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PATHOGENICITY OF *LEISHMANIA DONOVANI* IN MAN

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SUMMARY

On the basis of various clinicopathological conditions associated with visceral leishmaniasis in different areas — i.e., primary skin lesion, cutaneous or glandular involvement alone or concomittant with visceral involvement, post-kala-azar dermal leishmanoid, etc. — the Author presents his own original view on the pathogenicity of *Leishmania donovani* and the evolution of human infections by this parasite. He also speculates on the rôle of age, immunity and epidemics as causes of variation in severity of kala-azar and its response to treatment in different countries.

Editor's summary

Leishmania donovani was discovered by LEISHMAN in 1903 in the smears of splenic tissue of a soldier dying of a chronic febrile illness that he had acquired while living at Dum Dum, a military cantonment near Calcutta [16]. Subsequently during the year DONOVAN [6] found the same parasite in the splenic smears made ante and post mortem from cases under his care in Madras, South India. The former regarded the disease as related to trypanosomiasis and the latter as a cachectic fever that was not malaria. Ross [26] in 1903 named the protozoon as *Leishmania donovani* in honour of the two discoverers and recognized it as the causative organism of kala-azar in India. The leptomonad form was first discovered by G. C. CHATTERJEE & ROGERS in 1904 and reported by the latter [25]. Subsequently the parasite was found in other endemic areas of kala-azar in the world, viz., the Mediterranean countries, the Sudan, China and South America. *Leishmania infantum* found in the Mediterranean countries and *L. chagasi* in South America came to be regarded as identical as *L. donovani* [8]. With the description of the first case of dermal leishmanoid or post-kala-azar dermal leishmaniasis by U. N. BRAHMACHARI [4] in 1922, and subsequently of other cases in India and elsewhere, this condition came to be recognized as the second clinical condition caused by the parasite. Following the incrimination of the sandfly as the vector of kala-azar [15, 36, 38], it was recognized that the leptomonads of the parasite which showed massive anterior development in this insect vector, were introduced into the skin by the bite of this insect and that sooner or later, the parasite spread by the blood stream to the viscera and a generalized infection resulted. Persistence of infection in the skin after the cure of kala-azar led to the development of dermal leishmanoid in a proportion of cases.

Clinicopathological studies during the last two decades have shown that the host-parasite relationship of *L. donovani* is not quite as clear cut as indicated in the preceding paragraph. The distribution of the parasite shows distinct variation in different countries so that clinical variations occur in the diseases caused by this parasite.

It was held by the early workers on kala-azar that the introduction of *L. donovani* into the skin by the bite of the sandfly led to the production of an inconspicuous local focus of infection and tissue reaction. Dur-

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ing the nineteen thirties reports of occasional cases with localized skin lesions resembling oriental sore being followed by the development of kala-azar appeared from the USSR [19] and the Sudan [9]. It was felt that the initial lesion was comparable to the primary sore, generalized infection during visceral leishmaniasis to the secondary stage and post-kala-azar dermal leishmaniasis to the tertiary stage of syphilis [10]. It was not, however, suggested that the three stages of leishmanial infection were fully comparable to those of syphilis or that they occurred in every case. Introduction of leptomonads of *L. donovani* intradermally by injection was found to cause the development four months later of small nodular lesions from which the parasite was isolated in smears and culture [35]; no visceral leishmaniasis developed subsequently in the case of myeloid leukaemia in which this was done. Recently evidence has been produced by P. E. C. MANSON-BAHR [17] from East Africa that a primary skin lesion, which has been called a leishmanioma, is probably produced following the bite of the infected sandfly and visceral disease may follow about four months later. In the immune individual and in cured cases of kala-azar, inoculation of *L. donovani* is followed by the Arthus phenomenon and no visceral infection results. ANDRE *et al* [1] have recorded that a man and a woman who had been in an endemic (*L. infantum*) *L. donovani* area subsequently developed cutaneous lesions from which leishmania could be demonstrated. In the man, glandular enlargement (lymphadenopathy) followed and his blood transfused into a child caused kala-azar in the latter. The man had to be treated for leishmanial infection but in the woman, the leishmanial papules subsided spontaneously with minimal scarring. These facts indicate that the primary lesions caused by *L. donovani* are not always followed by kala-azar, thus confirming the hypothesis postulated by NAPIER & KRISHNAN [21] many years ago that infection was more widespread than the actual incidence of kala-azar in an endemic area. It is also shown that infection with this parasite may result in cutaneous and lymph glandular lesions which may be followed by kala-azar indicating that the infection from the skin may pass to the regional lymph node and then through the blood stream to the internal viscera.

