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THE "PSEUDOEXACERBATION" REACTIONAL STATE OF LEPROSY[1]

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Among the reactional states of leprosy, which we may define as acute phases interposed in the usual chronic evolution of the disease, there is one that is striking because of the special conditions in which it occurs. That is the one we have called "pseudoexacerbation," which is characterized by two peculiar features: (*a*) it occurs only in patients of the lepromatous type under sulfone treatment, and yet (*b*) it has the clinical appearance of the reactional tuberculoid eruption.

Perhaps these reactions occurred spontaneously before the advent of sulfone treatment, when little attention was paid to cases of the lepromatous type because the specialists were concentrating on the cases called incharacteristic and tuberculoid.[2]

At the time of the Second Pan-American Leprosy Conference, held in Rio de Janeiro in 1946, I said (3) in reporting the results obtained with the sulfones, and commenting on the structural changes:

> We must record, although with due reservation, an aberrant and paradoxical finding observed in the examination of the structure of the lesions of the exacerbations provoked by the medicament.
>
> In two of these cases we made biopsies before treatment, and found typically lepromatous infiltrations with numerous bacilli. In the biopsies of the exacerbation lesions, to our great surprise, we met with a totally different condition. The infiltrates were composed predominantly of epithelioid cells and lymphocytes forming nodular

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[1] Reprinted, in translation approved by the author, from Memoria de la Tercera Conferencia Panamericana de Leprologia [1951], Vol. 1, 1953, pp. 184-188, with references and certain footnotes added. The word *surto*, used almost exclusively in the original, signifies in Portuguese "outbreak," as the acute symptoms in smallpox, measles, etc. Here it has been rendered "outbreak," "reaction," "condition" or otherwise as indicated; the word "eruption" has been used in some instances where the whole syndrome is not indicated.—EDITOR.

[2] It cannot be said positively whether or not this condition—which, incidentally, Rabello has suggested should be called "induced tuberculoid"—happened in the past. It seems improbable that it can occur in a primarily lepromatous case, but again it cannot be said definitely that it cannot. There are so many possibilities in the evolution of leprosy that it may be that sulfone treatment, while causing considerable diminution of bacilli, can provoke or precipitate in such cases organic reactions of the slightly favorable nature that this kind is.

structures, loose and dissociated by edema, presenting the structural picture of the reactional variety of the tuberculoid form, with bacilli in small numbers and of modified morphology.

In three other cases the structural findings in the exacerbation lesions were even more extraordinary, because we found in the same section both typically lepromatous infiltrates and accumulations of epithelioid cells with lymphocytic halos arranged in the manner of nodular structures presenting, also because of the edema, the aspect of the reactional variety of the tuberculoid form.

In the two last cases, unquestionably of the lepromatous form, the exacerbation lesions presented completely the picture of reactional tuberculoid leprosy.

We also emphasize, as of capital interest, the bacteriological findings in the preparations with both lepromatous and tuberculoid features together. In one of them we found abundant bacilli in the lepromatous infiltrations, and in the peripheries of the nodular structures, while those structures themselves were free from bacilli or contained only a few.

In that report I recorded, for the first time in the study of leprosy, three important facts consequent on sulfone treatment:

1. The occurrence of exacerbations of the disease at the beginning of sulfone treatment a certain proportion of which, although occurring in lepromatous cases, nevertheless presented the clinical and structural picture of the tuberculoid type.

2. The concurrence, in the same patient and even in the same histological section, of frankly tuberculoid and frankly lepromatous features.[3]

3. The observation of structures which present the reactional tuberculoid picture, without the corresponding clinical aspect.

Because of the small number of cases in which these features were seen, I was obliged to regard them with reserve, designating them as aberrant and paradoxal. Two years later, at the V International Congress in Cuba, in 1948, our observations having become much more numerous, I presented in collaboration with Rath de Souza a further communication on the subject (4). We wrote:[4]

Among the incidents observed during our experience with sulfone therapy there is one which, because of its significance and its importance, may be considered as one of the most demonstrative proofs of the activity of these drugs. This is the phenomenon which, for lack of a better term, we have called "pseudoexacerbation" of leprosy.

