In the modern literature on leprosy, reference to the so-called "lepra lazarina" is much less frequent than was apparently the case in the past. The earliest authenticated reference we have found is the article by Lucio and Alvarado, published in 1852 (5), but neither the original nor a summary is available to us. According to Jeanselme (7) these authors considered the mixture of macules, ulcers (following bulla formation) and cicatrices as the elements which give lazarine leprosy its special character. Another writer who is frequently cited in connection with this type is Poncet. Klingmüller (4) lists five articles by him, the earliest of which appeared in 1864 (8).

Previous to that, Danielssen and Boeck (1), who did not include this condition in their list of the different forms of leprosy recognized by the older writers, laid much stress on the occurrence of bullae ("pemphigus") as the first definite manifestation of the disease in the anaesthetic type. Because it shows what was thought in those days of the onset of this type, at least in the North, there is some interest in their description, which we quote in somewhat condensed translation. First referring briefly to vague general prodromal symptoms, it continues:

..... [The patient] may remain for months or years without showing any essential change, until large bullae appear on any region of the body but especially on the extremities; there may be several of them but usually they are solitary. They appear suddenly, not preceded by any local symptom perceived by the patient. In size they vary from that of a hazelnut to that of a hen's egg; they are semi-transparent and filled with a viscous humor of greenish-yellow color, sometimes milky; they burst after some hours and the area presents a reddish ulcerated surface, often painful, that does not extend either in depth or size. For a long time these surfaces may continue to secrete a pale yellow, viscous humor, which frequently hardens.
forms brownish crusts. Sooner or later, often before the ulcerated surfaces of the previous ones have healed, a new bulla or several of them which follow the same course appear in new regions, and in this manner long periods, sometimes several years, may pass during which the patient is free from them only for short intervals. The ulcers heal, leaving cicatrices which are of the size of the bullae, a little sunken, pale and shiny, and usually a little hyposexitive.

Only once have we seen these bullae on the face; on the other hand they often occur on the palms and soles; and they may develop anywhere except on the hairy scalp. This solitary pemphigus is of such short existence and appears so insensibly that we have not observed it at the moment of its formation, or succeeded in obtaining from any patient a definite description of the condition before the bulla has formed. It often appears in the night and is broken in the morning, and the patient is astonished to see a large round ulcer formed so rapidly. Healing may, rarely, occur without scar formation, but it is usually a matter of months.

Though twice we have seen the condition in a more advanced period of the disease, and though it may be lacking, we nevertheless have a sufficient number of observations of their primary development to authorize us to place it among the prodromata. When it appears one can be quite sure that the anesthetic form of leprosy will develop sooner or later.

From a review of the available literature of lazarine leprosy it is apparent that, aside from the common feature of bulla formation either early or late in the course of the disease, the concomitant manifestations and the progress of this special form of the disease vary greatly in the different reports of it. Thus Jadasohn (2) describes it as characterized by the appearance of blisters at one stage or another but more often early, sometimes as the only manifestation for a long time. The blisters pass into or are substituted by necrosis, which in late stages may be extensive and may on healing leave pigmented or spotted scars. He considers this type as nothing more than an especially intense and acute exanthema made up of blisters and necrosis. On the other hand, the description of the same type by Klingmüller (4a) gives a rather different picture, one that fits remarkably well a case of so-called lepra reaction in the lepromatous type of the disease, with a severe course leading to the formation of bullae, ulceration and scarring to be described later. Finally, there is a tendency to associate this type with the ordinary cases of neural leprosy with more or less conspicuous bulla formation, "lèpre bulleuse." This, we gather, is the conception of Nicolas, Gatté, and Ravault (6), although the case reported by them showed, in addition to classical dystrophic changes, bullous and dyschromic elements with predominance of achromic macules, all at the same time.

