SESSION 5-13 MAY 1965

Dr. Binford. This morning we shall continue with our plan of presenting each day a speaker to discuss leprosy as a disease, because primarily we are concerned with the patient. Dr. Jose G. Tolentino, the first speaker, who, since 1951, has been engaged in the research activities of the Leonard Wood Memorial in the Philippines, is head of the Clinical Research Branch of the Philippine Division of the Leonard Wood Memorial. He will speak to you on "Acute manifestations of leprosy."

Acute Manifestations of Leprosy

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All forms of leprosy undergo phases of acute manifestation called lepra reactions, which are recurrent inflammatory conditions appearing during the course of the disease. Various forms of lesion have been described by several authors, who call the same condition by different names, thereby creating much confusion $(^{2})$. For example, what was called "lepra reaction" by the Madrid Congress in 1963 (3) is among the conditions collectively called "surtos" by de Souza Campos and Rath de Souza (8) in 1954, which included all outbreaks of acute reactivation and exacerbation of the disease occurring in any of its forms. It is also probably what Tajiri (10), in 1955, called "acute lepromatous infiltration" or reactivation. The condition designated "erythema nodosum leprosum" by the Madrid Congress (³) was called "acute panniculitis nodosa leprosa" by Pepler and associates (5) in 1955, and "relapsing lepromatous nodular hypodermitis" by Ramos e Silva in 1963 (⁶). The condition described and named "pseudoexacerbation" by de Souza Lima in 1951 (9) is probably what Tajiri described and called "acute infiltration" in 1955 (10), for both of which Wade (13) proposed the designation "reversal phenomenon." Lesions described by different authors for what appears to be the same condition and given different names should be identified and put together under, one classification.

The Madrid Congress (3) classified acute manifestations of leprosy in five categories, de Souza Campos and Rath de Souza (8) in three, Tajiri (10, 11) in five, and Ridley and Jopling (7) also in five. They differ from each other in many respects. All these classifications, however, can be put together in one common classification consisting of eight categories. In the lepromatous type we have three: (1)acute lepromatous infiltration or acute exacerbation, (2) erythema nodosum leprosum, and (3) the Lucio phenomenon, or necrotizing vasculitis. In the tuberculoid type, we have two: (1) the tuberculoid in reaction, or tuberculoid reactivation, and (2) reactional tuberculoid, or akuter Schub (11). In borderline leprosy we have three: (1) tuberculoid borderline (TB), (2) typical borderline (BB), and (3) borderline lepromatous (BL), or the reversal phenomenon of Wade (13).

Acute lepromatous infiltration is acute exacerbation of lepromatous leprosy. The disease becomes worse in this condition. In some cases there is only a generalized thickening and reddening of the diffuse infiltration all over the body, while in others

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FIG. 1. Acute lepromatous infiltration with diffuse generalized reddening and thickening of the skin.

FIG. 2. Acute lepromatous infiltration with nodulations on the face.

the condition produces also elevated patches, and nodulations and ridges, especially in the face, ears, and extremities. (Figs. 1 and 2.)

In the case of the erythema nodosum leprosum, occurring during the course of lepromatous leprosy, painful, acutely inflamed papules, nodules, and large patches appear in various parts of the body, but usually in the face and extremities. The condition is accompanied in the more severe cases by constitutional symptoms of varying severity (4). Frequently acute neuritis in the great auricular, ulnar, and common peroneal nerves may develop, and less frequently conjunctivitis and orchitis also. The papules, nodules and patches may produce blebs and pustules, which may, or may not, rupture. The intact blebs and pustules remain sterile as far as secondary infection is concerned, and heal without scar formation. The papules may disappear in three to five days, the nodules in five to eight days, and the patches in eight to 15 days. As the lesions subside, the bright red color changes to livid red and then to yellowish brown before it finally fades into the normal skin color. (Figs. 3 and 4.)

