Reprinted from Annals of Tropical Medicine and Parasitology, Vol. 73, No. 1 (1979)

Racial differences in espundia

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Received 19 November 1977

The principal characteristic which distinguishes *Leishmania braziliensis* from other species causing cutaneous infections in man is its propensity to manifest a secondary stage of infection in which metastatic spread to the nasal, pharyngeal and buccal mucosa can result in the complete destruction of these tissues and associated cartilage. This manifestation, commonly called espundia, is generally regarded as a relentlessly progressive process which can be interrupted or slowed only by specific therapy (Leon, 1957). The primary lesion is usually a cutaneous ulcer, which is often self-limiting, and heals after a period of one to several years. However, unlike *L. tropica* in the Old World, *L. braziliensis* frequently persists as an occult infection with the ability to produce secondary manifestations of mucosal involvement over a period ranging from several months to many years after the primary cutaneous infection (Walton, Valverde and Eguia, 1973).

Racial differences in the course and outcome of disease have been well documented in certain bacterial and mycotic infections (Rich, 1951; Huntington, 1959; Stein, 1959), but have rarely been recorded as an influencing factor in protozoan infections, other than malaria, and to our knowledge have not been reported in leishmaniasis. We wish to report here that there are distinct differences in the rapidity of evolution and in the end consequences of espundia between indigenous Amerinds and persons of African ancestry.

During the course of a clinical drug trial in the Yungas district of Bolivia on the eastern slope of the Andes, we observed that severe facial mutilation due to espundia occurred almost exclusively among Negroes, and that this condition was rare in other racial groups. In this region there are three distinct ethnic groups: the indigenous Amerinds (predominantly Aymara, though there are some Quechuas), the Negroes (descendants of African slaves brought to the area in the Spanish colonial era), and the Latinos (predominantly of European stock, but with some admixture from the Amerind gene pool). The Negro and Amerind population groups have coexisted while retaining their genetic integrity almost intact for more than two centuries. Where there are small villages, or clusters of two to three houses, the communities are almost invariably inhabited by only one racial group. However, geographically they are well intermingled, with the small plots of land of the blacks interspersed among those of the more numerous Amerinds.

Differences in susceptibility to primary infection or in the evolution of the cutaneous ulceration were not noted between the two groups. Similarly, we were unable to determine if a greater proportion of infected Negroes developed espundia, but it was apparent that,

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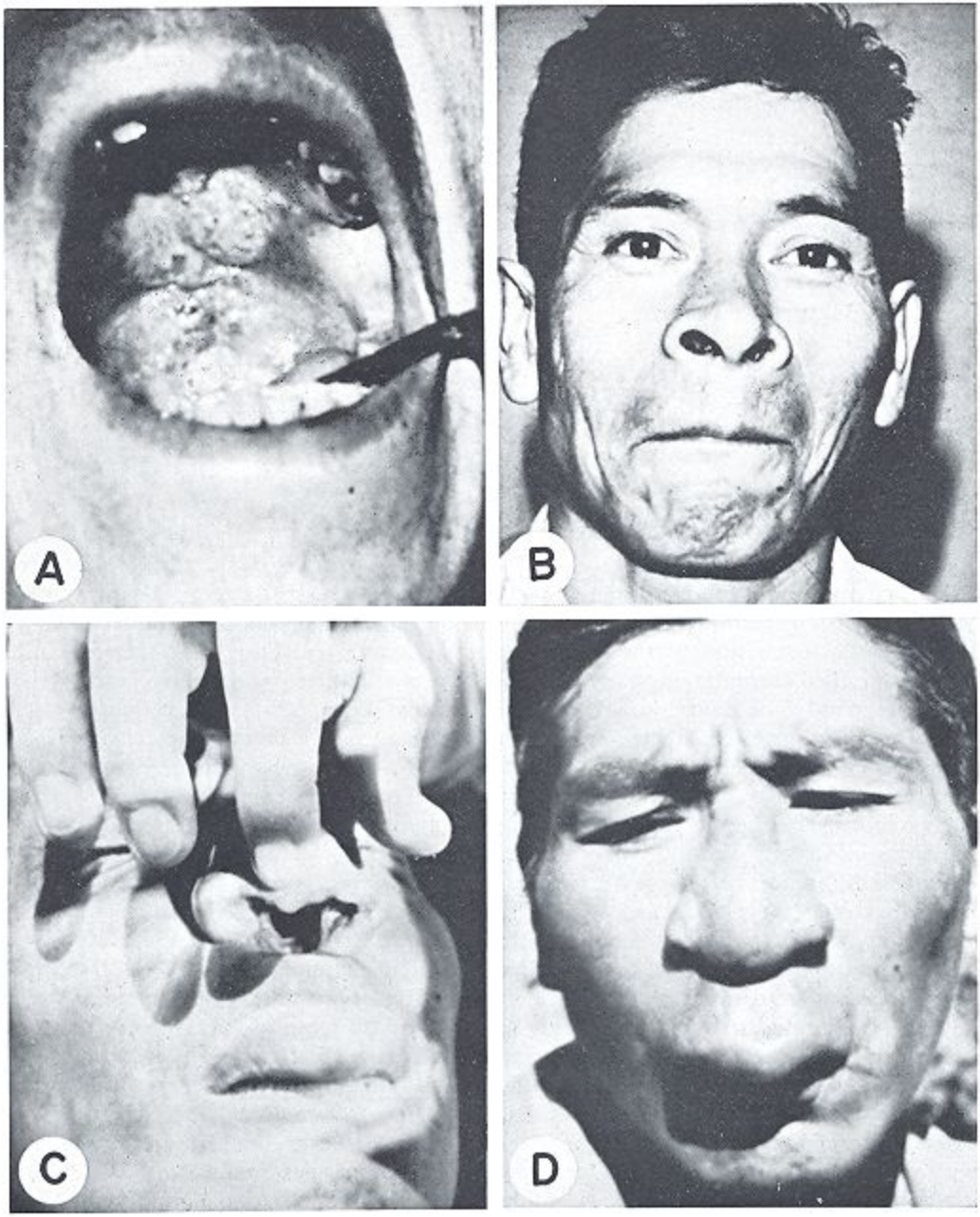