Recent interest in lazarine leprosy was aroused by the article of
Pardo-Castello and Caballero which appeared in 1931 (7). Their study was based on 23 cases, all of which except one had no lepromatous manifestations at all other than destructive gangrenous ulcerations following bulla formation. Large numbers of leprosy bacilli were found in the blister fluid, and especially could be obtained from the sides of the ulcers. The characteristic course of these interesting cases is described by the authors as follows:

The beginning is usually rapid, sometimes sudden; the patient, apparently in excellent health, presents an erythematous patch about the size of a silver dollar, usually located in one of the extremities, and on which a blister develops containing clear, hemato or slightly cloudy fluid. The blister soon breaks down, leaving a raw, oozing surface which gradually assumes a darker hue, and finally, in the course of a few days, turns into a hard, dry, well-limited ulcer. At this time the lesions may be quite large, reaching a diameter of 4 to 5 inches (10.5 to 12.7 cm.). In some cases, when blisters develop in close formation, the result may be an enormous sphenoedermata. Under the sloughing tissue an ulceration progresses, destroying the subcutaneous structures, muscles, tendons, and bones, opening the joints and ending in tremendous mutilations....

The gangrenous tissues are eliminated in three or four weeks, and deep, irregular ulcers remain, from which tendons and even pieces of bone are eliminated. The granulation process is very slow, and in the course of several months to a year, cicatrization is completed, with atrophic depigmented scars as the final result.

In some cases, instead of erythema, a solitary nodule first appears, breaks down and leaves a deep ulcer. In still other cases a tremendous pachydermic edema of the arm or leg is observed; as a rule, bullae develop on the distended skin and follow the same course to gangrene and ulceration. The disease may be confined to one extremity, but often two or more extremities are affected simultaneously or successively.

In 1935 one of us (J.N.R.) reported a case which presented lesions somewhat similar to the monosymptomatic form described by Pardo-Castello and Caballero. The patient, previously healthy, had two successive crops of multiple macules. At the first attack blisters and pustules formed on some of the macules, leading to ulcers which enlarged in spite of all treatment. Three months later, before the ulcers had healed, a second eruption of irregular erythematous areas appeared, accompanied by high fever. These areas rapidly sloughed off, without preliminary bleb formation, producing ulcers that took many months to heal. Numerous acid-fast bacilli were found in scrapings from the sides of the ulcers and in tissue sections. For the first time, the tuberculoid structure of the macules and the walls of the ulcers was reported. In listing the characteristic features of lazarine leprosy, that finding was recorded as one of them.
Whether cases of this kind as seen on this side of the world are similar to the monosymptomatic form described by Pardo-Castello and Caballero remains to be established. There is certainly much more sphaeolomatous and gangrenous sloughing of tissues in the Cuban cases, with less constitutional symptoms, than in those observed in the Orient or anywhere else. Moreover, the histological findings reported by the Cuban authors do not clearly indicate tuberculoid leprosy. They report, from sections made by Drs. Recio and Hoffmann:

There is a very rich cellular infiltrate in the corium, especially around the blood vessels and glands. This infiltrate is composed of proliferating conjunctive tissue cells, lymphocytes, and plasma cells. There are no giant cells. In sections with Ziehl-Neelsen stain, there are some acid-fast bacilli in groups and some inside the cells.

A report by Dr. Satenstein on a section submitted to him by these authors from one of their cases is exceedingly poor in details but there is a hint of tuberculoid leprosy in the distribution of the infiltrate:

There are two zones of leprous tissue in this slide. One is rather deep in the cutis around the nerve trunks, and the other is superficial near the epidermis.

Ryrie, in 1938 (10), described cases of acute tuberculoid reaction with sloughing of the involved tissues and accompanied by low fever and rapid loss of weight. Considerable deformity and scarring was the usual result. Ryrie's cases will be mentioned again.