It was known that the parasite *L. donovani* could be demonstrated in the lymph glands in Mediterranean, Sudanese and Chinese kala-azar but not in Indian kala-azar [20]. It has now been shown that occasionally leishmanial lymphadenopathy may occur in cases of Indian kala-azar [34]. Recent reports indicate that *L. donovani* may produce lymphadenopathy only without visceral involvement (presumably the initial lesion in the skin was either inconspicuous or not recognized). Such cases were regarded as exceedingly rare in the past only one case being reported from China and two in American servicemen. Four cases of this type have been reported from among British soldiers posted in Malta. The condition was apyrexial and no parasites were found in the sternal marrow. *L. donovani* could be isolated in 3 of the cases from lymph glands and identical histological picture was noted in the fourth. The lymphadenopathic type of leishmaniasis may be more frequent than previously believed and constitutes a distinct type of disease caused by *L. donovani.* As there is more or less insignificant lymphadenopathy that is not associated with general illhealth in this condition, such cases may readily be missed [3].

Leishmania donovani could rarely be demonstrated in the skin in Indian kala-azar. The parasite, was, however, demonstrated in the normal looking skin in Chinese and Mediterranean kala-azar. Recent work in East Africa has shown that the parasite could be found in the skin in 11 per cent of untreated cases and that the infection was widespread [17]. From Brazil, a case of kala-azar showing numerous nodular lesions on the arms and the body caused by leishmanial infection has been reported [23]. It thus appears that the sandfly feeding on cases of kala-azar may take up the parasitized histiocytes from the skin. The presence of the parasite in the skin in East African type of kala-azar was held responsible for the recent case of marital transmission of leishmanial infection from the husband to the wife who developed a genital sore caused by this parasite [18, 39].

The degree of parasitization and pathological changes caused by the parasite in

the internal viscera often shows wide variations. The spleen is generally the most heavily infected organ and the parasite may be demonstrated in spleen puncture smear in 95 per cent of cases of kala-azar [20]. This indicates that in 5 per cent of the cases, the parasites are too scanty to be readily demonstrable (it is possible to demonstrate leptomonads of *L. donovani* in culture of spleen puncture material in such cases). KIRK [13] had noted that in some chronic cases of Sudanese kala-azar with firm or hard splenic enlargement, spleen puncture failed to show the parasite which was, however, present in lymph gland puncture smear. It has been noted that in liver biopsy specimens, there may be very scanty infection associated with practically normal hepatic histology in some cases. Others would show moderate to heavy infection with leishmanial granulomata in the sinusoidal spaces and portal tracts [33]. Though fibrosis is rare in the uncomplicated cases of kala-azar in India, South American workers have found intralobular fibrosis in a fair number of cases [22]. ROGERS had, however, recorded such fibrotic changes in post mortem material from very chronic cases of Indian kala-azar [24]. The bone marrow also shows similar variation in the degree of parasitization [28]. It is possible that in the cases with slight visceral infection, the symptoms of kala-azar may be mild or absent and subside without any specific treatment. It has been observed that in about 4 per cent of cases of dermal leishmanoid, there is previous history of fever and splenomegaly and that in 13 per cent of the cases prolonged fever and splenomegaly had subsided without specific treatment [31].