Fig. 1. Amerinds with espundia. A. Leishmanial granulomata of palate without ulceration after 20 years' duration. B. Same patient, showing lack of mutilation. C. Total destruction of cartilage, including columnella. D. Same patient, showing oedema and infiltration but lack of ulceration.

once invasion of mucosal tissue occurred, there was a pronounced difference in the rapidity and extent of evolution of lesions, and that the effects were much more damaging in Negroes.

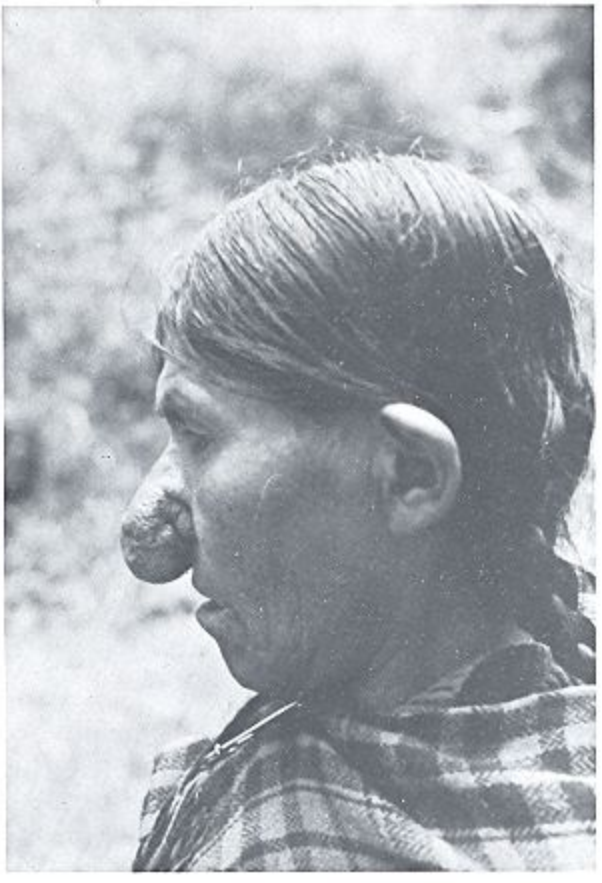

Fig. 2. 'Tapir nose' from long standing espundia in Amerind.