The diagnosis of Ryrie's cases as tuberculoid (certainly of major grade) was made, we understand, for the most part on clinical grounds—which to one familiar with the condition is usually sufficient. In the decidedly different case that is the occasion of this discussion the tuberculoid nature of the lesion process was established histologically while it was of only the minor grade. Another specimen taken early in the relapse phase, later in which the bulla formation occurred, was of indeterminate nature, but the subsequent clinical developments show beyond question that there had been no transformation of type from the tuberculoid to the lepromatous. Of interest is the fact that in this case the alterations were, and remained, superficial.

REPORT OF CASE

The earlier developments in this case have been dealt with in two reports of the present series, first (11) regarding the evolution, by reaction, of the major tuberculoid stage from the minor tuberculoid condition in which the patient was first seen, with subsequent
recession and parole, and second (12) regarding the relapse phase in which there appeared numerous and extensive new lesions, upon which later there was superimposed the bullous eruption under discussion. These previous phases will be reviewed summarily.

Previous history.—This patient (T.C.) was first seen in 1933 with extensive, rapidly spreading minor tuberculoid lesions, smears from which were highly positive (3+). Histology: tuberculoid, with numerous bacilli. The second phase, that of evolution to the major tuberculoid form, was initiated by an acute, incapacitating febrile reaction during which the previously affected areas flared up to a considerable extent and extensive new lesions developed. Trophic changes were present, mostly affecting the hands, when the patient was hospitalized in March, 1934. Four months later he was transferred to the Culion colony, though the condition was well along in the third phase, that of recession. Bacteriologically the case did not clear up until the middle of 1936. Paroled in March, 1937.

The fourth phase, that of relapse, began abruptly in September, 1938, when extensive, new, erythematous lesion areas appeared in immediate proximity to or completely surrounding areas previously affected by the major tuberculoid phase. Certain features of these lesions departed considerably from those typical of tuberculoid leprosy, most strikingly in that the edge toward the normal skin sloped off, having a diffuse character more like the lepromata. Around the enclosed unaffected areas, on the other hand, the elevation ended abruptly, the reverse of what is seen in tuberculoid plaques that have undergone central resolution, and the same condition existed where lesion zones lay beside other previously affected areas. All smears made were positive, some of them strongly so. Histologically the lesion in no way suggested the tuberculoid condition, but rather a very active, nonfoamy lepromatous one. These features we have called attention to as characteristic of the "relapse tuberculoid" lesions, which may easily be mistaken for leprosy transformed to lepromata.

Condition on admission (December 1, 1938).—Two months after the relapse there had been some recession of the lesions, and at the time of readmission to the Cebu leprosarium some six weeks thereafter it was recorded (Dr. J. G. Tolentino) that for the most part the areas were bluish-red and flat or only slightly elevated. Within their boundaries, however, though usually not coextensive with them, there were reactivated areas, bright red, thick and elevated, and lesions of similar character had also appeared in other places. There were now rather extensive ones on the face, which had been involved in the major tuberculoid phase. The ears were markedly involved, having much the appearance that would be expected in a rather advanced lepromatous case. On the extremities there was, it seems, a considerable extension of the affected areas, while completely new, relatively small ones had appeared on the trunk, front and back, on the palms, and perhaps elsewhere. Blebs were present on some lesions. A second reaction had occurred before the first one had completely subsided and all active areas, both the new ones and those within the older ones, were regarded as of the second reaction.

Other findings: Marked enlargement and induration of the ulnar and
great suralial nerves and thickening of the common peroneal. Trophic
to the lower extremities: paralysis of the right foot, with plantar ulcers of the right big toe and ball of left
Lymph nodes: inguinal, femoral, occipital, axillary, and epitrochlears not. A smear (right cheek) was strongly positive (4+). Diagnosis: NTb-major tuberculosis in reaction.

Reaction with ulceration.—Regarding the condition of primary interest
here, the following history has been obtained from the patient himself and
others associated with him.