The Lucio phenomenon is a special type of acute manifestation of leprosy, observed almost exclusively in the Latin American countries. It is described as a necrotizing vasculitis beginning as purpuric lesions that become necrotic in the center and break down into ulcers. It is observed chiefly in advanced cases with diffuse lepromatous infiltration.

The lesions of the tuberculoid case in reaction are plaques, usually not less than 5 cm. in diameter, and few to several in number, which are in a state of acute inflammatory reactivation. They consist of bright red, raised, infiltrated areas with well defined borders and flat surfaces. In some subsiding lesions resolution begins in the center and proceeds outward, so that the center is thinner than the outer margin, which develops concave circinate macules. A few smaller tuberculoid lesions may appear in different parts of the body. (Fig. 5.)

In those acute manifestations of leprosy designated as reactional tuberculoid, or akuter Schub, one or more large, initial, International Journal of Leprosy



FIG. 3. Erythema nodosum leprosum (ENL) with typical red painful nodules on the upper extremities.

typical tuberculoid lesions may be reactivated, and at the same time numerous tuberculoid papules and nodules, superficially located, succulent in appearance, and bright-red or livid-red in color, appear in various parts of the body. They are well defined at the borders. The lesions are usually negative bacteriologically, or may harbor a very few acid-fast bacilli, which disappear rapidly. The lepromin test is usually positive, but generally slight. This type of acute manifestation of leprosy also may be observed in indeterminate cases that are being transformed into tuberculoid, and in cases of minor tuberculoid leprosy. The lesions subside rapidly as a rule, with or without the formation of depressed atrophic scars. (Fig. 6.)



FIG. 4. Erythema nodosum leprosum with a large patch below the right jaw. A pustule is seen in the center.



FIG. 5. Tuberculoid in reaction. The lesions are large, elevated and well-defined.



FIG. 6. Reactional tuberculoid with large initial lesions on the right hand and forearms, and small secondary lesions on arms and trunk.



FIG. 7. Tuberculoid-borderline (TB). Infiltration zones around central immune areas. FIG. 8. Another tuberculoid-borderline case with formerly tuberculoid lesions now undergoing transformation to borderline. Note the ill-defined borders.

Two types of borderline lesions were originally described by Wade and Rodriguez (¹²). One was an infiltrated area bordering the site of a healed tuberculoid plaque that became immune. In most of these cases, the infiltrated zone surrounds the immune area completely, but in a small number of cases it consists only of a segment of a ring. Characteristically this lesion ends abruptly at the border toward the immune area, sloping gradually toward the outer border, where it merges diffusely with the surrounding skin. Although the infiltration looks like lepromatous involvement, it subsides rapidly like tuberculoid. (Fig. 7.)

The other lesion of borderline leprosy described by Wade and Rodriguez, is a convex plaque or nodule, the thickest portion of which is in the center, while the outer portion slopes toward an ill-defined border. As a rule, there are many of these lesions, distributed bilaterally and symmetrically all over the body, in the manner of lepromatous leprosy except that they subside rapidly like tuberculoid lesions. (Fig. 8.)

These two types of lesions of borderline leprosy are highly positive for M. leprae, and the cases are negative in the lepromin reaction. They are, therefore, clinically, bacteriologically, and immunologically similar to the lepromatous type, but subside rapidly in the manner of the tuberculoid. Histologically, they show an admixture of lepromatous and tuberculoid elements (1).

Knowledge of borderline leprosy has advanced greatly since Wade and Rodriguez first described it, so that it now comprises a very wide zone in the spectrum of leprosy, so much so that the lesions have recently been subdivided into three classifications by Ridley and Jopling $(^{7})$, viz., (1) tuberculoid-borderline (TB), (2) borderline (BB), and (3) borderline-lepromatous (BL).

The tuberculoid-borderline (TB) lesions are those of tuberculoid cases undergoing transformation into lepromatous lesions as a result of repeated reactions. They may correspond, therefore, to what Wade and Rodriguez originally described as infiltrated lesions with central immune areas, and also to reactional tuberculoid cases in which both the mother tuberculoid lesion and its satellites have become ill-defined, or diffuse, at the borders. These tuberculoid cases undergo transformation as a result of repeated reactions, and they acquire characteristics of the lepromatous while still showing signs of the original tuberculoid state. (Figs. 7 and 8.)