CLINICAL OBSERVATIONS

Most Indians showed little external evidence of their mucosal lesions, although many were extensive and of many years duration. They characteristically had a perforated anterior nasal septum, extensive involvement of both hard and soft palate, and the larynx was often heavily involved to the extent that the patients were very hoarse or almost voiceless. There was hyperplasia and oedema of the involved tissues, and although there were often large granulomata, there was no extensive ulceration and little visible disfigurement. Representative cases are shown in Fig. 1. Photos A and B are of a patient with a history which suggests nasal involvement for approximately 20 years. The anterior septum was perforated, the uvula destroyed, and there was involvement of much of the hard and soft palates. There were large granulomata over the affected areas, but no extensive ulceration. The larynx was evidently heavily involved, with the voice characteristically hoarse and weak. Figs. 1C–D are of a patient with a history of at least 16 years' duration. The cartilage of the nasal septum, including the columnella, was completely destroyed. There was hyperplasia of the nose and upper lip, but no externally apparent ulceration or tissue destruction. The hyperplasia and oedema of long duration may result in fibrosis and permanent gross enlargement (Fig. 2). This characteristic elongation has been termed 'tapir nose' because of the fancied resemblance to the proboscis of that animal (Leon, 1957). Our observations in

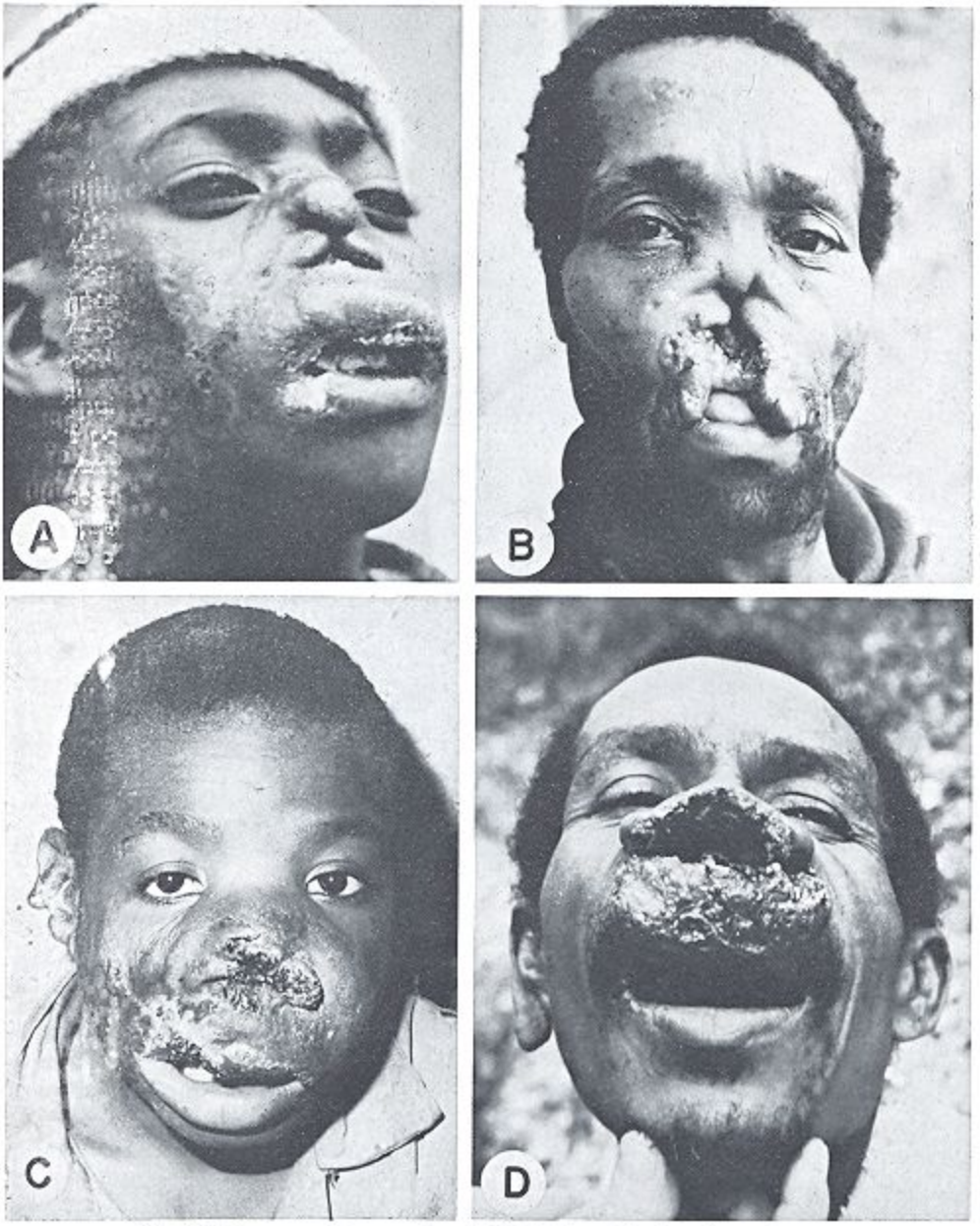

Fig. 3. Negroes with espundia. A. Mutilation after less than three years. B. Mutilation from eight years' infection in spite of antimonial therapy. C and D. Active necrosis in spite of sparse parasites.

this series included over 40 Amerinds with mucosal involvement. Among these we found only one with extensive mutilation from necrotizing ulcerations.

