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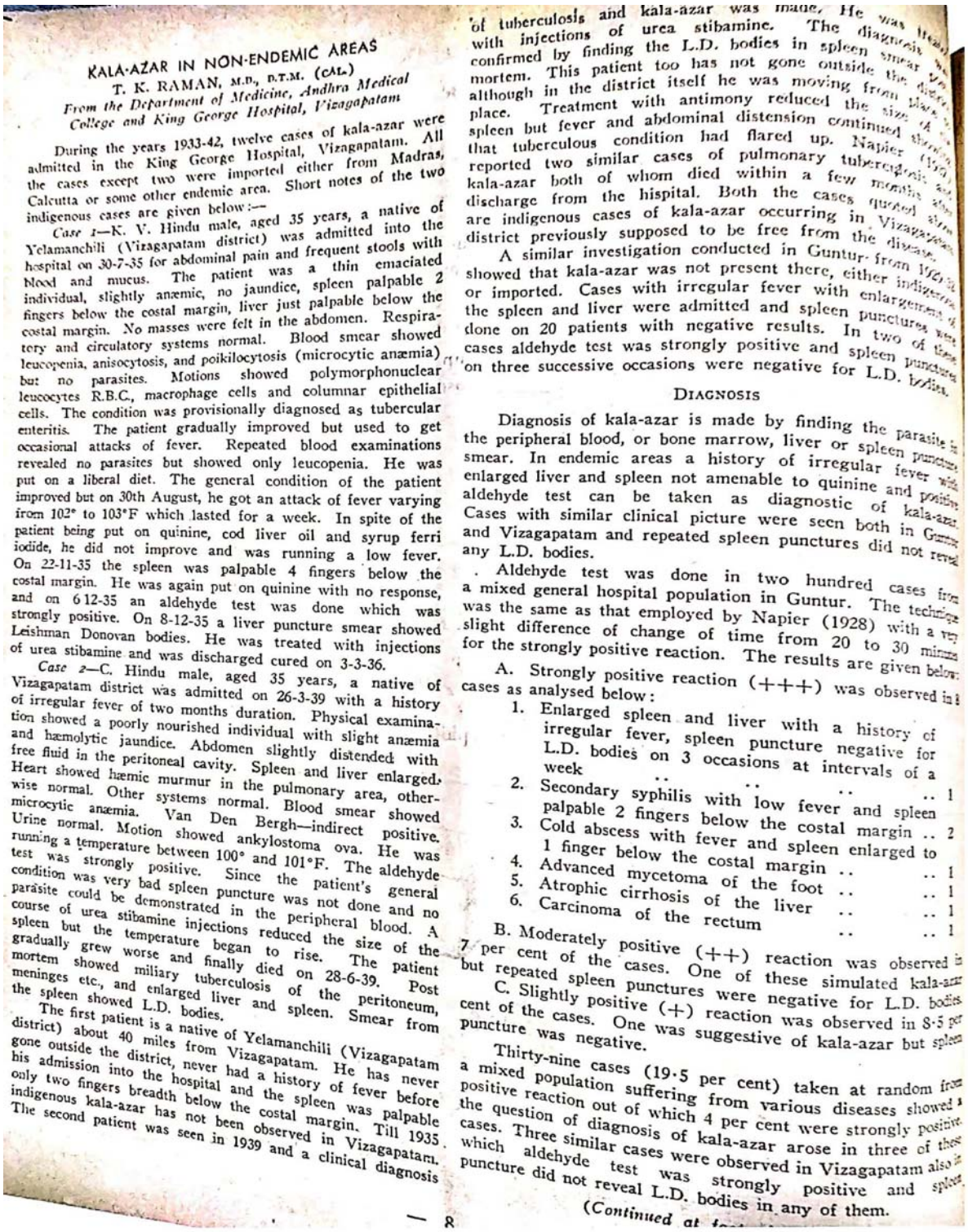

KALA-AZAR IN NON-ENDEMIC AREAS

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During the years 1933-42, twelve cases of kala-azar were admitted in the King George Hospital, Vizagapatam. All the cases except two were imported either from Madras, Calcutta or some other endemic area. Short notes of the two indigenous cases are given below:—

Case 1—K. V. Hindu male, aged 35 years, a native of Yelamanchili (Vizagapatam district) was admitted into the hospital on 30-7-35 for abdominal pain and frequent stools with blood and mucus. The patient was a thin emaciated individual, slightly anæmic, no jaundice, spleen palpable 2 fingers below the costal margin, liver just palpable below the costal margin. No masses were felt in the abdomen. Respiratory and circulatory systems normal. Blood smear showed leucopenia, anisocytosis, and poikilocytosis (microcytic anæmia) but no parasites. Motions showed polymorphonuclear leucocytes R.B.C., macrophage cells and columnar epithelial cells. The condition was provisionally diagnosed as tubercular enteritis. The patient gradually improved but used to get occasional attacks of fever. Repeated blood examinations revealed no parasites but showed only leucopenia. He was put on a liberal diet. The general condition of the patient improved but on 30th August, he got an attack of fever varying from 102° to 103°F which lasted for a week. In spite of the patient being put on quinine, cod liver oil and syrup ferri iodide, he did not improve and was running a low fever. On 22-11-35 the spleen was palpable 4 fingers below the costal margin. He was again put on quinine with no response, and on 6-12-35 an aldehyde test was done which was strongly positive. On 8-12-35 a liver puncture smear showed Leishman Donovan bodies. He was treated with injections of urea stibamine and was discharged cured on 3-3-36.

