average of two years.

It is to be emphasized that these figures do not give any indication as to the relapse rate or the frequency of histoid lesions among them, since it had not been possible to include the number of those who had not relapsed in the estimation.

The availability of these readmitted cases with their complete records has permitted a continuing study of the relapsing lesions as compared with those before negativity.

Case Reports

Case reports were prepared for each of the 28 cases in this group, but in order to save space, only seven of the more representative ones are given.

Case 1. (A.C.) Male, age 32 years. About three years after the patient became bacteriologically and clinically negative following sulfone treatment, a crop of numerous small cutaneous nodules about the size of rice grains appeared on each forearm, in addition to moderate lepromatous infiltration on the face and ears according to the patient. When he was readmitted and ex-

aminated four months later, many cutaneous nodules ranging in size from pin-head to 2 cm. in diameter, of generalized distribution, were found; some subcutaneous nodules were also pointed out by the patient.

Two cutaneous nodules removed for biopsy, one of four months' duration (Path. No. S-268-A-66, Abalos) and another eight months old (Path. No. S-278-B-66, Abalos) were diagnosed as lepromatous leprosy, histoid lesion, while another still older nodule (Path. No. S-439-67, Ortigoza) was also diagnosed as leprosy, LL, histoid lesion.

In the course of the follow-up, it was observed that some of the smaller nodules had increased in size, and that others disappeared while new crops arose, usually only a few at a time, not accompanied by constitutional symptoms. Thus nodules of

various sizes and duration were present in different parts of the body at the same time.

On biopsy, a subcutaneous nodule on the right arm was found to be composed of two attached nodules (Path. No. S-42-A & B-67, Ortigoza). One was diagnosed as lepromatous, histoid lesion, and the other as lepromatous, LL.

At an examination on 5 November 1967, the newer, younger lesions had become much more numerous and had increased in size in a spectacular manner; the patient had first noticed these two months previously (Fig. 1). Subsequent examinations showed a gradual enlargement of most of the nodules without any increase in their number. The duration of the observation period was three years.



FIG. 1. Case 1 (A.C.) Numerous histoid nodules of different durations and morphology; a typical clinical picture in relapsed cases.

Case 3. (R.E.) Female, age 38 years. Negative for 10 years following sulfone treatment, she had suffered a relapse. A year later numerous small pinkish nodules appeared on the forearms, wrists, legs, and elbows. Most of these disappeared in about three months, after treatment with a few injections of "Duo-strep," but a few remained on both wrists and the dorsa of the hands. At the first examination (23 Jan. 1967), in addition to slight infiltration on the face, seven deep-seated cutaneous nodules, each measuring about 1 cm. across, firmly adherent to the keratotic skin, were present on the left wrist and lower forearm; one of these with a duration of about one year was biopsied (Path. No. S-73-B-67, Ortigoza) and diagnosed as leprosy, lepromatous, histoid lesion.

There was also a pea-size, reddish, slightly oval, almost pedunculated shiny nodule on the right loin (Fig. 2). This lesion was said to be the only remaining one of a new crop that had appeared after my first examination. It was biopsied (Path. No. S-73-A-

67, Ortigoza) and a diagnosis was made of leprosy, lepromatous, histoid lesion BL. A larger and older one from the left wrist (Path. No. S-73-B-67, Ortigoza) was similarly diagnosed; the duration of this nodule was approximately six months. The remaining keratotic nodules on the left forearm had persisted.

On 21 August 1967, a subcutaneous nodule on the back of the right hand was biopsied (Path. No. S-351-67); Dr. Ortigoza's report revealed that the lesion consisted of two nodules, a smaller encapsulated one showing primarily an infiltrate composed of elongated histiocytes and a larger one not encapsulated. The latter nodule contained an admixture of spindle-shaped and polygonal histiocytes with abundant eosinophilic cytoplasm, and small numbers of poorly formed globi, as well as occasional histiocytes with foamy cytoplasm. Both were diagnosed as histoid lesions.

On 6 November 1967 a solitary red papule that had developed on the left loin was



FIG. 2. Case 3 (R.E.). Two young isolated histoid nodules.



FIG. 3. Case 6 (A.Ni.). "Soft" histoid nodules showing tendency to grouping and fusing together (photo taken 23 June 1965).

found to have doubled in size in three months. In addition, several small typical histoid nodules had appeared just above and below the biopsy scar on the right loin. These new nodules probably appeared at the same time as others, which disappeared after eight injections of streptomycin. The duration of observation was one and a half years. The period of negativity was 10 years.

Case 6. (A.Ni.) Male, age 36 years. Readmitted as a relapsed case after having been "negative" for three years during which he had received irregular sulfone treatment. The presenting lesions at the first examination, on 2 June 1965, consisted of slight lepromatous infiltration limited to the face and ears; on the abdomen, back, arms, and left wrist were several soft pinkish nodular lesions clinically recognizable as "soft" histoid lepromata as described elsewhere in this article. One of the larger nodules on the abdomen (Fig. 3), and another belonging to a group on the left forearm, each of about five months' duration (Path. No. S-57-65 and S-63-65, Abalos) were given the histologic diagnosis

of lepromatous leprosy, histoid lesion. Most of the nodules, both large and small, tended to group and fuse to form irregular plaques.

At an examination two years and one month after the initial one, the papules and nodules on the chest and abdomen, except for a few small flattened ones, had disappeared (Fig. 4).

Less than two months later the nodular lesions reappeared, this time tending to fuse to form larger nodule-studded plaques and streaks. At this stage the clinical diagnosis of borderline leprosy was unavoidable; it was confirmed by two biopsies (Path. No. S-408-67 and S-420-67, Abalos), each diagnosed as borderline lepromatous leprosy.

Again the lesions gradually subsided, although not completely, until the last month of the study (10 May 1968), seven months after the last attack, when the most severe eruption occurred. Fusion of the papules and nodules was more nearly complete; the irregular plaques were larger and more pinkish, and extensive areas of the trunk