It is known that during the initial stages of sulfone treatment a certain proportion of patients (12% to 15% in our cases) show a slight to moderate exacerbation of the symptoms. This condition ordinarily appears in the form of an aggravation of the preexisting cutaneous elements, with the appearance of new ones of the same aspect and nature. In pseudoexacerbation, which is the subject of this paper, there is also an aggravation of the cutaneous symptom but in a quite different way. Like

[3] It was by unfortunate phraseology that this statement indicates that lesions with mixed histology had not been seen before. Lowe had reported tuberculoid and lepromatous together a decade previously [THE JOURNAL **8** (1940) 515 (correspondence)], and I believe that Rath de Souza and Alayon once reported tuberculoid structure in the nerve and lepromatous in the skin.

[4] The following quoted paragraphs are verbatim as in the translated version which appeared in THE JOURNAL (4).—EDITOR.

the ordinary exacerbation referred to, this condition is also seen in the first months, when the patient has received around 200 to 300 cc. of promin solution or 100 to 200 capsules of diasone, rarely later; but the clinical aspect and the nature of the skin lesions are different from those of the preexisting elements.

There is an acute outbreak of well-defined, infiltrated, erythematous patches, some of them with a tendency to a brownish (*ferruginoso*) color; nodular and papular lesions surround the patches; and the patient frequently shows edema of the hands and feet. If the case is of the lepromatous form, as most of them are, the original lesions of that type are masked or replaced by those of the new eruption, though the latter sometimes coexist with them. The condition develops without any prodromal manifestations, and it has very little effect on the general condition of the patient.

What is really interesting in these cases of pseudoexacerbation is the structural aspect of the lesions. Biopsy shows a structure consisting predominantly of epithelioid cells arranged in nodular fashion, with or without giant cells, these foci disturbed by a more or less marked edema. In short, they present the picture described for the reactional variety of the tuberculoid type, even with respect to bacteriological findings.

Not infrequent, on the other hand, are lepromatous cases in exacerbation in which we find truly mixed structures that indicate the existence of the tuberculoid and the lepromatous processes side by side, in the same section or in different sections but at the same time. Perhaps in these cases they represent examples of a state of transition between the two polar processes.

These reactions, which apparently aggravate the cutaneous condition of the patient, actually signify a considerable improvement. They transform cases of the malign form, incapable of defense against the germ, into a condition in which there is a defense by means of the tissue response characteristic of the benign forms.

The exacerbations due to the action of the sulfones follow, in general, the course of the spontaneous outbreaks of the reactional tuberculoid type. This was observed in 17 of our 68 lepromatous cases, in which the new lesions completely replaced those of the original form. In the others the reacting elements and the lepromas coexisted, at least for a time; in some of them the former disappeared completely while the latter continued their ordinary evolution.

It is a remarkable feature of this condition in these lepromatous cases that the alteration of the capacity of the tissue to react, as shown by the appearance of elements which morphologically and structurally are tuberculoid, is not also evidenced in the results of the Mitsuda test. That test gives the results as before the exacerbation. Tested with the Dharmendra antigen after the exacerbation, 66 of our 68 cases remained negative; only 2 became weakly positive.

In the present second, synthetic report on the subject are confirmed the aberrant and paradoxal features recorded in the preliminary one just cited. The prominent aspects of the pseudoexacerbation are described and summarized as follows:

(1) Exacerbation outbreaks occur at the beginning of sulfone treatment in about 12 per cent to 15 per cent of the patients.

(2) Noteworthy among these reaction cases are those of pseudoexacerbation, which is defined as an acute outbreak which occurs in patients of the lepromatous type but with lesions of reactional tuberculoid structure.