The typical borderline (BB) lesions are papules, nodules and plaques that look like tuberculoid, but have diffuse borders. They are found in cases with lepromatous infiltration in the ears, cheeks, chin, and elsewhere in the body. These cases usually do not have an initial tuberculoid lesion, to distinguish them from the reactional tuberculoid that became borderline, and did



FIG. 9. Typical borderline (BB) lesions. The nodules have thick centers, sloping outer margins and diffuse borders.

not begin as tuberculoid. (Figs. 9 and 10.)

As noted above, tuberculoid-like lesions appearing in lepromatous cases were described in 1951 by de Souza Lima (⁹), who called this condition "pseudoexacerbation." Independently in 1955 Tajiri (11) described similar reaction as "acute infiltration." Wade (13) proposed the designation "reversal phenomenon," because it is a reversal from the usual course of leprosy, which proceeds from the milder tuberculoid to the more severe lepromatous form, to a course in which it passes from the more severe lepromatous to the milder tuberculoid type. Since it appears that there is a mixture of lepromatous and tuberculoid lesions in the same case, and, histologically, elements of the two types are also seen, cases of reversal phenomenon undoubtedly belong to the borderline type of leprosy.

Borderline-lepromatous (BL) cases are in the reversal phenomenon group of Wade, in which lepromatous cases develop tuberculoid-like lesions and, hence, are being transformed into the borderline form,

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FIG. 10. Large borderline lesions on the face. The lesions have the shape of an inverted saucer.

from which they probably came originally. (Figs. 11 and 12.)

De Souza Lima (⁹) described these tuberculoid-like lesions as acute outbreaks of well-defined, infiltrated or succulent, erythematous patches, some of them with brownish (ferruginoso) color; the group includes also nodular and papular lesions, and frequently edema of the hands and feet.

Tajiri (¹⁰) described his cases as having an abrupt but transitory erysipelas-like eruption with hyperemia and edematous infiltration. The lesions are of dark-red color and the counterpart in the lepromatous of reactional tuberculoid lesions in the tuberculoid cases.

Histologically, the lesions are like those of the reactional tuberculoid form, with more numerous bacilli, although much fewer than in acute lepromatous infiltration or reactivation. The Mitsuda reaction usually becomes positive. Our cases, however, were usually negative in the lepromin test.

De Souza Lima described two types of lesions, viz., (1) reddish brown (ferrugin-



FIG. 11. Borderline-lepromatous (BL). The face shows typical lepromatous involvement. FIG. 12. Same case as in Fig. 11, showing tuberculoid-like lesions on the trunk (reversal phenomenon).

oso) colored plaques, and (2) nodular and papular lesions. Tajiri described only one kind of lesion, i.e., dark-red erysipelas-like lesions with edema and infiltration.

In indeterminate leprosy we observe no acute manifestations, because, when in reaction, it is transformed into one of the three major forms.

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REFERENCES

- ALONSO, A. M. and AZULAY, R. D. Observations upon the borderline form of leprosy. Internat. J. Leprosy 27 (1959) 193-200.
- COCHRANE, R. G. and DAVEY, F. W. Eds. Leprosy in Theory and Practice. Bristol, John Wright and Sons Ltd., Baltimore, Williams and Wilkins, 2nd ed., 1964.
- [CONGRESS, MADRID.] Technical Resolutions. Classification, Mem. VI Congr. Internac. Leprol., Madrid, 1953, 75-80. (Also in Internat. J. Leprosy 21 (1953) 504-516.
- 4. DAVISON, A. R. and KOOIJ, R. Is erythema nodosum leprosum a favorable

occurrence? Internat. J. Leprosy 25 (1957) 91-98.