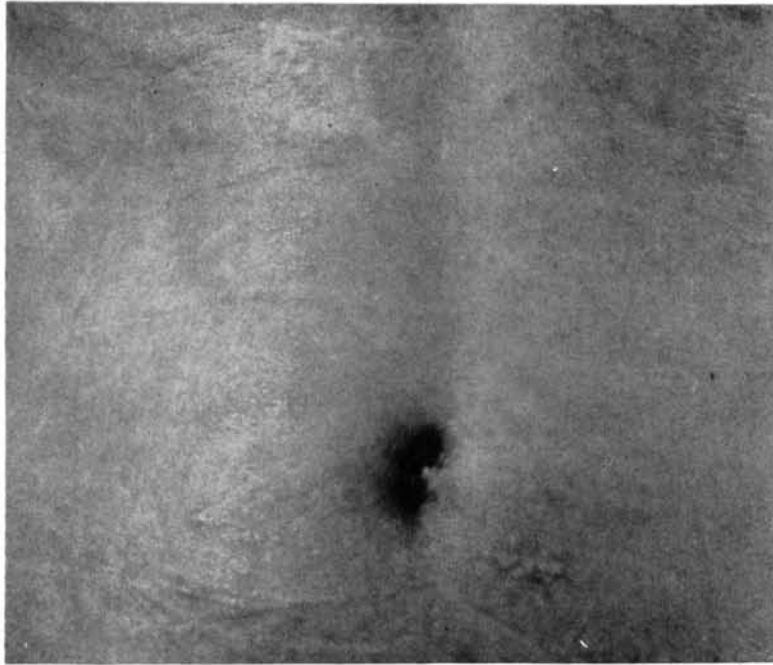


FIG. 4. Case 6 (A.Ni). Marked subsidence of the histoid lesions. Same patient as in Figure 3 (photo taken 2 August 1967).

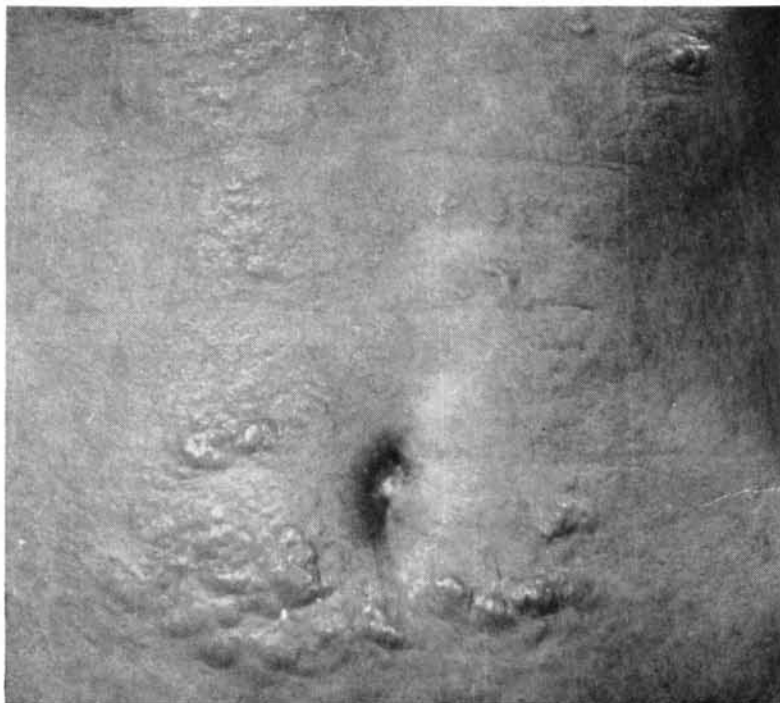


FIG. 5. Case 6 (A.Ni). Sudden appearance of diffuse and nodule-studded plaques and a few "soft" nodules. Grouped nodules forming irregular plaques had been diagnosed histologically as "borderline-lepromatous leprosy (histoid lesion)." Same patient as in Figures 3 and 4 (photo taken 6 June 1968).

were irregularly thickened and flushed (Fig. 5).

During all this period, covering three years, the patient was receiving adequate doses of DDS.

Case 9. (A. No.) Male, age 38 years. After being "negative" for three years following sulfone treatment, he relapsed. At an examination made five years after this event, there was a widespread distribution of numerous reddish nodules ranging in size from pin-head to 1 cm. across, most numerous on the back, chest, abdomen and extremities. They were shiny, succulent in appearance and hemispheric in shape. Some of the larger ones showed depressed crusted centers, forming cup-like tops bordered by thickened over-hanging lips. There were also long-standing nodules covered with keratotic skin and several so-called "pads" of Wade located over the bony structures of the elbows and ankles.

Of particular interest in this patient was that, under direct observation, the smaller nodules were found to increase and decrease in numbers at some of the successive examinations only a few weeks apart. The new lesions appeared at different special regions of the body each time, such as the chest, left arm, one side of the loins or both sides.

There was the usual diffuse infiltration on the face, more marked all over the ears, which were studded with split-pea size papules. Biopsy of one of these nodules (Path. No. S-130-67, Ortigoza) was diagnosed as lepromatous leprosy, histoid lesion. The patient refused biopsy of typical histoid nodules in various stages of development all over the body, but remained until the end of the study as a good example of what has been considered by Wade as a "histoid sub-variety of the lepromatous type." The duration of observation period was three years.

Case 10. (B.L.) Female, age 39 years. This patient was admitted as a slight lepromatous case in 1945, but did not receive sulfone treatment till 1949. She became negative in 1960, relapsed in 1963, and was readmitted in 1965 after about three years without evidence of leprosy. She was examined on 20 June 1966, and found to have

slight diffuse infiltration on the face and elsewhere. A few old histoid lesions were found on the extremities. Two subcutaneous nodules were found on the right forearm (Fig. 6), one of which (Path. No. S-350-67, Ortigoza) was reported to show two types of infiltration as follows: (1) spindle shaped histiocytes occurring in small discrete nodules, in one of which small foci of epithelioid cells and giant cells are seen; (2) masses of histiocytes adjacent to these small nodular infiltrates with abundant eosinophilic cytoplasm, insinuating between mature collagen bundles. This infiltrate was divided into ill-defined lobules by mature collagen. No globi or Virchow cells were seen.

Several hard cutaneous nodules covered with keratotic skin were present on the right elbow. One of the latter, of at least three years' duration, was biopsied (Path. No. S-272-66, Abalos) and reported as a typical histoid lesion of lepromatous leprosy with flattened epidermis and a pseudocapsule. At a subsequent reexamination a few subcutaneous nodules still remained. The duration of the observation period was one and a half years.

Case 12. (F. Pa.) Male, age 45 years. The patient received private treatment with weekly injections of Promin for six months in 1964, after which the lesions improved, followed by DDS treatment for one year with further improvement. The following year, however, small papules and nodules appeared in various parts of the body with some infiltration on the face. While some of these disappeared, others took their place. Six months later rapidly enlarging nodules reappeared on the forearms, back and buttocks, which resisted further treatment with DDS, and the patient sought admission to Eversley Childs Sanitarium.