(3) In some of these cases are found mixed structures, lepromatous and tuberculoid together.

(4) The lesions of the acute pseudoexacerbation may (*a*) replace those of the lepromatous type, or (*b*) only mask them, or (*c*) coexist with them.

(5) The pseudoexacerbation condition may evolve thereafter either entirely as of the reactional tuberculoid type, or in parallel with the lesions of the lepromatous type, the former ultimately disappearing and the latter continuing their ordinary course.

(6) There was no change in the lepromin reaction—the Dharmendra antigen being used—in any but two of the cases, and in them it was only weakly positives.[5]

Our findings so far have had no confirmation from the writings of other workers, except Davey (1) who, in reporting the results of treatment with sulphetrone, told of a particularly interesting case:

> Here a lepromatous condition of many years duration, already extensive and degenerating, began to improve steadily during sulphetrone therapy, until without warning and without constitutional symptoms, five months after the first dose, a papular exanthem appeared, the lesions of which proved on biopsy to be a typically tuberculoid in nature, while the lepromin reaction changed from negative to strongly positive.[6]

More recently Rodriguez (2), among his Filipino patients, confirmed our findings although he attributed them to a previous borderline condition. He said:

> I have read the article of de Souza Lima and Rath de Souza on pseudoexacerbation of leprosy with much interest. My own observations among Filipino patients are quite similar to the experience of these Brazilian workers, with regard to their findings on pseudoexacerbation and also the onset and development of reactive tuberculoid lesions. Even the greater part of their interpretation of the findings are in fairly close agreement with our own conclusions, which have been arrived at independently.
>
> We have been following for years some "borderline" (or "intermediate" or "doubtful") cases which had developed some of the typical characteristics of the lepromatous type, such as reversal of a previously positive Mitsuda reaction, diffuse infiltration of the earlobes, and occurrence of mild but typical lepromatous lepra reaction. In such cases, however, some reminiscence of their part-tuberculoid nature is manifested clinically by the persistence of well-delimited macules, papules or nodules, which may be conspicuous and easily recognized or minimal and vestigial.
>
> In my experience, these are the cases which are liable to develop pseudoexacerbations under sulfone treatment. These drugs seem to have the capacity of stirring up and reactivating the tuberculoid portion of the dual nature of these cases. It is possible that they do have the faculty of stimulating the reticuloendothelial system, as stated by the authors. If so, it should not be too difficult to prove this point more directly. Oftentimes, this development leads to improvement of *all* the lesions.

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[5] In subsequent work the classical lepromin has been used, but even with that the results were negative.

[6] Davey added, "The change from the lepromatous to the tuberculoid phase is an extremely rare phenomenon, and was probably influenced by the sulphetrone in this case."—EDITOR.

Now, with more than two years observations, and with our material increased by new cases, we can state our concept of this particular variety of reaction in lepromatous leprosy. Primarily—and this is most important—we can verify the influence which its occurrence exercises on the prognosis of the cases.

Let us begin with the definition. The pseudoexacerbation is an acute episode, recurrent or not, which may occur in a lepromatous case under the influence of sulfone therapy, transforming it, totally or partially, to the clinical and structural aspect of the reactional variety of the tuberculoid type.

The term "pseudoexacerbation" is justified by the consequences of the phenomenon on prognosis, in that instead of aggravating the case clinically it makes it more favorable, since the patients afterward react to the infection more effectively, in the manner of persons naturally resistant to the disease.

By this definition, there are two classes of patients involved in the pseudoexacerbation: (1) those whose clinical and structural aspects are completely transformed to the reactional variety of the tuberculoid type; and, (2) those whose transformation is only partial.