After admission the patient was put under the usual chaulmoogra
aspiration and, after about five injections, all of the elevated, active lesions
became more acutely reddened and thicker, and the patient developed high
fever with chills. All of these reacting lesions except those on the face
acquired large blisters, or bullae. Each lesion had one; it was not a matter
of groups of small ones running together. Each blister spread rapidly until
the whole lesion was covered.

The content of these bullae was at first clear but in many, especially
the smaller ones, it became cloudy, almost purulent. The larger ones of
them ruptured, and for some days they gave off an oozing serum dis­
charge. Those that did not rupture gradually dried up, forming crusts,
beneath which there were shallow ulcerations. At no time was there any
scabbing; the ulcers healed, with more or less scarring. Altogether, the
duration of this condition, from the appearance of the bullae to the com­
plete healing of the ulcers, seems to have been about two months. No
special local treatment was applied. Antileprosy treatment was of course
interrupted during this period.

Reexaminations, 1939.—Three special reexaminations were made, one in
June by Dr. Tolentino at our request, the others by us in August and
October. On the first occasion it was noted that the lesions of the face
and ears had subsided completely and were hardly noticeable. Those of the
trunk and extremities were either flat or depressed, some paled and others
pale pink in color, with dark, irregular scars left by the superimposed lesions.
Smears: four negative, one positive (1+).

We, later, found no sign of activity. The face was free from infiltration,
the earlobes very thin and slightly wrinkled. The sites of the
previous extensive lesions now showed scars, of three degrees: (a) Pig­
mented scars, partly atrophic and partly keloidal, over the sites of the
thickest portions of the affected areas on the backs of both arms and back
of right thigh. (b) Atrophic leucodermic scars on the less infiltrated patches
on the front and the lateral side of the left thigh, the inner side of the
right thigh, the left buttock and the left scapula; also scattered spots on
the chest and back. These leucodermic scars were surrounded by irregular
areas of hyperpigmentation, and many of them showed pigmented spots
within the leucodermic areas, apparently at the sites of the hair follicles.
(c) The least infiltrated areas showed only hyperpigmentation, with irregular
pigmented areas within; these scars were seen on the left scapula, the in­
nner surfaces of both arms, and the chest.
Biopsy: specimen from the left hip, including both scar and normal skin. Histology: An inactive, residual lesion, with a broad band of rather delicate-fibered scar tissue superficially and only very slight infiltrative changes elsewhere, at wide intervals. Usually only a small collection of round cells, both large and small, in the usual locations, but at one or two points in each section a tiny, "subtuberculoid" group of epithelioid cells. One deeply-placed nerve, in contact with the subcutis, is more markedly affected, with definite though small tuberculoid foci. There remains, therefore, a residuum of the lesion-process, now definitely tuberculoid.

The picture seen at this time was that of one of those rare cases of acute tuberculoid reaction leading to extensive scar formation, suggestive of the so-called lazarine leprosy. The skin changes described are illustrated in Plate 23. It will be noted, by comparison with the illustrations in our previous report (12), that in most places only parts of the lesions that had existed in 1938 show definite scarring. On the right buttock, however, the leucodermic and the hyperpigmented scars together demonstrate the extent of the affected area, and set off in contrast the immune area within it, much more clearly than when the condition was active.

DISCUSSION

Since the formation of bullae is the one characteristic feature of lazarine leprosy, and since there has been confusion in the past as to what particular bullous phases of the disease should be placed under this category, it may be well to discuss in summary the conditions under which bullae may occur.

1. In "pure" neural leprosy (anesthetic or Na form).-In such cases the bullae develop in normal-looking but usually anesthetic skin, and can appear overnight without any subjective symptoms. Sometimes neuritic pains and even slight fever may precede their appearance. Their content is usually clear, limpid, and yellowish in color, though sometimes it may be blood-tinged or slightly cloudy. The blister fluid as well as the base of the resulting ulcer are negative of the leprosy bacillus, save in exceptional cases when a few may be found with difficulty.