The back presented a varied collection of closely-set nodules ranging in diameter from pinhead to over a centimeter. Although the configuration of some was round, many others were irregular in shape. Typical young shiny histoid nodules were scattered here and there (Fig. 7). Two nodules of different size and aspect were biopsied (Path. No. S-274-66 and S-

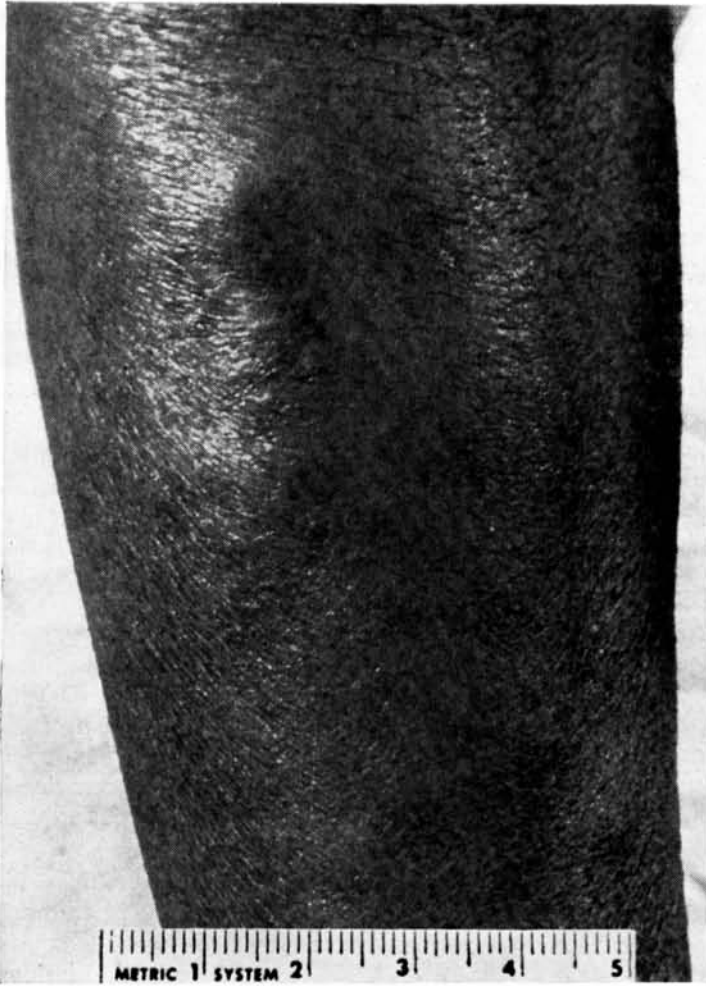


FIG. 6. Case 10 (B.L.).
Two small subcutaneous
nodules on the forearms.

274-B, Abalos); each was diagnosed as a typical histoid nodule of lepromatous leprosy. During the first year, the nodules on the back had greatly subsided and become pigmented. Exactly a year later, however, new lesions appeared on the loins (Fig. 8).

Case 16. (E.S.) Female, age 35 years. After four years of treatment with sulfones, the patient was markedly improved, with all the skin sites negative although nasal smears remained positive. She was transferred to the Culion Sanitarium, where the skin remained clear of active lesions for about five more years, while she was receiving irregular DDS treatment. After delivery of her third child, the disease rapidly became worse, but this time, in addition to the infiltration on the face and ears, numerous nodules appeared, increasing rapidly in size and number in a few months. While

still at Culion she was injected with 30 vials of streptomycin; during this treatment some of the nodules disappeared, with cicatrix formation.

On her admission, the back was studded with closely set typical histoid nodules from 2 to 10 mm. in diameter, some of which tended to fuse, forming lesions of irregular contour, while a few presented the shape of budding yeast cells (Fig. 9). Two nodules of different size on the back were biopsied (Path. No. S-280-66, Abalos and Path. No. S-59-67, Ortigoza) and diagnosed as lepromatous leprosy, histoid lesion.

A third nodule of unknown duration, biopsied later (Path. No. S-201-67, Ortigoza), was considered an atypical histoid lesion. At the last clinical examination (8 May 1968) many of the small lesions, especially on the left scapula, have practically

disappeared, but most of the remaining ones on the back have enlarged. Deep-seated ENL lesions, which appeared for the first time in November 1967, were observed for some months. The total period of observation lasted two years.

Clinical Features

The cutaneous histoid leproma. The presenting lesions may be cutaneous, subcutaneous, or both. The cutaneous was the only histoid lesion in 20 relapsed patients. In six patients both cutaneous and subcutaneous lesions were present; one had a subcutaneous histoid nodule only, while in another case information was not available.

Typical young histoid cutaneous lepromas are reddish, round or oval, regular in contour, shiny, and luxuriant in appear-

ance. Some of them appear a deeper red and more perfectly hemispheric, with a slight constriction around their bases; in other words they are the perfect representation of the young histoid leproma. These are relatively rare, seen singly or only a few at a time, more frequent in nonrelapsed cases, and transitory.

The "soft histoid nodules," found only in Cases 6 and 27 (C.L.) are characterized by being flatter and less well-defined than ordinary histoid lesions. They are surrounded by smaller, fainter and deeper papulonodules, which are arranged in loose groups, forming plaques that change in size, location and number within the space of a few weeks.

Other cutaneous lesions. There were seven nonnodular histoid lesions (18%) con-



FIG. 7. Case 1 (F.Pa). Skin studded with numerous closely-set histoid lesions of all stages. Relapsed case (photo taken on 5 July 1966).



FIG. 8. Case 12 (F. Pa.). Reappearance of a few small nodules of 3 weeks' duration on loins and arms. Same patient as in Figures 8 and 9 (photo taken on 6 May 1968).

sisting of papulated plaques, infiltration, and small red patches.

The subcutaneous nodule. This distinctive lesion was found only in relapsed cases. The nodules varied from 1 to 3 cm. in diameter, and were located on the extremities, particularly near the elbow and wrist joints. The characteristic clinical feature of the nodule was that the skin slid easily over it (Fig. 6). Tenderness was not observed. There was no caseation or supuration.

Although the majority of the subcutaneous nodules remained unchanged, some were noted to increase or diminish in size. Finally, a few were reduced to elongated strands of subcutaneous scar tissue. In Case 10 (B.L.) they were observed to appear in small crops; one lesion appeared and disappeared well within the period of one year.

Eight subcutaneous nodules were biopsied; in two the lesions were found to be composed of two closely adherent smaller

nodules. On cross section the color of the cut surface varied from grey to yellowish, reflecting the underlying pathology.

The statement of Wade (⁹) that he had never seen subcutaneous nodules in the lepromatous type may surprise some leprologists; in reality, the usual lesions in this type are deep cutaneous nodules embedded in areas of thick lepromatous infiltration and covered with adherent skin.

Development of histoid cutaneous nodules. Many young histoid nodules are transient; others persist and enlarge gradually, some of them terminating in ulceration followed by scarring. The oldest nodules, usually located around the joints of the extremities, are fibrotic and covered with keratotic skin. Hence, in relapsed cases, different varieties and stages of histoid leproma may be present in the same patient (Fig. 1).

