THE METHYLENE BLUE TEST IN LEPROSY

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In a previous paper we reported (1) some observations on the results of intravenous injections of a 1 per cent solution of methylene blue in cases of borderline leprosy.

The present report deals with a more extensive investigation of the response to that dye observed in patients of the borderline and indeterminate groups, as well as in cases of the lepromatous and tuberculoid types. We think that the facts observed are interesting enough to warrant publication.

MATERIALS AND METHODS

A total of 112 cases were selected from among the patients of the Cabo Blanco Sanatorium in Maiquetía, and of the Vargas Hospital in Caracas. Of these cases, according to clinical, bacteriologic and histopathologic findings and the results of the Mitsuda-Hayashi test, 65 were lepromatous, 37 borderline, 6 indeterminate and 4 tuberloid. All the patients chosen for the experiment were in good general condition as shown by routine laboratory tests.

In almost all the cases the methylene blue was given intravenously in a 1 per cent aqueous solution; only a small group received it orally. The intravenous injections were made daily, in doses of from 1 to 3 cc. at first, gradually increased until doses of 10, 15 and 20 cc. daily were reached.

The aggregate of the daily doses was about 100 cc. for each individual, except in the lepromatous cases of which a great majority gave rapid and intense colorations with the first few injections. In the others it was thought that a total of 100 cc. would be sufficient to show retention of the dye, if the lesions were capable of retaining it at all.

The average period during which the injections were given was 2 weeks; but some patients received them for longer periods, even up to 4 months.

The patients of the small group which received the dye orally were given 1.5 gm. daily in 3 doses of 0.5 gm. each. These large doses were necessary in order to produce coloration in the lesions in the course of 2 weeks

The majority of the persons who received the dye intravenously tolerated it very well, although a small number of them showed a slight neutropenia with lymphocytosis and moderate anemia, besides pain along the blood vessels; but these symptoms disappeared spontaneously. This was not the case, however, with the patients who received the dye orally. In all of these, dysuria was observed, and there was one case of jaundice; but the symptoms disappeared when the dye was discontinued.

RESULTS

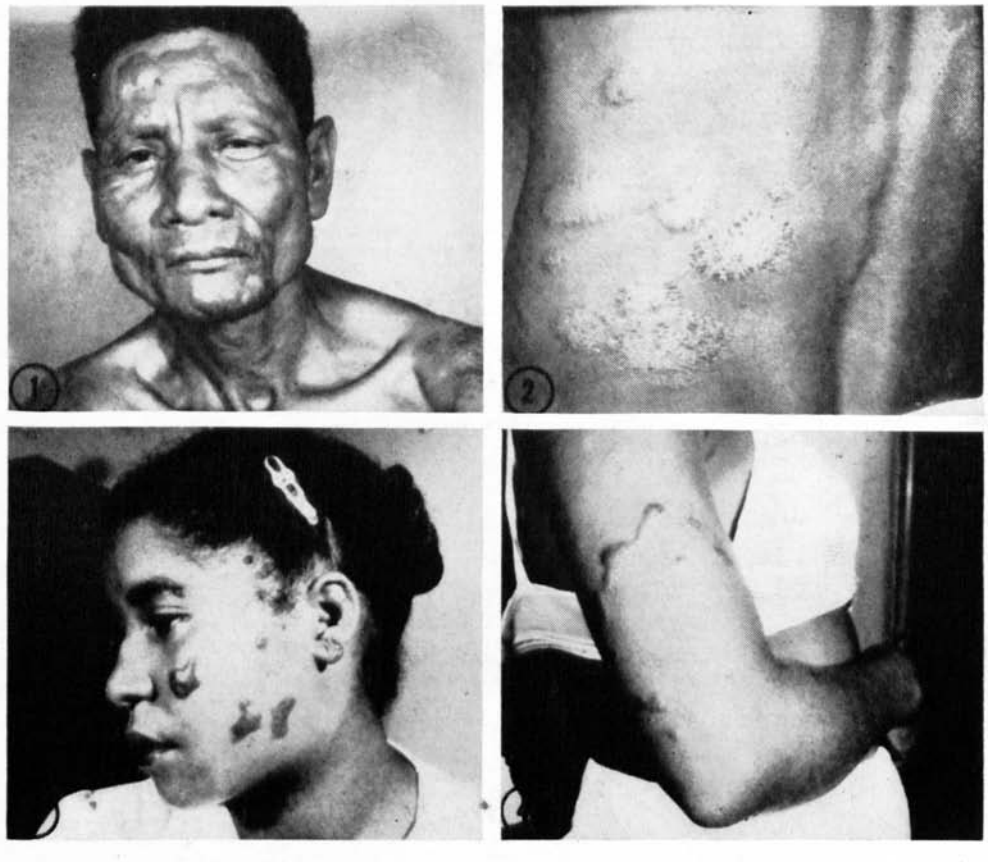
Borderline cases.—The patients of the borderline group reacted to the methylene blue test in the following manner:

(*a*) In many cases retention of the dye was observed in some lesions and not in others (Figs. 1 and 2). The differentiation between stained and unstained zones was remarkable. There were cases which showed very small areas with intense retention of the dye in the midst of extensive lesions which remained unstained. The histopathologic examination showed that the dye was retained only in the lesions that had a lepromatous structure.

(*b*) There were cases in which the retention was strong in some lesions and weak in others.

(*c*) Sometimes in infiltrated lesions with well-defined borders there was an intense retention of the dye, with none in the parts of the skin of the same patients that remained unaffected by the disease (Figs. 3 and 4).

(*d*) In the hypochromic macules left by borderline lesions in regression—a phenomenon observed in 61 per cent of the cases—the dye was retained, and the histopathologic study showed the persistence of a



lepromatous granuloma, while the nonlepromatous granuloma had regressed. In one case of this group, we observed in the course of the administration of the dye a reaction phenomenon of the erythema multiforme type.

Lepromatous cases.—Each and every one of the patients of the lepromatous type with active lesions in the skin and in the mucous membranes became pigmented. The great majority of them began to retain the dye in the early stage of the experiment, with as little as 6 to 20 cc. as a total dose. The following peculiarities were observed:

In the advanced cases with severe lesions of the skin and mucous membranes, the retention of the blue pigment was a general phenomenon throughout the skin and in the buccal, nasal and pharyngolaryngeal mucous membranes. In the moderately advanced cases, unpigmented areas were observed side by side with diffusedly-defined pigmented zones.

In other cases, in which the clinical examination did not reveal very extensive lepromatous infiltrations, the dye was retained in large areas and gave apparent evidence of important lesions that had passed unnoticed by experienced leprologists. This revelation of "inapparent" lesions by methylene blue was repeatedly noted by Montel and others,

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DESCRIPTION OF PHOTOGRAPHS

These photographs are all duplicated in color transparencies, which because of the expense cannot be reproduced here. In none of them does the blue color show up well as such in the brownish skin, but only—as in the black-and-white pictures reproduced—as a darkening of the natural color.

FIG. 1. Marked infiltration of the face, with strong retention of the dye. (Cf lighter color of the upper forehead above the plaque.) Note that the spotty old lesions on the shoulders show no evidence of activation. In one side view (color transparency), as here, the ears seem to be unaffected.

FIG. 2. Lesions of the trunk of the same case (major tuberculoid, of chronic aspect) have not retained the dye. (The same is true of similar lesions on the limbs.) The large plaque (?) on the right scapular region seems to be the most active of the lesions here shown.

Note: This case is an atypical example of the multiform condition described by Wade as "relapsing tuberculoid." It is atypical, for one thing because of the sharp limitation of the infiltrate on the forehead, suggestive of ordinary reactional tuberculoid, but side views (color transparencies) show diffusion of the lesions on the cheek to the normal skin, as is characteristic of the morphology of borderline infiltrates. This is in keeping with the diagnosis of borderline which is unavoidable in view of the retention of methylene blue by the face lesion. The case is also unusual in that the tuberculoid lesions on the body show no signs of reactional disturbance, or activation.