The parasite was occasionally isolated from the nasal secretion and urine in Indian kala-azar. NAPIER was of the opinion that its presence was accidental and due to separation of small pieces of mucosa and submucosa by secondary infection and not due to leishmaniasis [20]. In the Mediterranean type of kala-azar, *L. donovani* has more readily been demonstrated in smears made from the nasal mucosa by scraping [2]. In the Sudanese and East African types of the disease, leishmania has been demonstrated in the tonsils. Also in Sudanese kala-azar granulomatous lesions may develop in the oronasal mucosa in association with or following kala-azar [12]. The latter is of course not unknown in dermal leishmanoid as seen in India.

Dermal leishmanoid was known to be rare in China, one or two cases being reported during the nineteen thirties. But recently about a dozen cases have been reported from that country. No cases have so far been reported from the Mediterranean countries and the USSR. In a series of papers published since 1938, KIRK & co-workers [11, 13, 14] described the occurrence of dermal eruptions after treatment of kala-azar in the Sudan. KIRK [10, 31] is of the opinion that despite difference in relation in time to recovery from kala-azar, the condition differed in degree only and not in essential nature from dermal leishmanoid. It must, however, be noted that the dermal lesions reported from Africa show considerable difference in onset, clinical feature and course from dermal leishmanoid as seen in India. In an earlier publication on the subject, KIRK & SATI [14] noted that the temporary cutaneous manifestations during or 1-2 weeks after treatment of kala-azar, bore some similarity to the exacerbation of skin lesions in canine leishmaniasis after treatment and this phenomenon was similar to the Herxheimer reaction. In view of the well marked difference from dermal leishmanoid, it is hard to rule out the probability of this mechanism being responsible for the Sudanese type of post-treatment dermal lesions. Detailed histological study may possibly help in determining the causation of these lesions. It may be noted that the occurrence of this type of lesions immediately after successful treatment of kala-azar in the Sudan is a distinctive feature of the disease in that country.

In this connection *Leishmaniasis tegumentaria diffusa* described by CONVIT from Venezuela requires consideration [5]. In this condition the initial lesion is an erythematous nodule which gradually reaches about an inch in diameter. After some months satellite nodules develop and ultimately a thick plaque is formed. During the subsequent years, the infection spreads all over the surface of the body which becomes covered with numerous nodules and plaques. The viscera are not involved and the lesions are restricted to the skin and may ulcerate. CONVIT regards this condition as a new

clinical entity that is caused neither by *L. brasiliensis* nor *L. donovani* because the Montenegro reaction was negative and injection of culture of leptomonads isolated from the lesions into the hamster, white mouse and the squirrel and man produced local lesions. In this connection it may be recalled that kala-azar occurs in Venezuela though the incidence is low. The lesions as depicted in the excellent photographs published by CONVIT are not inconsistent with extensive dermal leishmanoid which may occasionally ulcerate. It is also known that as in the cases reported by CONVIT, there may be no history of kala-azar and its specific treatment in a total of 13 per cent of cases of dermal leishmanoid; in 4 per cent of cases there may be no history of fever. The initial lesion in dermal leishmanoid may be hypopigmented macule, erythema or nodule; and extensive lesions may subsequently develop all over the body. Also the reaction of experimental animals to *L. donovani* isolated from cases or dermal leishmanoid has not been fully worked out and inoculation of leptomonads of *L. donovani* into the skin of a man usually produces a nodule [17, 35]. Whether *L. donovani* isolated from dermal leishmanoid can produce kala-azar subsequent to the development of leishmanioma is unknown. It appears reasonable to regard leishmaniasis tegumentaria diffusa as a severe type of dermal leishmanoid till further investigations indicate it to be different in aetiology.