- PEPLER, W. J., KOOIJ, R. and MARSHALL, J. The histopathology of acute panniculitis nodosa leprosa (erythema nodosum leprosum). Internat. J. Leprosy 23 (1955) 53-60.
- RAMOS E SILVA, J. Relapsing lepromatous nodular hypodermitis. Presented at VIII Internat. Congr. Leprol. Rio de Janeiro, September 1963. Abstract in Internat. J. Leprosy **31** (1963) 537-538.
- RIDLEY, D. S. and JOPLING, W. H. A classification of leprosy for research purposes. Leprosy Rev. 33 (1962) 119-128.
- Souza Campos, N. and Rath de Souza, P. Reactional states in leprosy. Internat. J. Leprosy 22 (1954) 259-272.
- SOUZA LIMA, L. DE. The "pseudo-exacerbation" reactional state of leprosy. Mem. 3rd Conf. Panamer. Leprol., Buenos Aires, December 1951, 1 (1953) 184-188. (*Reprinted in Internat. J. Leprosy 23* (1955) 429-434.)
- TAJIRI, I. The "acute infiltration" reaction of lepromatous leprosv. Internat. J. Leprosy 23 (1955) 370-384.
- TAJIRI, I. The "acute infiltration" reaction of lepromatous leprosy. Internat. J. Leprosy 23 (1955) 316-317. (Correspondence.)
- WADE, H. W. and RODRIGUEZ, J. N. Borderline-tuberculoid leprosy. Internat. J. Leprosy 8 (1940) 307-332.
- WADE, H. W. A tuberculoid-like reaction in lepromatous leprosy. Internat. J. Leprosy 23 (1955) 443-446.

Dr. Binford. Dr. Jack Millar, who was scheduled to preside at this session was called out and in my desire to start this meeting on time I overlooked the fact that he was originally scheduled to introduce Dr. Tolentino. Dr. Millar, do you care to comment.

Dr. Millar. Remarks from me are really unnecessary. After-the-fact situations are never very productive, but I must say that in the past few days we have seen beautiful presentations of sophisticated work. I would add a comment not facetiously but as a challenge. As some of us noted last night in a not too smoke-filled room, we have DNA and RNA before us, but they have not saved one life or prevented the disease. As Dr. Tolentino has shown us, the clinician is faced with clinically acute manifestations of leprosy. Many of us have heard people say, after a visit to a leprosarium, "Where are the patients?" Normally, the average leprosy patient handles his disease fairly well, but for those complications that Dr. Tolentino described, with acute skin manifestations and other acute conditions, such as iridocyclitis and polyneuritis, the clinician has had no real rational approach for treatment other than 33, 3 (Pt. 2)

Discussion of Dr. Tolentino's Paper

empirical ones. It is of importance, I think, that we apply some of the more sophisticated approaches that have been presented earlier in these sessions so that we can get an understanding of what is happening in the individual, the host, possibly do something directly for him, and prevent further progression of his disease. Now as a normal situation with the good treatment that we have, we may reduce mortality, but when vou reduce mortality, you may actually increase morbidity. It is very difficult, when treating a disease rather empirically without a good basis for the therapy, to get a better understanding as to why reactions occur and what can be done to predict or prevent them. I believe that tomorrow this will be discussed more fully in connection with avenues of potential clinical research. I wanted to say this now because I know that those who have to treat patients, rather than just treat the bacteria, have a real problem on their hands. They need to have other biologic disciplines look at some of their problems. For instance, it has been known for many years that amyloid disease in tuberculous rabbits can be prevented very easily simply by giving estrogens. Amyloidosis is still the main cause of death in the treated lepromatous leprosy patient. Also, I would like to see the epidemiologic approach used in the clinical disease, for it may give us leads in problems of prevention. I want to congratulate Dr. Tolentino on his excellent presentation this morning. All of you who have treated patients know that when they suffer these acute exacerbations they are very sick. Their illness is very serious and it is difficult for the physician really to do much for them. More study is needed.

Dr. Binford. Thank you very much, Dr. Millar, for putting that in the record of the *Proceedings* of this meeting.

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