Appearance of histoid nodules at relapse. It was possible to obtain this information

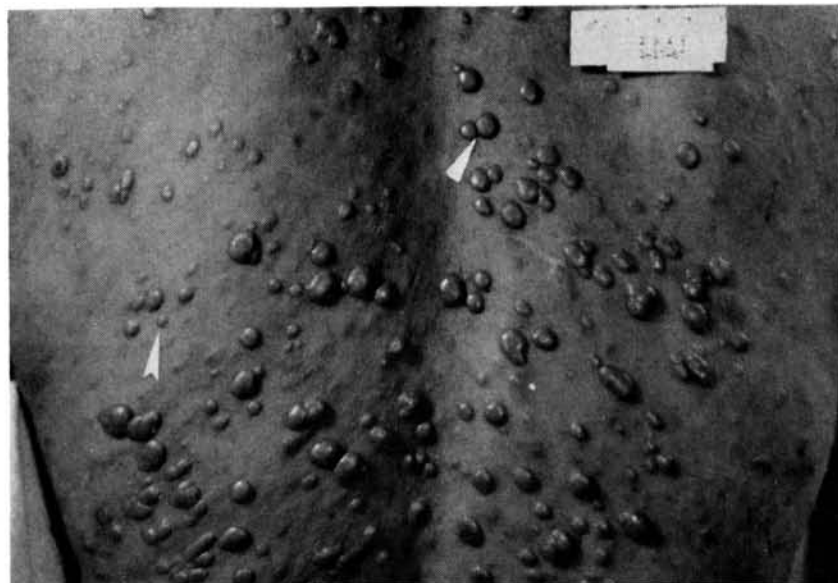


FIG. 9. Case 16 (E.S.). Typical rounded or oval histoid nodules of various sizes; note some tendency to group and fuse together.

from 19 cases, which was partly confirmed by the presenting lesions. The appearance of histoid nodules in crops was actually observed by the investigator in six patients. In Cases 6 (A. Ni.), 9 (A. No.), 12 (F. Pa.) and 13 (L. B.) the crops recurred in certain specific areas suggesting regional distribution; in Cases 1 (A. C.) and 5 (A. L.) this pattern was not observed. The disappearance of young histoid nodules was confirmed not only in these six cases but in several others as well.

Other accompanying leprotic lesions. Moderately advanced lepromatous infiltration, at first limited to the face and ears, was always present in relapsed cases, whether there were histoid lesions or not. On the trunk and extremities the skin appeared to be uninvolved except for the presence of the histoid nodules. However, some bacteriologic smears taken from the normal-looking skin were found to be positive for *M. leprae*. Occasionally lepromatous plaques were present, and transient histoid nodules appeared between them; in two instances borderline lesions also were found. Further progress of the infiltrations in relation to the histoid nodules in relapsed cases will be taken up under treatment.

Clinico-Pathologic Correlation

The two pathologists of the Leonard Wood Memorial working in the Eversley Childs Sanitarium at Cebu, Drs. Rodolfo M. Abalos and Corpus O. Ortigoza, who examined all the biopsy specimens taken in the study here reported, will report later on the pathology of histoid lesions. However, their routine tissue reports have been found essential in making the diagnosis of individual lesions and in correlating these with the types and stages of leprosy of the patients in which they occurred, as noted in the case reports above.

Among other findings, it was established that in only 15 of the 28 relapsed cases were all the biopsied nodular lesions diagnosed histologically as "lepromatous leprosy, histoid lesion." In seven others, there were other nodules diagnosed simply as "lepromatous leprosy"; in four, papulonodular borderline lesions coexisted, and in two both lepromatous (LL) and borderline (BL) nodules were present in the same patients with the histoid leproma. These findings indicate that varying degrees of immunologic response at the cellular level appear to exist in the lesions of the same patients; that is likely to happen in BL cases.

Two clinical observations may be emphasized in this connection, viz., (a) that in about 50 per cent relapsed cases, all biopsied nodules were histoid lepromata, a finding not observed in nonrelapsing cases, and (b) that the term "histoid" should be limited to characterize lesions and should not be applied to patients or to any subvariety of the disease.

The case histories furnish some information on the question of "maturation" of the histoid lesions, that is, their progression to the more usual lepromatous cytology, with vacuolization of the histiocytes and globus formation. Forty-two biopsied cutaneous lesions were diagnosed as "lepromatous leprosy, histoid lesion," 25 of which presented typical histoid structure, while in 17, globi, or vacuolated histiocytes, usually both, were found in the sections. Wade himself noted that failure to produce globi, while characteristic, is not absolutely invariable, since a few of his specimens had undergone "reverse" change and produced globi. When the lesions presenting these histologic findings were compared and correlated with the other lesions of the patients, the latter could be divided into two groups:

(a) Case 1 (A.C.), 2 biopsies; Case 3 (R.E.); Case 15 (G.P.); Case 5 (A.L.); Case 25 (E.L.); Case 7 (J.R.), 2 biopsies; and Case 24 (P.K.), 2 biopsies. These seven patients had histoid lesions of various stages, including old ones of several years' duration, which showed vacuolization and globus formation suggesting that the histologic changes noted in this group represented aging of the lesions.

(b) In contrast, Case 20 (L.G.), Case 17 (D.P.), Case 2 (A.D.), Case 13 (L.B.), Case 9 (A.No.), Case 22 (C.C.), and Case 19 (M.W.) were among the cases in which lepromatous lesions had gradually spread over the body and presumably infiltrated into the histoid nodules as well. One biopsied lesion however (Case 11, O.P.), already encircled by infiltration, still showed uncomplicated histoid histology.

It was noted in these biopsies, however, that globi and vacuolated cells were few, and therefore that there was no actual transformation to lepromatous (LL) struc-

ture. Not even in Case 5 (A.L.) and Case 22 (C.C.), whose biopsies had been diagnosed by Dr. Ortigoza as "atypical histoid," did the changes appear so marked as to indicate conversion. The pathology of these two cases appeared to be analogous, although to lesser degree, to that in Wade's two "mixed" cases (9).

Bacteriologic Considerations

Wade (9) found that the stained bacilli were notably larger than ordinary bacilli, even in the same section; he stated that "the bacilli of the histoid lesions constitute one of the most striking and distinctive features of those lesions, first in the absence of globus formation, and also by their size." He described as the "histoid habitus" spindle-shaped lesions where groups or clumps of bacilli elongated correspondingly, their numbers varying with the age of the lesions and their occurrence in dense rounded masses in areas of free phagocytes.