While this report was in press it was learned (Dr. Tolentino, May, 1940) that six monthly bacteriological and clinical reexaminations were made by the local examining committee and the general disposal committees between September, 1939, and March, 1940. During that period the patient was in a quiescent state, with negative bacteriological findings in previously positive areas. The sites of the former red lesions showed merely leucodermic pigmentation, and the nasal septum was normal in appearance. However, at the last examination, made in April, 1940, the pale brown macules on the right chest, back of left arm, left wrist, and both buttocks showed suspicious signs of activity, and smears taken from these sites were found positive (from 1+ to 3+). It is possible that this is the onset of another phase of reaction.
These bullae are usually located in regions most exposed to pressure, friction and small repeated traumatisms, such as the feet, hands, elbows, and knees, though they are believed to be due to trophic influences, perhaps comparable to the eruption of bullae along the course of certain nerves following crises of fulminating pains in tabs. Their average size is around 4 cm., and there is usually a surrounding narrow erythematous margin. Unless there is secondary infection the contents dry up in a few days and exfoliation with complete healing follows, or, if the bulla is ruptured, a very superficial ulcer is exposed. This soon dries, leaving a pinkish macule. The color soon changes to dark-brown, or there may be hypochromia; but the return to the normal color of the skin is usually not long delayed.

Generally, in the later stages of the neural type, only a few such bullae appear at a time, but many workers in different countries have reported bulla formation early in the course of the disease, sometimes to the exclusion of other signs so that a "pemphigus precoce" has been mentioned among the prodromal symptoms, as by Danielsson and Boeck. In the late stages the bullae may be so numerous, or may reappear so frequently, as to merit the designation of "bullous" or pemphigoid subtype. In the Philippines, where the pure neural type is relatively uncommon, bulla formation in this type is only rarely observed, and in cases which are encountered many of the blisters are evidently produced by burns which were not perceived by the patient because of deep anesthesia, or are due to prolonged friction or pressure. However, almost all trophic plantar ulcers start as bullae.

2. In the lepromatous type.—Bulla formation can also take place during the course of the so-called lepra reaction in well-established cases of the lepromatous (L) type, particularly in the severest grades of the reaction. After a prodromal stage with high fever, joint pains, and general prostration an eruption of red papules and nodules of the erythema nodosum type appears, usually accompanied by activation of the preexisting lepromatous lesions. In the course of a few days blisters develop on the largest nodules, but subsequently smaller ones are also involved. Irregular blisters which usually run together to form large blebs may also appear on the most inflamed portions of the activated lepromatous patches. At the outset, the contents of the bullae may be cloudy or blood-tinged, but sooner or later the fluid becomes purulent. Clean-cut ulcers are formed under them; these may vary in number from a dozen to a hundred. Several may fuse together to form irregular, linear,
or serpiginous ulcers. Usually, however, they remain discreet, and if they are closely set together they may be separated from each other only by thin strands of normal-looking skin. Most of these ulcers heal fairly soon under antiseptic dressings, but some, especially those around the ankles, may last for months.

Attacks of bullous lepra fever may come at long intervals; frequently, however, these reactions with formation of fresh nodules, bullae, and ulcers are more or less continuous, or the attacks follow one another so closely, with hardly any respite, that the patient is bedridden for months or years. He becomes anemic and there is marked anorexia. Sometimes old tuberculous foci in the lungs become activated, and the patient dies of tuberculosis; at other times the cause of death is chronic nephritis. More typically the patient dies from real cachexia, with or without amyloidosis of the liver and spleen. At Culion it is chiefly among these cases of recurrent bullous lepra reaction that leprosy itself is the cause of death, and not intercurrent illnesses or complications.