In either of these classes the acute episode appears with characteristics that are distinctive, and which add two new notions to our original concept of the phenomenon. The first refers to the time of occurrence of the outbreak, which we believe to coincide with the first series of the treatment, after about 200 to 300 cc. of promin, or from 100 to 200 tablets of Diasone, although we have seen it appear much later, 12 to 16 months after the beginning of the sulfone therapy. The second concerns the possibility, not yet verified, of relapse of the acute condition, reproducing in general but in more attenuated fashion the characteristics of the initial outbreak.

Let us now review some of the pertinent facts concerning each of these two groups of cases.

Group 1.—Patients whose pseudoexacerbation exhibits entirely, clinically and structurally, the reactional tuberculoid condition. There were 29 cases in this group. The reaction occurred in them either in the first series of the treatment or later. It usually appeared without prodromal symptoms and without affecting the general condition. In some cases it was accompanied by slight fever and marked edema of the hands and feet, the appearance being that of the borderline reactional tuberculoid condition. It is characterized by the appearance of new lesions, usually erythematous or erythemato-brownish patches, much infiltrated, succulent, and accompanied by papuloid elements; at other times it assumes an erythrodermic aspect. In some instances it is accompanied by severe neuritis.

The duration is usually from three to six months, after which the inflammatory phenomena subside leaving pigmented residual lesions, sometimes atrophic, which may also disappear and leave the patient com-

pletely cleared up. In a certain number, however, more or less marked muscular atrophies developed as sequelae of the neuritis which accompanied the outbreak, quite as in cases tuberculoid from the start; and nothing remains of the "lepromatous" aspect that existed before the reaction.

In some cases the condition has recurred, with the same characteristics as at first but less intense. After its substance there is clearing up of the patient's skin.

This complete clearing occurred in all of the cases in this group, although in 22 of them the disease had become more or less advanced. In 6 of them, however, more or less marked atrophies commenced at the time of the reaction, as is also seen in typical reactional tuberculoid outbreaks.

Group 2.—The second lot consisted of 61 patients in whom the pseudoexacerbation was partial, i.e., the lesions of tuberculoid aspect, not numerous, coexisted with those of the lepromatous type.

In spite of this fact the influence of the outbreak was beneficial, leading to clearing up in much less time than usual, so that 44 out of the 61 cases were transferred to the outpatient clinics. Of the other 14 patients, 10 showed after the reaction a new phase of reactivation manifested by eruptions of erythema nodosum.

It is to be noted that in this group, perhaps because of low intensity of the acute process, there was no involvement of the peripheral nervous system.

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DESCRIPTION OF PLATES

[The original of this article was not illustrated, but the author was asked to supply demonstrative pictures. Circumstances prevented his sending original photographs, but he suggested reproducing the plates from the section on "Pseudo-Exacerbação" in his monograph Estado Atual da Terapêutica da Lepra (São Paulo: Servicio Nacional de Lepra, 1950). This is done here, as well as possible, because of the importance of illustrations for the appreciation of the condition described. Of the six plates, three are reproduced as they were; the fourth is made up from two others.—EDITOR.]

PLATE (15)

FIGS. 1-3. Acute pseudoexacerbation reaction occurring in a patient with incipient lepromatous-type leprosy. The edema of the hands and feet shown in the pictures frequently accompanies these outbreaks, which transform lepromatous cases to the reactional variety of the tuberculoid type.