In smears taken from histoid and from ordinary lepromatous infiltration at Cebu it was found that the bacilli from the former were measurably longer, but not thicker, than the ordinary *M. leprae*. Reich (personal communication), however, has stated that the acid-fast organisms associated with young histoid nodules are not really longer than those found in other lepromatous lesions, and that a large proportion of them in stained smears are of even average length. At any rate, the unusual features of length of the bacilli and alignment along the long axis of the spindle-shaped histiocytes make possible a bacteriologic diagnosis of histoid leproma.

NONRELAPSING CASES WITH HISTOID LESIONS

It was possible to examine most of the 310 admissions to the Eversley Childs Sanitarium from 1 January 1965 to 31 May 1968, and to read the reports of the entrance clinical examinations of all of them. Seven of the patients had histoid lesions, or a proportion of 2.2 per cent. Their ages ranged from 24 to 62 years, with a mean of 34 years. There was only one female. The duration of leprosy was from six months to four years, the average being one year and five months. None of them had received

treatment for leprosy before inclusion in the study. On the basis of their clinical manifestations, the seven may be divided into two groups, viz., (a) patients with lepromatous leprosy (LL), and (b) patients with both lepromatous and typical borderline lesions (LL and BL). Accordingly, the case reports are presented under two headings below.

CASE REPORTS

Cases with Lesions of the Lepromatous Type Only

Case 1. (I.M.) Male, age 25 years. Admitted to Eversley Childs Sanitarium (ECS) on 12 February 1965, and diagnosed as a slight lepromatous case. No antileprosy treatment received previously; duration of the disease about one year.

Examination 30 May 1965: Small red shiny nodules were noted on the forearms, thighs, and buttocks, ranging in diameter from 3 mm. to 1.2 cm.; they were not hot or tender. There were other nodules, more numerous, which could be distinguished by their normal skin coloring, greater irregularity in shape, lesser circumscription, and larger size. All of them appeared suddenly about a year before admission. There was no fever or joint pain, but the patient felt weak. There was moderate infiltration on the face, ears, and forearms, and there

were multiple coppery macules on the trunk.

One nodule, on the right wrist (Fig. 10), with "perfect" histoid appearance, was diagnosed on biopsy (Path. No. S-56-A-65, Mabalay) as "histoid lesion of lepromatous leprosy," although the tissue report mentions the presence of a few giant cells and globi. Another nodule, on the pinna of the right ear, with granulated surface and oblong shape (Path. No. S-56-B-65, Mabalay), was diagnosed simply as "lepromatous."

It was possible to follow this case for about a year; at the last examination all the nodules had disappeared or greatly subsided; the reddish macules were no longer present and the leprotic infiltrations on the face had shown some improvement. The patient received DDS tablets in the sanitarium.

Case 2. (E.Pas.) Female, age 19 years. Admitted on 4 June 1965, she was diagnosed as a moderately advanced lepromatous case. There was infiltration on the face and extremities, but the skin of the trunk appeared free from lesions except for fairly numerous small nodules, while others were more irregular in contour, dull in appearance, and of normal skin color. These were mixed in distribution, and located chiefly on the extremities, although some of the



FIG. 10. Case I (I.M.). A "perfect" shiny cutaneous nodule with smaller not well defined ones. Nonrelapsed case.

latter kind were grouped in certain areas of the back, surrounded by the succulent nodules. The duration of leprosy was two years, but the nodular eruption appeared less than one year before admission. The patient received no treatment outside.

Three biopsies were made at the same time: (1) A shiny nodule on the back (Path. No. S-60-A-65, Abalos) was diagnosed histologically as lepromatous leprosy, histoid lesion, although focal infiltrates of histiocytes possessing pale vacuolated cytoplasm were present. (2) A dull-looking nodule near the same site (Path. No. S-60-B-65, Abalos) was diagnosed as leprosy, lepromatous, early histoid; in this case also there were histiocytes with vacuolated cytoplasm. (3) A patch (Path. No. S-60-C-65, Ortigoza) was considered to be a histoid lesion also.

This patient continued to receive DDS treatment rather irregularly because she complained of dermatitis due to the drug, until 20 April 1967, when she was transferred to the care of the Traveling Skin Clinic. It was possible to examine her after the transfer on 15 September 1967. No histoid nodules had reappeared, but the entire integument was covered with thick diffuse infiltration. A few weeks later she was known to have developed severe ENL and disappeared from observation. The total duration of observation period was two years and three months.

Case 3. (E.Pac.) Male, age 22 years. Admitted on 16 July 1965, with moderate infiltration on the face and ears. There were several raised macules on the trunk and fairly numerous small nodules scattered on the forearms, trunk, buttocks, thighs, and ankles. Duration of the disease about one year. No previous treatment with sulfone drugs.

A macule on the left loin (Path. No. S-82-A-65, Abalos) was diagnosed as lepromatous leprosy. Biopsy of one of the nodules on the right buttock (Path. No. S-82-B-65, Abalos) was diagnosed as lepromatous leprosy, histoid lesion, early, with some globi present. A section of a small reddish infiltrated area on the right forearm (Path. No. S-82-C-65, Abalos) was diagnosed simply as lepromatous leprosy. The duration of

observation was three years. At the last examination, infiltration on both ears was still present, but the trunk was apparently free of lesions; a few ENL papules were found on the extremities. The patient presented the picture of moderately advanced lepromatous leprosy; no histoid nodules had reappeared. During his stay in the Sanitarium, he received a special sulfone preparation.

Case 4. (V.M.) Male, age 25 years. On admission to ECS on 22 July 1965, this patient had an infiltrated face studded with small nodules and showed a few red plaques on the trunk. In addition, there were numerous nodules, ranging in diameter from 2 to 4 mm., on the trunk and the extremities. Some of these were globular and reddish, with a distinct shiny sheen (Fig. 11). The duration of leprosy was one year; no sulfone treatment was received outside. One week before the patient's admission a nodular eruption occurred all over the body, including the trunk.

A small red, shiny nodule on the left arm was biopsied on 27 July 1965; the duration of this nodule was known to be only a few days. The histology was reported as lepromatous leprosy, histoid lesion (Path. No. S-87-A-65, Abalos); numerous globi were present. For control, another biopsy was made of a red plaque on the abdomen (Path. No. S-87-B-65, Abalos); this was diagnosed as lepromatous leprosy. On 2 October 1965, again for the purpose of control, a nodule on an infiltrated area was biopsied (Path. No. S-87-C-65); this was diagnosed by Drs. Wiersema and Ortigoza as leprosy, lepromatous, active. The period of observation was only six months; the histoid and other nodules were still present when he left the Sanitarium, and the treatment was DDS.