Because they constitute a much smaller population, we saw many fewer Negroes with espundia, only 12 proven cases. However, of these, ten (83%) exhibited mutilating lesions similar to the representative cases illustrated in Fig. 3. Photo 3A is of a nine-year-old Negro with a history of espundia of less than three years' duration. The mucosal surface of the lips

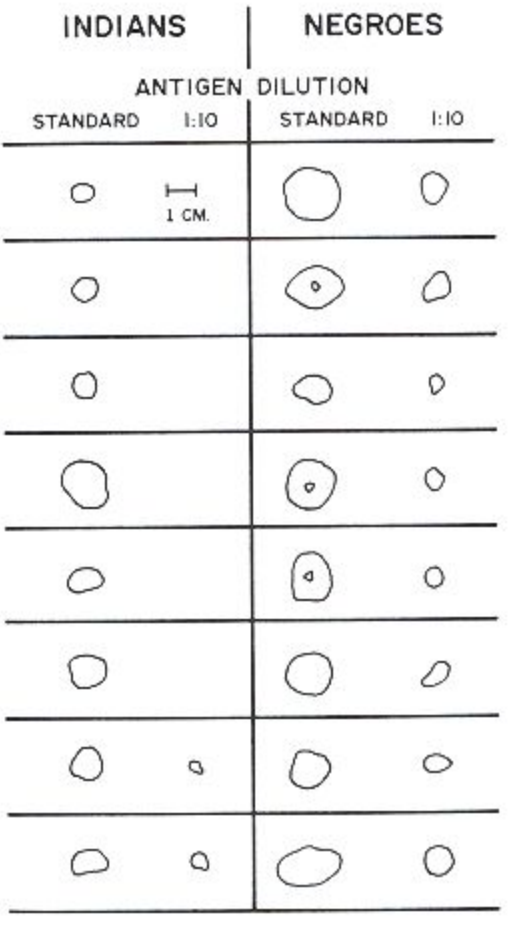

Fig. 4. Extent of intradermal reactions of Negroes and Amerinds to two strengths of leishmanin antigen after 48 hours.

and the entire soft palate had ulcerations. The patient shown in Fig. 3B was successfully treated with antimonials, but extensive tissue destruction had occurred during eight years of evolution before the parasites were eliminated. Figs. 3C–D illustrate the active phase of the necrotizing ulcerative process evidently responsible for the mutilations seen among Negroes. The 12-year-old boy in Fig. 3C had a history of mucosal involvement of six years at this stage of disfigurement. The patient shown in Fig. 3D had a possible ten year history, but the extensive open ulcers and erosion of the nares occurred in the last 2½ years.

We first considered the possibility that a lesser inherent resistence of the Negroes permitted exceptional proliferation of the parasites, with tissue damage resulting directly from destruction of cells invaded by parasites. The tissue sampling was inadequate for a final conclusion, but biopsies and tissue smears did not appear to support this explanation, since there was a remarkable scarcity of parasites seen in the lesions of both racial groups. Among the Negroes the pronounced inflammatory response and the extent of mutilation, in spite of few demonstrable amastigotes, suggested that tissue destruction was due to a cell mediated hypersensitivity phenomenon. The overall appearance of the lesions of active cases, as well as the histological appearance, suggested a destructive delayed type reaction to parasite antigens in a host with exaggerated dermal hypersensitivity.