To summarize, the present position regarding the pathogenicity of *Leishmania donovani* appears to be as follows:

Introduction of the leptomonads into the skin by the bite of the sandfly is followed by local histio-lympho-plasmacytic reaction. No visible lesion may be produced.

Or, a visible nodular or oriental sore like lesion may be caused; this usually subsides spontaneously with minimal scarring.

The infection may not spread any further particularly in immune people. Or, it may spread directly to the blood stream.

Or, the infection may spread to the regional lymph nodes. The infection may stop at this level causing lymphadenopathic leishmaniasis only. Or, it may pass on to the blood stream and there is general spread of infection.

Spread to the internal viscera usually causes kala-azar. If the parasitization in the internal organs is mild or immunity high, there may be spontaneous cure of the visceral disease which might have been asymptomatic or associated with fever and splenomegaly.

During the general spread, if there has been a very severe skin infection, cutaneous nodules may be produced along with kala-azar as in the case reported from Brazil. If there has been a mild asymptomatic visceral infection associated with extensive dermal infection, leishmaniasis tegumentaria diffusa or dermal leishmanoid may be produced. In cases with widespread but moderate skin infection, the parasite would be fairly readily demonstrable in the skin (African kala-azar). If the degree of parasitization of the skin be slight, it would rarely be possible to demonstrate leishmania in it during kala-azar (Indian type); but subclinical or florid dermal leishmanoid may follow cure of the visceral disease. Moderate skin infection may show "reaction" (Herxheimer phenomenon) during or soon after treatment of kala-azar and cause eruptions which subside within a few months and may leave depigmented patches (post-treatment dermal rash of Sudanese kala-azar).

Finally the question of variation in the severity of kala-azar and its response to chemotherapy in different countries may be considered. It has been held that Sudanese kala-azar was more severe and less amenable to antimonials than Indian kala-azar; the results of treatment with urea stibamine type of compounds was not very satisfactory in Chinese kala-azar and that relatively large amounts of antimonials were required for the treatment of Mediterranean type of the disease [20]. Experience gained during the outbreaks of kala-azar in different parts of Eastern India during the nineteen forties indicates that kala-azar is more severe and more frequently associated with serious complications during epidemics than during interepidemic periods and the mortality rate was higher [30, 32]. It seems likely that the early series of cases reported from the Sudan and East Africa were during the height of

epidemics [7, 37]. As the epidemics waned the disease became less severe and more amenable to antimonials [27]. The relatively high requirement of antimonials for the treatment of Mediterranean kala-azar is partly due to the fact that infants and little children form the vast majority of cases and as in India, children tolerate and require relatively higher dose per kilo body weight than adults. In China during the nineteen thirties it was noticed that sodium stibogluconate was better tolerated than urea stibamine. During the recent years vast number of cases has been treated with sodium stibogluconate and good results reported in spite of relatively small total doses being employed in many cases. It may be mentioned that during the nineteen forties and subsequently many antimony resistant cases were met with in China which had to be treated with stilbamidine and even with splenectomy [40]. During the mass treatment campaign initiated in 1950 when the epidemic was past its initial stage, the cases were thus less serious and readily amenable to the easily administered antimonial sodium stibogluconate which is comparatively less effective than the older antimonials urea stibamine and neostibosan [29].

SUMÁRIO

Patogenicidade da "Leishmania donovani" para o homem.

Tendo por base as várias condições clinico-patológicas, associadas com a leishmaniose visceral em diferentes regiões geográficas, tais como a lesão dérmica primária e o envolvimento glandular ou cutâneo posterior, só ou concomitante com o comprometimento visceral, bem como a leishmaniose dérmica pós-calazar, etc., o Autor apresenta seu ponto de vista original sôbre a patogenicidade da *Leishmania donovani* e a evolução da infecção humana produzida por êsse parasito.

Discute, ainda, a influência da idade, da imunidade e da fase epidêmica como fatôres de variação na gravidade do calazar e na maneira como a mesma responde ao tratamento em diferentes regiões.

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