Case 5. (F.T.) Male, age 24 years. Admitted on 11 September 1967, presenting patches of localized infiltration on both cheeks and diffuse infiltration on both ears, all studded with nodules. There were also macules on the chest and back, probably representing subsided plaques, and more diffuse infiltration on the forearms and legs. The patient gave a history of only six months' duration; no treatment was received before admission.



FIG. 11. Case 4 (V.M.). Young "perfect" shiny nodules mixed with others that are not typical. Untreated nonrelapsed case.

An elongated lesion composed of two fused reddish nodules on the left loin was biopsied (Path. No. S-414-67, Abalos) and diagnosed as LL lepromatous leprosy, histoid lesion. At an examination on 22 March 1968, six months after admission, the localized patches of infiltration on the face had improved markedly, and the nodules on them had become flatter. No new nodules had appeared elsewhere.

Last examination (20 May 1968): Five large ENL lesions were seen on the forearms, and a few were present on the legs, all of them of one week's duration. This was the first time a reaction had appeared; slight infiltration was present in the ears and cheeks. The temperature was 37.9°C. The nodules on the ear lobes were

fewer and smaller than at the first examination, their diameter being reduced by one half. Macules were no longer present on the chest; those on the back were hardly noticeable. The duration of observation was about eight months, during which the patient received nonsulfone preparations.

Cases with Borderline Leprosy

Case 6. (M.R.) Male, age 59 years. On admission on 12 November 1965, the diagnosis of the admitting physician was "borderline in reaction." The duration was two years, initiated by numbness of the extremities. In December 1963, red, thick patches appeared in different parts of the body; these were treated with herbs locally. On examination, the patient was found to have



FIG. 12. Case 6 (M.R.). Three histoid nodules in the "clear" center of two imperfect rings formed by "bands" and plaques of typical borderline leprosy.

moderate infiltration on the face and ears; on both thighs and the trunk there were typical borderline lesions.

Of particular interest in this case was a group of three small nodules in the center of the so called "immune area" of a large borderline lesion on the posterior surface of the right arm (Fig. 12). The largest nodule, quite separate from the smaller two, was biopsied (Path. No. S-132-A-65, Ortigoza); it was diagnosed as leprosy, lepromatous, histoid. Its duration was four months. The skin of the circular clear area at the center of the large lesion (Path. No. S-132-B-65, Ortigoza) was diagnosed as borderline (BL), and the red border (Path. No. S-132-C-65, Ortigoza) was similarly diagnosed. The duration of the observation period was three months. At the last examination, the skin lesions had not changed. The patient refused DDS during that period.

Case 7. (O.L.) Male, age 62 years. First admitted on 10 July 1967, diagnosed as borderline leprosy. The duration of the illness was said to be four years; the patient did not receive any antileprosy drug before admission. He developed exfoliative dermatitis ascribed to diacetyldiaminodiphenyl sulfone during January 1968.

The border of an anesthetic, red, raised macule on the left loin (Path. No. S-275-67, Ortigoza) was diagnosed as leprosy, lepromatous (BL); two small ill-identified tubercles were seen in the section. Another biopsy of a cutaneous nodule below the right elbow (Path. No. S-317-67 Ortigoza) was reported as leprosy, lepromatous, histoid variety. The tissue report contained the following statement: "The infiltrate is composed primarily of spindle-shaped histiocytes in small nodules separated one from the other by incomplete bands of collagen. There is no vacuolization of the cytoplasm. At the periphery small ill-formed globi are seen, and the histiocytes have foamy vacuolated cytoplasm. No capsule is seen."

A third biopsy involving a deep seated nodule on the left arm (Path. No. S-368-67, Ortigoza) was reported as leprosy, lepromatous (BL), early histoid. Still another biopsy of a deep nodule above the right knee (Path. No. S-369-67, Ortigoza) was diagnosed as leprosy, borderline-lepromatous histoid nodule, early BL; there were tubercles in the deep dermis, but no globi were seen.

At the last examination, on 31 May 1968, the diffuse infiltration on the face and extremities showed partial improvement. Large pinkish diffuse macules were present on the trunk and the site of the large oval patch on the left lower back was still surrounded by reddish thickened skin. No histoid nodules were present. The total duration of the observation period was nine months; treatment was with DDS and a nonsulfone preparation.

In four of the lepromatous group, the "perfect" histoid nodules—red, hemispheric, shiny, and semipedunculated—were mingled with other nodules that could be distinguished from them by their color, irregular size and shape, and lusterless appear-

ance (Fig. 11). On biopsy, the sections showed a few globi or vacuolated histiocytes among spindle-shaped histiocytes. One in this group, Case 5 (F.T.), with lepromatous leprosy of only six months' duration, had a single nodule.

Most of the histoid nodules observed in the nonrelapsing lepromatous group were of the perfect-looking kind and transitory. No other nodules were left behind after their disappearance.⁴

In the follow-up of four cases where histoid lepromas were associated with borderline skin lesions (2 among relapsed and 2 of the nonrelapsing cases) there seemed to exist a special association between borderline leprosy and this variety of leproma. If papulo-nodular lesions were more frequently included among the biopsied lesions, particularly those within the immune areas, histoid pathology would be more frequently associated with borderline cases. Among such cases, the histoid nodules were found to be of the "soft" kind, diagnosed histologically as "BL, histoid lesion."

DIAGNOSIS

The histologic diagnosis of histoid lesions requires familiarity with all kinds of leprotic lesions, particularly borderline, and proper orientation on the part of the pathologist. While the tissue report invariably mentioned the typical alignment of the acid-fast bacilli along the long axis of the spindle-shaped histiocytes in young histoid lesions, this finding was not reported regularly in the older nodules. In about 10 per cent of suspected leprotic papules and nodules, the diagnosis could be made only by combined clinical, histologic and bacteriologic examinations.

The differential diagnosis with regard to diseases other than leprosy is of particular interest to pathologists. These include nodular subepidermic fibrosis, fibrosarcoma of the skin, keloid, and xanthoma. The diag-

nosis can easily be clarified by acid-fast staining.

HISTOLOGIC CONTROLS

In the numerous biopsies made during the period of the study, the two pathologists had probably not missed the presence of the histoid pattern in many of the 593 sections not diagnosed by them as histoid lesions. The patients were divided into the following groups:

Admitted to ECS with papular and nodular lesions	57
Other admissions with non-nodular lesions	253
Outpatients with different lesions of all types of leprosy	283

In the dispensary group, three cases with histoid lepromata were discovered, but these were not included in the study because they were not followed-up.

SULFONE TREATMENT AND ITS EFFECTS ON HISTOID LESIONS

All the relapsed cases, which had previously been rendered negative or markedly improved by sulfone drugs, later received no treatment or at most only irregular doses of DDS during the period of temporary arrest of the disease. After relapse and readmission, records of treatment were available for assessment and correlation with the changes manifested by the histoid and other leprotic lesions.