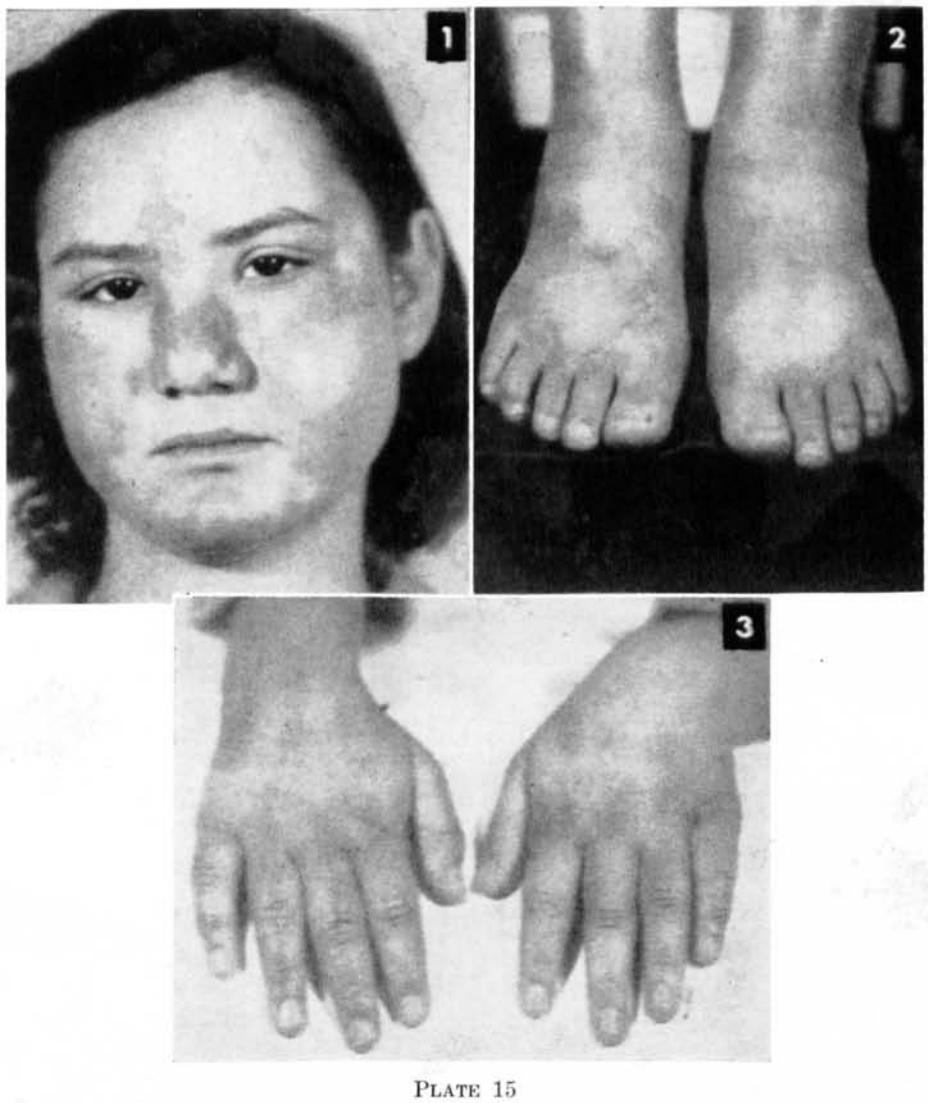

Plate 15

PLATE (16)

FIGS. 4-6. Clinical aspect of the pseudoexacerbation reaction in a patient with moderately advanced lepromatous leprosy, which is thus transformed to the tuberculoid type. Note in this case, also, the edema of the hands.