FIG. 3. Intense retention of methylene blue in markedly elevated nodules and plaques, sharply delimited from the normal skin of the face. There is a discrete, nodular lesion limited to the left earlobe; the right lobe is quite unaffected (other picture, color transparency). The eyebrows are not affected.

FIG. 4. Lesion of the arm with discontinuous elevated ("figured") margin, same case as in Fig. 3. The features of this lesion resemble the tuberculoid type, but the border retains the methylene blue very strongly. Other pictures (color transparencies) show the interrupted, elevated portions of this marginate lesion to be of the same color and apparent texture as those of the face.

Note: This case is of special interest, not only because of the lesions shown in the pictures, but also because there were lesions of another type on the back which retained the dye much less strongly. Sections showed the deeply staining lesions of the face and arms to be lepromatous granulomas with numerous bacilli, whereas the lesions of the back seemed to be predominantly composed of epithelioid cells, and the bacilli were much less in evidence.

as for example Flavio Maurano ([2]), in the period when the dye was being tried extensively for its supposed therapeutic effect.

In cases with lepromatous lepra reaction (polymorphous erythema nodosum), no methylene-blue retention was observed, but the dye was retained in the hyperchromic, residual lesions that remained after the reaction had ceased.

In several of the most retentive cases the blue coloration persisted for a whole year after the injections had been discontinued.

In lepromatous cases with minimal residual lesions remaining after proper sulfone treatment, difficult to detect by clinical examination, very small blue-tinged areas were observed. Smears from these areas were bacteriolgically positive and showed on histopathologic study a lepromatous granuloma.

Tuberculoid and indeterminate cases.—The methylene blue was not retained in the lesions of these cases, in spite of the fact that they had received much larger total dosages than had the patients of the lepromatous type.

DISCUSSION

The methylene blue test we consider to be a valuable aid in the diagnostic differentiation of leprous infiltrations. It is positive only in the lesions of lepromatous cases and to variable degrees and in variable ways in those of borderline cases because of the presence of a lepromatous element. We have studied the test in the granulomas produced in other parasitic diseases, such as leishmaniasis, mycosis and treponematosis, but have been unable to produce any retention of the dye in those lesions.

We are inclined to believe that the positivity of the test may be due to a lipid component in the lepra cell. We are therefore preparing to apply the test in diseases in which there is an aberration of fat metabolism.

In the patients of the borderline leprosy group, the retention of the dye was directly proportional to the intensity of the lepromatous infiltration, and served as a means of prognostic orientation. Retention in the hyperchromic recessional or residual macules in the same group served to distinguish these spots from the lesions of the indeterminate group. We are quite aware, however, that the methylene blue would also be expected to be retained in a case of indeterminate leprosy in the course of transformation to lepromatous nature.

In reactional cases of the tuberculoid type, which may be confused clinically, and even histologically, with those of the borderline group, the negative result of the test serves to clarify the situation. In a case with extensive reactional tuberculoid lesions, it was observed that the dye was not retained, in spite of the very massive doses that were injected, but a limited retention was found in the nasal mucous membrane, which was bacteriologically strongly positive.

When the test was given to lepromatous patients undergoing treatment, it served as a guide in the discovery of residual lesions. We believe that its use is important, when it is a question of continuing or suspending treatment.

The attempts in years past to use methylene blue as a therapeutic agent, or as a coadjuvant in the treatment of leprosy, have now only historical interest. However, the observations of Montel ([3]) on the differential retention of the dye in the different forms of the disease are of lasting value as an aid in diagnosis and prognosis. Our present work has amply confirmed this conclusion.

SUMMARY

The use of the methylene blue test for the differential study of cases of leprosy is recommended. In the borderline group, the retention of the dye in the experiment reported was directly proportional to the quantity and extension of the lepromatous component of the lesions, and it is thus a prognostic test in such cases.