Stated briefly, the clinical findings show that of 18 patients with histoid lesions who received full doses of DDS for varying periods of time up to three years, the histoid lepromata persisted and the clinical picture presented by the patients remained unchanged in 10; in five others lepromatous lesions spread on the skin around the nodules, while in three the lepromata had disappeared and infiltrations covered the entire body. Ten other patients had taken inadequate doses of sulfone drugs or none at all. Among these, the histoid lepromata persisted in seven; infiltrations appeared on the body and extremities in two, while subcutaneous nodules only remained in one.

⁴ After completion of this stage of the study, a nonrelapsing patient presenting new and old nodules, making it impossible to distinguish him clinically from relapsed cases, was admitted to the Eversley Childs Sanitarium.

All of the six cases that showed crops of histoid nodules during the period of observation were receiving full doses of DDS during the entire period, indicating that the sulfones did not immobilize or prevent the acid-fast bacilli in the nodules from multiplying rapidly. Thus, most of the histoid lesions of relapsed cases did not improve under sulfone treatment, regardless of the dosage. Furthermore, this treatment did not prevent the appearance of fresh crops of histoid lepromata nor the multiplication of *M. leprae* associated with them.

It is difficult to explain the spread of lepromatous infiltrations in some of the cases with resistant nodules in spite of continuous sulfone treatment. At any rate, the infiltrations began to subside after about one year of sulfone treatment. All seven nonrelapsing cases received DDS, but only four of them could be kept under observation longer than one year. In all these, the histoid nodules had disappeared and other leprotic lesions present showed improvement.

DISCUSSION

The histoid leproma as a recent lesion among relapsed cases. Over a period of 42 years, starting as a member of the Local Negative Committee of the Culion Leper Colony in 1923 and ending as Chairman of the National Disposal Committee, I have conducted routine examinations of a few hundred relapsed cases as part of my duties. These have included a field survey of "negatives" in 1929 at Cebu during the chaulmoogra era⁽⁵⁾ and more recently, surveys of negatives, published⁽⁶⁾ and unpublished, who were discharged from the leprosaria in the early sulfone period. In all these examinations and reexaminations, I have not come across nodular lesions with acid-fast smears similar to those being reported in this article.

The appearance of histoid lepromas is a late phenomenon of the sulfone period; these lesions were not observed among patients relapsing earlier than 12 years after the full-scale introduction of the sulfone drugs in the Philippines.

Some theories on the significance of the histoid leproma. Wade emphasized the

basic histiocytic nature of the spindle-shaped structure of the histoid lesion as demonstrated by the Mallory aniline-blue stain. He found only spindle-shaped elements exclusively in the earliest nodular lesions without any collagenous fibers except in the pseudo-capsule.

Melamed *et al.*⁽²⁾ reported an unusual case passing through a reactional state in which histologically-proven histoid lesions were present. At the same time lesions diagnosed as indeterminate with one indisputably tuberculoid lesion were also seen. They concluded that the histoid structure appears to represent the early or initial stage of the leproma, which, however, can be seen only in transitional phases "borderline reactions, interpolar, or paralepromatous ones."

Pettit *et al.*⁽³⁾ believed that the histoid lesions were at a stage of their development acutely progressive to an unusual degree. In their opinion the undifferentiated cytology of the granuloma, the fact that borderline features and tubercles were sometimes superimposed on an otherwise purely lepromatous structures, and the occasional occurrence of localized reactions, may indicate that an acute increase of bacilli at one site may incite even a pure lepromatous (LL) lesion into some degree of tissue reactivity. Hence the histoid leproma may be indication of very acute leprosy.

While these assumptions may account for the occurrence of histoid lesions in borderline and early lepromatous leprosy, they cannot explain the findings obtained in this study with regard to the unusual behavior of this newly recognized form of leproma in relapsed cases. Here, after reactivation of the lesions, some of the histoid nodules evanesced, as they do in nonrelapsed cases; others persisted, however, and developed into older nodules that did not respond to sulfone therapy. Pettit *et al.*⁽³⁾ have established, by direct laboratory proof, the existence of DDS-resistant strains of *M. leprae* in lesions histologically resembling histoid lesions. It is not unreasonable, therefore, to assume that organisms found in the histoid lesion are refractory to the sulfones. Animal foot pad experiments are

now in progress to establish if "histoid bacilli" are resistant to DDS.

On the assumption that "histoid bacilli" are resistant, it would seem reasonable to postulate that they are mutant organisms that have emerged from a predominantly sulfone-susceptible bacterial population following treatment with DDS. Treatment with sulfones creates a selective environment by killing or at least inhibiting multiplication of drug-sensitive organisms, allowing growth of the resistant "histoid bacilli."

On the other hand, in early borderline and lepromatous cases, the ascendancy of the sulfone-susceptible organisms is not yet complete and the mutants are able occasionally to produce transitory histoid lesions on the skin.

It can be assumed that the histoid lesions as seen in relapsed patients are the result of activity of hidden foci of "histoid bacilli" after the patient has undergone clinical and bacteriologic improvement as a result of destruction and elimination of sulfone-sensitive organisms responsible for the non-histoid lesions. These resistant mutants are now present in an environment favorable for active proliferation and multiply rapidly. Phagocytosis of these organisms by spindle-shaped histiocytes results in the production of the histoid nodule. The elimination of the usual lepromatous infiltrations makes it possible for the histoid lesions to develop on the skin, leading to the display of nodules at various stages of development on the trunk and extremities. If conditions allow for the renewed multiplication of the sulfone-sensitive organisms, the nonhistoid lesions they produce spread and cover the histoid nodules. This development has been seen frequently in many relapsed cases studied thus far.

The possible sites of these sulfone-resistant clones may be speculated upon. It would appear that internal viscera such as the spleen, liver, lymph glands and even peripheral nerve trunks would provide suitable areas, but the most likely site is the subcutaneous tissue. This concept finds some support in the observation of Wade that histoid lesions begin as independent subcutaneous nodules and are the sources of most of the lesions that affect the dermis

as "the result of a sort of outward migration."

It is possible that the presence of varying proportions of mutants may be responsible for the different clinical manifestations and/or the varying degrees of infectivity of the host.

Furthermore, the five cases mentioned elsewhere in this paper whose histoid nodules were overrun and covered up by leprotic infiltration while under observation, suggest the possibility that many moderately advanced and advanced lepromatous cases, whether relapsed or not, may be harboring hidden pockets of histoid tissue buried in the thick lepromatous infiltrate enveloping the entire body surface.