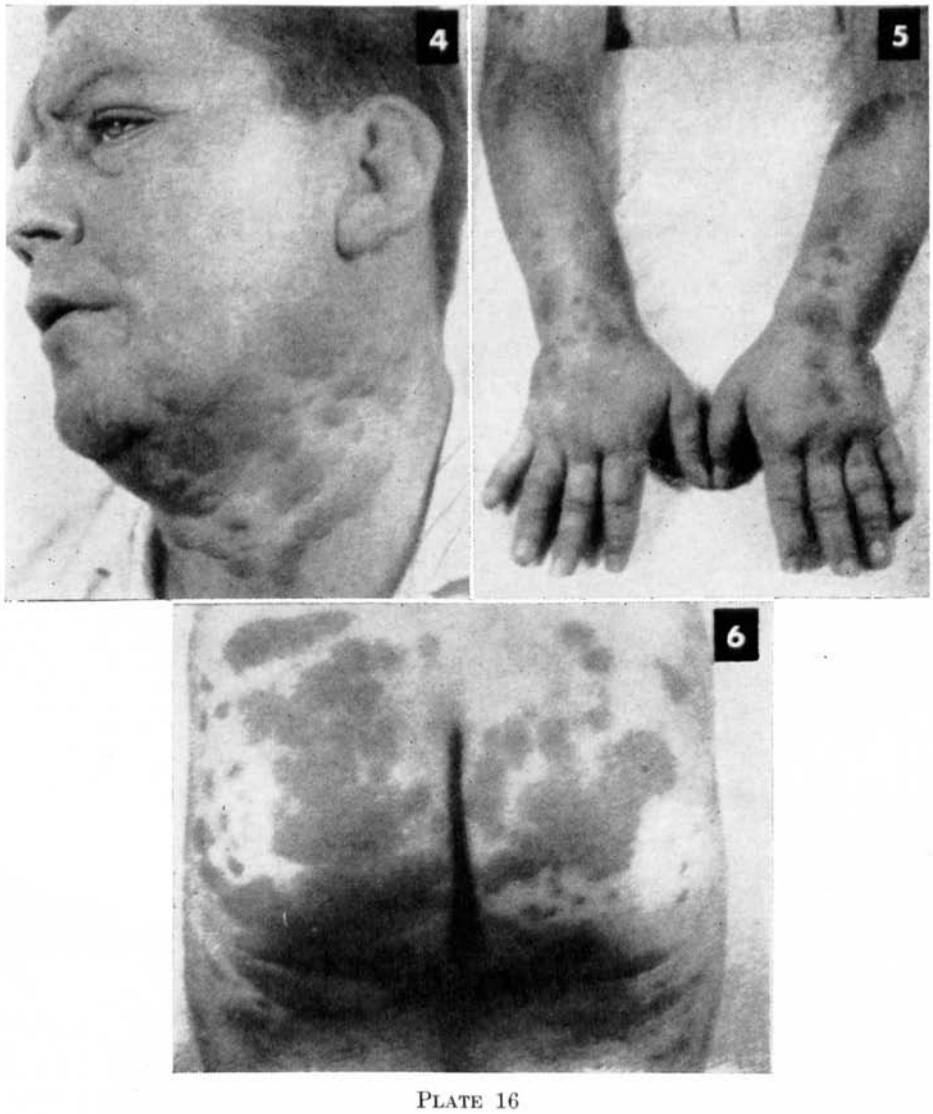

Plate 16

PLATE (17)

FIG. 7. The clinically lepromatous appearance of this case before the occurrence of the reaction.

FIG. 8. Showing discretely infiltrated erythematous plaques superimposed on the lepromatous lesions.

FIGS. 9 and 10. Lepromatous lesions and lesions of the exacerbation reaction existing together in this case.