RESPONSE TO ANTIGENS

To test this hypothesis and to compare the severity of the specific allergic inflammation to the parasites elicited in the two racial groups, leishmanin skin test antigen was utilized in two different concentrations. The modified Montenegro type antigen was prepared from promastigotes pooled from ten-day cultures of two strains of *L. braziliensis* of human origin from Panama, washed in buffered saline solution and disrupted by sonication. The antigen had a final concentration of 85·4 μg nitrogen/ml, which had been empirically determined to be a concentration which produced wheals of approximately 1 cm in diameter when tested with six proven leishmaniasis cases in Caucasians in the Canal Zone. A wheal measuring 0·5 mm is considered positive with this antigen. A second strength antigen was prepared by further dilution 1:10 with buffered saline solution. Thiomersal 1:10 000 final dilution was added as a preservative.

Injections of 0·1 ml of each of the two concentrations of antigen and a buffered saline–thiomersal control were given intradermally on the volar surface of the forearm in a series of eight Amerinds and eight Negroes who had espundia and who agreed to the study. The induration was measured after 48 hours. The differences in reactions to the antigen among the two racial groups can be compared in the portrayal of the wheals in Fig. 4. The reactions among the Amerinds to the standard strength antigen were all positive and comparable in size to those elicited from Caucasians in the Canal Zone, averaging slightly over 1 cm in diameter. With the reduced strength antigen, only two exhibited any detectable induration, and these wheals were both indistinct and less than 0·5 mm. In contrast, all the Negroes had pronounced wheals from the reduced strength antigen, with half of them more than 1 cm in diameter. With the standard strength, the area of the wheal did not enlarge proportionately with the increase in antigen, but an area of necrosis and sloughing occurred in the center of the wheal in three patients. After 72 hours, another patient also developed a slough, bringing to 50% the total who were exhibiting necrosis from the delayed reaction. Thus, within the limits of this inexact means of measuring the apparent cell-mediated allergic response, the persons of African ancestry exhibited a sensitivity approximately ten-fold greater than that of the Amerinds. The antigen standardized at a strength to produce wheals of diagnostic dimensions among Caucasians and Amerinds was sufficient to produce open necrosis in Negroes. This strongly suggests that an exaggerated immune inflammatory response could be the mechanism responsible for the observed greater prevalence of mutilation from espundia among Negroes.

DISCUSSION

The observed differences appear to be independent of environmental factors, since the socio-economic condition, diet, and general mode of life of the two racial groups are essentially identical. Because they are in close geographic proximity, presumably they are subjected to bites by the same species of vectors and are infected by the same strains of the parasite. Both groups primarily engage in subsistence agriculture, often involving clearing of jungle, which imparts a high risk of leishmanial infection. The Latinos are almost exclusively town dwellers and have an extremely low incidence of leishmanial infection so their response could not be compared with the other two groups.

Evidently some thought was given to possible differences of response of Negroes to leishmanial infection by Pessoa and Barreto (1944), since they reported that Negroes who had infections of over one year's duration, and those with mucosal involvement, were more sensitive to skin testing with single strength antigens. However, in the population which they studied racial mixture was common and they reported no conclusions in this regard.

In a discussion of the phenomenon of extensive tissue destruction in spite of sparse *Leishmania* parasites, Heyneman (1971) speculated that the damage might be the consequence of development of autoimmune disease in the '. . . final self-destructive stage of mucocutaneous leishmaniasis.' However, no explanation was offered as to why the autoimmune destruction is restricted to the nasal and buccal mucosa and associated cartilage.

The role of the immunologic response is obviously of prime importance in the pathogenesis of espundia, and the existence of significant inherent differences in two population groups may afford a means of understanding the operative factors. The genetically distinct populations in an area of high disease prevalence in this region of Bolivia provide an unparalleled opportunity for such research. It is hoped that other investigators will take advantage of this situation to investigate additional parameters to expand upon our preliminary observations.

SUMMARY

Racial differences have not previously been reported as a significant factor in leishmanial disease. However, in the eastern Andes of Bolivia, extreme facial mutilation due to espundia was almost exclusively confined to persons of African ancestry, although many more cases of leishmaniasis were seen among indigenous Amerinds in the area. Skin testing with two strengths of antigen gave much greater reactions among the Negroes, suggesting that mutilation is due to necrosis resulting from an exaggerated immune inflammatory response.

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Printed in Great Britain by Henry Ling Ltd., at the Dorset Press, Dorchester, Dorset