It may be presumed further that the sulfones do not "cure" leprosy. These drugs act merely as selective agents permitting the emergence of a few sulfone-resistant mutants that multiply and result in a mutant-dominant *M. leprae* population for varying periods of time. It should be kept in mind that there may be patients with lesions in which these mutant populations predominate, with the ability to infect the healthy population, resulting in new types of lesions and modifying the epidemiology of the disease as we know it today.

SUMMARY

A total of 35 patients with confirmed histoid lesions were studied at the Eversley Childs Sanitarium, Cebu, Philippines. Twenty-eight were relapsed cases, while the remaining seven had not received sulfone treatment prior to joining the study.

Furthermore, the five cases mentioned elsewhere in this paper whose histoid nodules were overrun and covered up by leprotic infiltration while under observation, suggest the possibility that many moderately advanced and advanced lepromatous cases, whether relapsed or not, may be harboring hidden pockets of histoid tissue buried in the thick lepromatous infiltrate enveloping the entire body surface.

Detailed clinical observations supplemented by histologic and other corroborative laboratory examinations on the histoid and other coexisting leprotic lesions are

presented. Taken as a whole, these findings tend to show that changes affecting the manifestations of the disease take place when the patient relapses after receiving prolonged sulfone treatment. These investigations are being continued.

The study has established that the histoid leproma is evanescent in borderline and early lepromatous cases that have been under treatment with sulfones for only a short period of time. On the other hand, in relapsed cases, although some nodules were transient in character, many persisted as chronic lesions that did not respond to sulfone therapy. It is reasonable to assume, at this point in our studies, that "histoid bacilli" may be resistant to DDS. Animal foot pad studies are now in progress to verify this assumption.

If the "histoid bacilli" are truly DDS-resistant, one could theorize that these organisms are mutants of *M. leprae* that have emerged as a result of the selective action of DDS. By destroying or at least inhibiting sulfone-sensitive organisms, DDS has created an environment favorable for active proliferation of *M. leprae* mutants, which, in turn, lead to the formation of cutaneous and subcutaneous nodules. In this connection, one should keep in mind that the *M. leprae* organisms associated with histoid lesions have a distinct and unique morphology. The uniformity of length of the bacilli and their packet-like arrangement allow them to be distinguished readily from *M. leprae* seen in other nonhistoid lepromata.

RESUMEN

Un total de 35 pacientes con lesiones histoides confirmadas fueron estudiados en el Eversley Childs Sanitarium, Cebu, Philippines. Veintiocho fueron enfermos que recayeron, mientras los siete restantes no habían recibido tratamiento con sulfona anteriormente al estudio.

Observaciones clínicas detalladas suplementadas con exámenes histológicos y otros exámenes de laboratorio de corroboración en el aspecto histoides y otras lesiones hepáticas coexistentes son presentadas. Tomado como un todo, estos hallazgos tienden a mostrar que los cambios que afectan las manifestaciones de la

enfermedad tienen lugar cuando el enfermo recae después de recibir prolongados tratamientos con sulfona. Estas investigaciones se continúan.

El estudio ha establecido que el leproma histoides es evanescente en los casos borderline y casos lepromatosos tempranos que han estado bajo tratamiento con sulfonas en solo cortos periodos de tiempo. Por otra parte, en caso de recaída, aunque algunos nódulos fueron temporales en carácter, muchos persistieron como lesiones crónicas que no responden a la terapia con sulfona. Es razonable de asumir en esta etapa de nuestros estudios, que "el bacilo histoides" puede ser resistente al DDS. Estudios en el colchón plantar de los animales están ahora en progreso para verificar esta posibilidad.

Si los "bacilos histoides" son verdaderamente resistentes al DDS, se podría actualizar que estos organismos son mutantes de *M. leprae* que han aparecido como resultado de la acción selectiva del DDS. Destruyendo o al menos inhibiendo organismos sulfona-sensitivos al DDS ha creado un medio favorable para la activa proliferación de las mutaciones del *M. leprae* los cuales a su vez llevan a la formación de nódulos cutáneos y subcutáneos. A este respecto, se debe tener presente que los organismos de *M. leprae* asociados con lesiones histoides tienen una única y distinta morfología. La uniformidad del largo de los bacilos y sus formas de agrupación les permiten de ser distinguidos prontamente del *M. leprae* visto en otros lepromas no histoides.

RÉSUMÉ

A l'Eversley Childs Sanitarium, Cebu, aux Philippines, on a étudié un total de 35 malades présentant des lésions histoides confirmées. Vingt-huit de ces malades étaient des cas récidivants, tandis que les 7 autres n'avaient pas reçu de traitement sulfoné avant d'être inclus dans l'étude.

On présente des observations cliniques détaillées, étayées par des examens histologiques et par d'autres examens de laboratoire corroborant le diagnostic et se rapportant aux lésions histoides ainsi qu'aux autres lésions lépreuses coexistantes. Prises dans l'ensemble, ces observations tendent à montrer que les modifications affectant les manifestations de la maladie prennent place lorsque le malade présente une récurrence après avoir reçu un traitement sulfoné prolongé. Ces investigations sont actuellement poursuivies.

Cette étude a montré que le léprome histoi-
de disparaît chez les cas atteints de lèpre
borderline ou de lèpre lépromateuse récente,
quand ceux-ci ont été soumis au traitement
par les sulfones pour une courte période de
temps seulement. D'autre part, chez les cas en
récidive, et quoique certains nodules puissent
être de caractère transitoire, beaucoup de ces
nodules persistent sous la forme de lésions
chroniques ne répondant pas à la thérapeu-
tique sulfonée. Dans l'état actuel de ces
études, on peut raisonnablement estimer
que les "bacilles histoides" peuvent être résis-
tants à la DDS. Des études, entreprises sur la
sole plantaire de l'animal, se poursuivent ac-
tuellement afin de vérifier cette hypothèse.

S'il est vrai que les "bacilles histoides" sont
réellement résistants à la DDS, on pourrait
spéculer et dire que ces organismes sont des
mutants de *M. leprae* qui sont apparus en
conséquence d'une action sélective de la DDS.
Par son action consistant à détruire, ou tout
au moins à inhiber, les organismes sensibles
aux sulfones, la DDS a créé un milieu favor-
able à la prolifération active de mutants de
M. leprae, ce qui conduit alors à la formation
de nodules cutanés ou sous-cutanés. En rapport
avec ceci, on devrait garder à l'esprit que les
organismes *M. leprae* associés aux lésions his-
toides présentent une morphologie propre et
unique. La longueur uniforme des bacilles et
leur arrangement en paquets leur permettent
d'être aisément distingués de *M. leprae* tel
qu'il apparaît dans des autres lésions lépro-
mateuses non histoides.

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