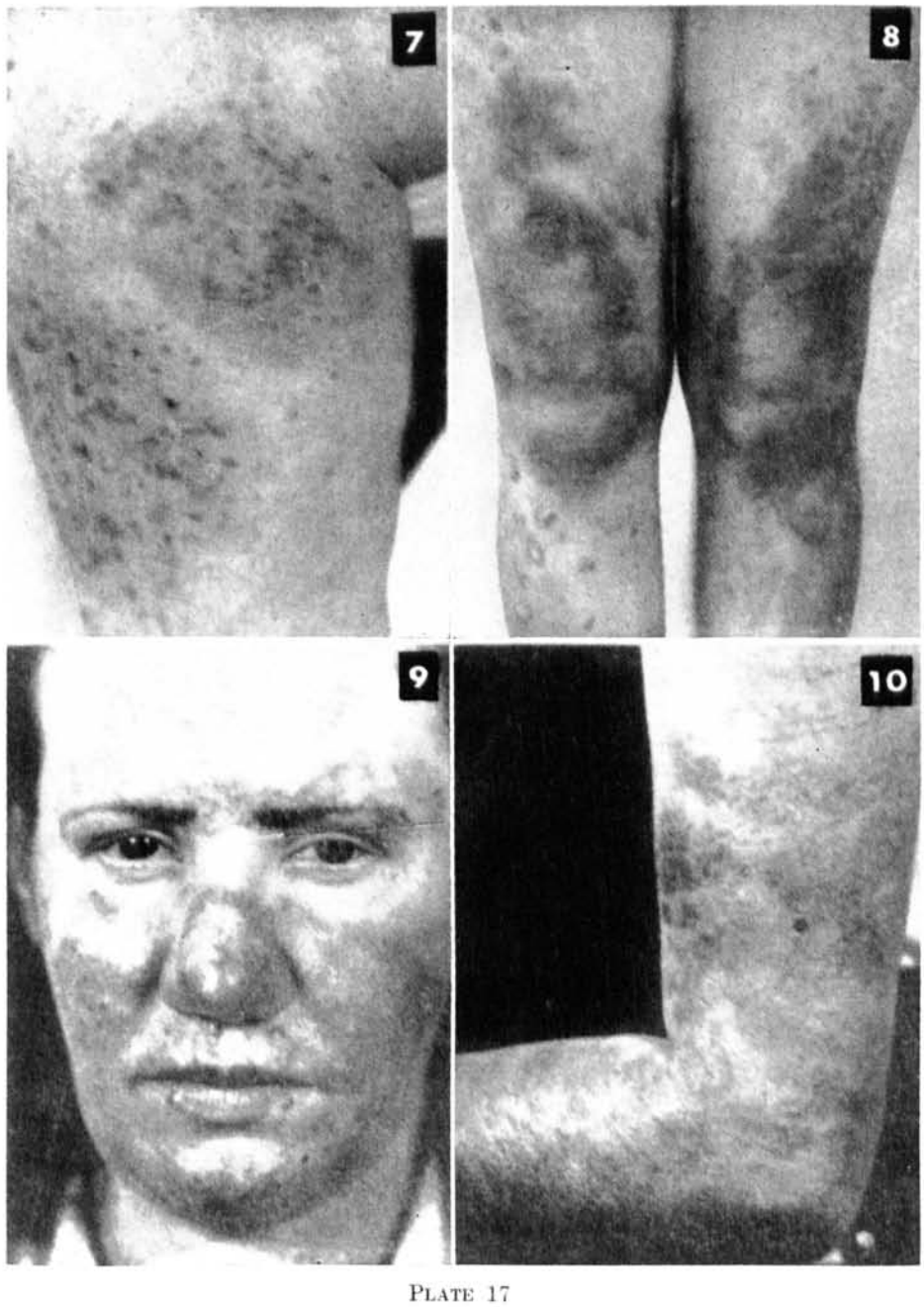

Plate 17

PLATE (18)

FIG. 11. The histological aspect of one of the lesions of the acute exacerbation reaction of the case shown in the preceding plate. Demonstrating the reproduction of the structural picture of the reactional variety of tuberculoid leprosy.

FIG. 12. A similar picture in a specimen from another case, showing nodular structures of epithelioid cells which reproduce the picture of reactional tuberculoid leprosy.

[The last plate on this subject, not reproduced here, shows two photomicrographs. One is of a biopsy specimen that was taken during the quiescent lepromatous phase, and it shows only slight infiltrations, mostly in the papillary layer, said to be of the lepromatous kind with acid-fast bacilli of 2+ degree. The second specimen, of a pseudoexacerbation lesion that had developed in the same case, shows a condition essentially similar as those shown in the last plate. This lesion, it is stated, had only rare acid-fast bacilli, of granular aspect.—EDITOR.]