In lepromatous cases with minimal lesions after prolonged treatment with present day antileprosy drugs, the test served to detect lesions that had passed unnoticed in clinical examinations.

RESUMEN

The effects of administration of methylene blue to leprosy patients have been studied in 112 cases, 65 lepromatous, 37 borderline, 6 indeterminate, and 4 tuberculoid. The dye was given mostly in daily intravenous injections of a 1 per cent aqueous solution, in doses increasing from 1-3 cc. to 10-20 cc. The usual average for cases not staining promptly was about 100 cc. total, given in about 2 weeks. There was little trouble from intolerance in the cases given the dye intravenously.

The lesions of the indeterminate and tuberculoid cases did not take the stain, even after maximum prolongation of the course of injections. Those of the lepromatous cases, on the other hand, usually stained readily and deeply, often after only a few doses (6-20 cc. total). The well-known demonstration of "inapparent" lesions occurred repeatedly, whereas lepra reaction lesions did not retain the dye.

The results in the borderline cases were variable. In general, there was retention of the dye in some of the existing lesions, or parts of lesions, but not in others, and intensity of staining varied similarly. Retention occurs only in the lesions and parts of lesions where the histologic structure is lepromatous, and its retention is in direct proportion to the relative amount of that component; hence the methylene blue test has prognostic significance in such cases.

The true nature of reactional tuberculoid cases which might be mistaken for borderline will be evidenced by lack of staining of the lesions. On the other hand, the test is also useful in borderline cases with residual macular lesions (resembling indeterminate) to see if any of the

lepromatous element persists in these lesions; also in lepromatous cases that have receded under treatment, for detecting residual lesions which have become indistinguishable but have not wholly cleared up.

RESUMEN

Los efectos de la administración del azul de metileno en enfermos de lepra ha sido estudiado en 112 casos, 65 lepromatosos, 37 borderline, 6 indeterminados y 4 tuberculoides. El azul de metileno fué administrado principalmente en inyecciones endovenosas diarias de una solución acuosa al 1%, en dosis crecientes, desde 1 a 2 cc. como dosis inicial hasta 10 a 20 cc. La dosis media total para los casos que no retuvieron el colorante prontamente fué alrededor de 100 cc., administrados en dos semanas. Hubo muy pocos fenómenos de intolerancia en los casos en que se hizo la administración del colorante por vía endovenosa.

En los casos tuberculoides e indeterminados las lesiones no tomaron el colorante a pesar de que en ellos se prolongó al maximum el período de aplicación de las inyecciones. Los casos lepromatosos por el contrario, usualmente tomaron el colorante rapida e intensamente, frecuentemente después de pocas inyecciones (6 a 20 cc. en total). El hecho bien conocido de la demostración de lesiones "inaparentes" ocurrió en muchas ocasiones; aunque las lesiones de reacción leprosa no retuvieron el colorante. Los resultados observados en los casos borderline fueron variables. En general, se observó retención del colorante en algunas de las lesiones, o en parte de éllas, pero no en otras, y la intensidad de la coloración también varió de manera similar. La retención del colorante ocurrió solamente en lesiones o parte de lesiones donde la estructura histológica era lepromatosa, y la retención fué directamente proporcional al componente lepromatosa, teniendo por esto el test al azul de metileno una significación pronóstica.

La verdadera naturaleza de los casos tuberculoides reaccionales que pueden ser confundidos clínicamente con los casos borderline, puede ser determinada por la ausencia de retención del colorante en las lesiones. Además el test es también útil en casos borderline con lesiones maculares residuales (semejando lesiones del grupo indeterminado) pudiéndose observar si persiste algún elemento lepromatoso en dichas lesiones; también en casos lepromatosos que han regresado bajo tratamiento, a fin de poner en evidencia lesiones residuales on visibles, y que por lo tanto no hayan regresado totalmente.

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