3. In acute tuberculoid reaction.—Finally, bulla formation may take place during acute reaction in the so-called tuberculoid subtype of the disease. In two Cebu cases personally observed by one of us (J.N.R.), not including the one here discussed, small, closely set blisters containing cloudy fluid and pustules formed simultaneously on the most thickened portions of the reacting tuberculoid plaques, and these fused together to form bullae containing thin matter of purulent appearance. The ulcers which formed beneath them rapidly sloughed off, exposing a friable shiny base. On healing they left quite characteristic scars, mostly achromic, some pigmented, a few spotted. Parts of the same scars were atrophic while the rest were sclerotic. In the case herein reported, the physician in charge of the patient at the time of the development of the bullae reports that there was high fever at the onset, and that blisters "similar to those produced by burns" appeared on the acutely reddened and thickened lesions. The entire process of bulla formation, rupture, and healing of the resulting ulcers lasted some 4 weeks. Among Ryrie's "more than twenty" cases of ulcerating tuberculoid leprosy he observed only one with blister formation. He noted more frequently, as the signs preceding ulceration: (a) fine exfoliation, (b) direct giving way of the thinned-out epidermis, and (c) the appearance of engorged venules or punctate hemorrhages.

To which of the conditions enumerated above, if any, should the term lazarine leprosy be applied? It may be that, to avoid confusion, its use should be discouraged, that it should not be employed to de-
signate any of them. However, it seems to fit remarkably well the peculiar monosymptomatic form described by Pardo-Castello and Caballero, and at least until the real histological nature of cases of that kind has been determined the term lepra lazarina should be reserved for the Cuban type. If it should ultimately be found that the Cuban cases do belong to the tuberculoid subtype, some may wish to apply the term lazarine leprosy to all cases of bullous, ulcerative or sloughing acute tuberculoid leprosy. In our patient, bulla formation was a prominent feature of the acute reactionary phase, and because it occurred upon a tuberculoid substratum, we have designated it tentatively as "bullous tuberculoid leprosy."

**SUMMARY**

Our records of the case here reported cover the period from 1930 to the present time, during which period the course of the disease has shown startling developments. In one phase there suddenly appeared numerous bullae, followed by ulceration and finally leading to the formation of a mixture of pigmented, achromic and spotted scars. These phenomena, taken together, used to be regarded by some of the old writers as characteristic of the so-called "lazarine leprosy." The original rapidly spreading macular lesions in our case showed a typical tuberculoid picture both clinically and histologically, with numerous bacilli.

The occurrence of bullae in the course of the different types of the disease is discussed. Perhaps because it is commonly known that blisters do sometimes occur in the "pure" neural and the lepromatous types, as well as in acute tuberculoid reaction, "lepra lazarina" is not at present looked upon as a separate type or subtype of the disease and is seldom mentioned.

However, the article of Pardo-Castello and Caballero (1931), which described a peculiar monosymptomatic form of the disease, accompanied by blister formation, which those authors called lazarine leprosy, has awakened anew considerable interest in this old term. Pending restudy of the histology of their cases in the light of current knowledge of tuberculoid leprosy, it is suggested the term lazarine leprosy be limited to this special Cuban form. We have tentatively designated our case as one of bullous tuberculoid leprosy.

**REFERENCES**

FIG. 1. Scars on posterior surface of the left arm (not illustrated in previous report). The upper one is certainly not smaller than the original lesion as seen in 1938, but the conspicuous, irregular lower one does not cover all of the area previously affected.

FIG. 2. Scars on left back. The three prominent patches that existed in the extensive affected area over the scapula had ulcerated, and above them a fourth one not distinguishable in the 1938 photograph. The similar but solitary patch situated low, near the midline, had also ulcerated and now has around it a distinct zone, presumably of slight infiltration (not noted in the physical examination).

FIG. 3. Scarring of right loin, buttock and thigh, also of posterior surface of right arm. The immune area on the buttock is conspicuously demonstrated, as is also the long immune zone on the lateral surface, since scars of one grade or another occupy practically all of the area that had been involved by the active lesion.

FIG. 4. The same regions on the left side, where the scarring is much more irregular than on the right, in keeping with the greater irregularity of degree of the original lesion.