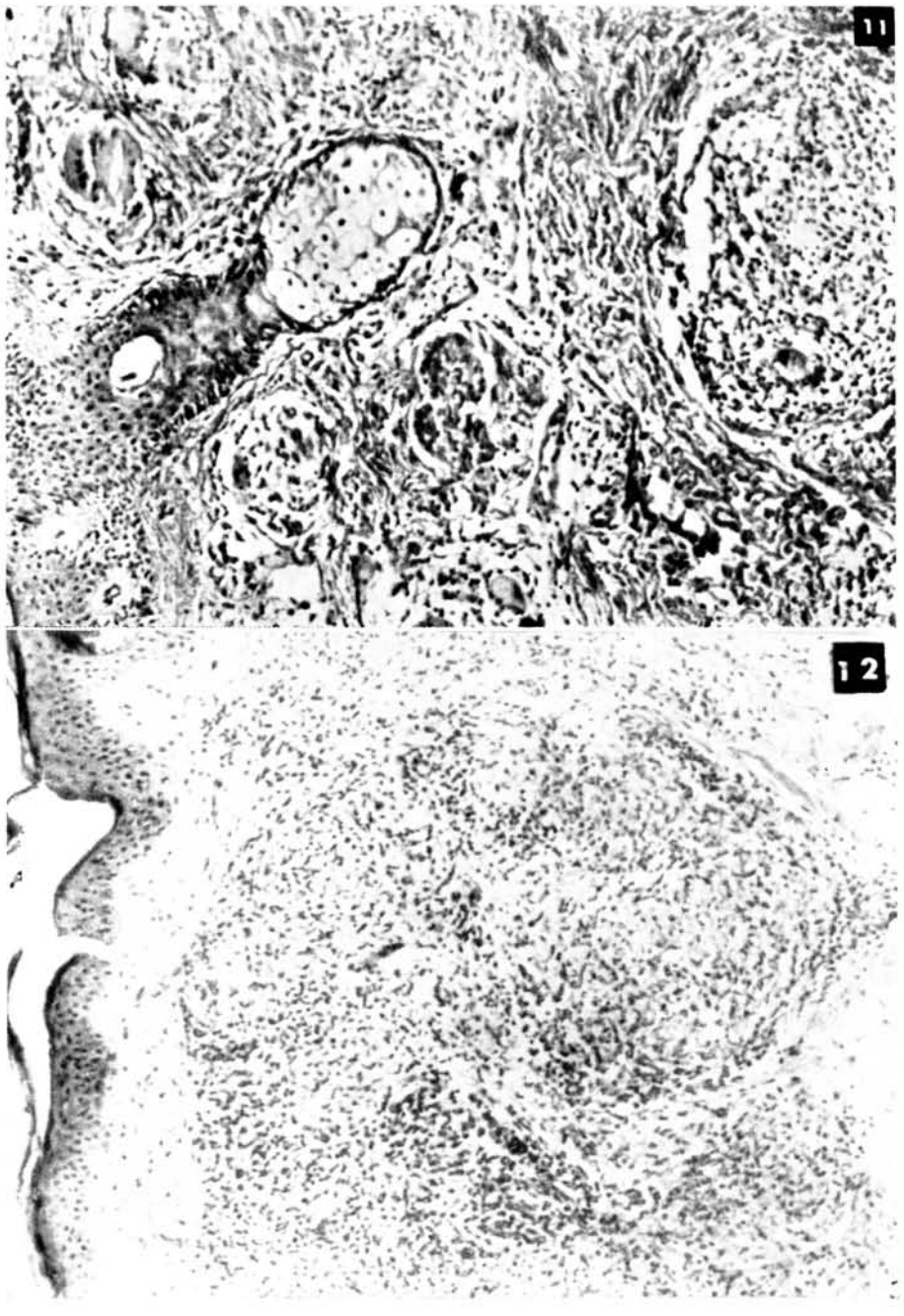

Plate 18