Case 2—C. Hindu male, aged 35 years, a native of Vizagapatam district was admitted on 26-3-39 with a history of irregular fever of two months duration. Physical examination showed a poorly nourished individual with slight anæmia and hæmolytic jaundice. Abdomen slightly distended with free fluid in the peritoneal cavity. Spleen and liver enlarged. Heart showed hæmic murmur in the pulmonary area, otherwise normal. Other systems normal. Blood smear showed microcytic anæmia. Van Den Bergh—indirect positive. Urine normal. Motion showed ankylostoma ova. He was running a temperature between 100° and 101°F. The aldehyde test was strongly positive. Since the patient's general condition was very bad spleen puncture was not done and no parasite could be demonstrated in the peripheral blood. A course of urea stibamine injections reduced the size of the spleen but the temperature began to rise. The patient gradually grew worse and finally died on 28-6-39. Post mortem showed miliary tuberculosis of the peritoneum, meninges etc., and enlarged liver and spleen. Smear from the spleen showed L.D. bodies.

The first patient is a native of Yelamanchili (Vizagapatam district) about 40 miles from Vizagapatam. He has never gone outside the district, never had a history of fever before his admission into the hospital and the spleen was palpable only two fingers breadth below the costal margin. Till 1935 indigenous kala-azar has not been observed in Vizagapatam. The second patient was seen in 1939 and a clinical diagnosis of tuberculosis and kala-azar was made. He was treated with injections of urea stibamine. The diagnosis was confirmed by finding the L.D. bodies in spleen smear post mortem. This patient too has not gone outside the district although in the district itself he was moving from place to place. Treatment with antimony reduced the size of the spleen but fever and abdominal distension continued showing that tuberculous condition had flared up. Napier (1928) reported two similar cases of pulmonary tuberculosis with kala-azar both of whom died within a few months after discharge from the hispital. Both the cases quoted above are indigenous cases of kala-azar occurring in Vizagapatam district previously supposed to be free from the disease.

A similar investigation conducted in Guntur from 1936 showed that kala-azar was not present there, either indigenous or imported. Cases with irregular fever with enlargement of the spleen and liver were admitted and spleen punctures were done on 20 patients with negative results. In two of these cases aldehyde test was strongly positive and spleen punctures on three successive occasions were negative for L.D. bodies.

DIAGNOSIS

Diagnosis of kala-azar is made by finding the parasite in the peripheral blood, or bone marrow, liver or spleen puncture smear. In endemic areas a history of irregular fever with enlarged liver and spleen not amenable to quinine and positive aldehyde test can be taken as diagnostic of kala-azar. Cases with similar clinical picture were seen both in Guntur and Vizagapatam and repeated spleen punctures did not reveal any L.D. bodies.

Aldehyde test was done in two hundred cases from a mixed general hospital population in Guntur. The technique was the same as that employed by Napier (1928) with a very slight difference of change of time from 20 to 30 minutes for the strongly positive reaction. The results are given below:

A. Strongly positive reaction (+++) was observed in 8 cases as analysed below:

1. Enlarged spleen and liver with a history of irregular fever, spleen puncture negative for L.D. bodies on 3 occasions at intervals of a week 1
2. Secondary syphilis with low fever and spleen palpable 2 fingers below the costal margin .. 2
3. Cold abscess with fever and spleen enlarged to 1 finger below the costal margin 1
4. Advanced mycetoma of the foot 1
5. Atrophic cirrhosis of the liver 1
6. Carcinoma of the rectum 1

B. Moderately positive (++) reaction was observed in 7 per cent of the cases. One of these simulated kala-azar but repeated spleen punctures were negative for L.D. bodies.

C. Slightly positive (+) reaction was observed in 8·5 per cent of the cases. One was suggestive of kala-azar but spleen puncture was negative.

Thirty-nine cases (19·5 per cent) taken at random from a mixed population suffering from various diseases showed a positive reaction out of which 4 per cent were strongly positive. The question of diagnosis of kala-azar arose in three of these cases. Three similar cases were observed in Vizagapatam also in which aldehyde test was strongly positive and spleen puncture did not reveal L.D. bodies in any of them.

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...of treatment.
...It is most important that a concentrated and coordinated effort is made to tackle the cancer problem in India.

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...non-endemic areas cases with irregular fever, enlarged ... and spleen and positive (+++) aldehyde test should ... be diagnosed as kala-azar unless the parasite is demonstrated either in the peripheral blood, bone marrow, liver or ... Some of these cases respond to pentavalent antimony. ... negative aldehyde test is much more significant in a ... case with spleen reaching the level of the umbilicus ... it might be used to eliminate kala-azar.

Indigenous cases have been reported from other non-... areas in India *viz.*, the West Coast (Mudaliar ... 1926), Dera Ismail Khan (Honce, 1924) and Malabar ... Coimbatore (Shortt and Swaminath, 1937).

How do patients in these non-endemic areas get infected? ...ramath *et al* (1942) succeeded in transmitting kala-azar ... all the five (100 per cent) human volunteers by the bite ... infected sand flies (*Phlebotomus Argentipes*). The other ...rnative method of transmission is by the oral route. ...ishmania were isolated from the fæces (Shortt *et al.*, 1929), ...m the urine (Shortt, 1923) and from the nasal smear (Shortt *et al*, 1937). Hamsters were infected by oral and conjunctival routes (Shortt *et al*, 1928-29).

In all probability the mode of infection in these indigenous cases in non-endemic areas is by the oral route.

CONCLUSIONS

1. Two indigenous cases of kala-azar are reported from Vizagapatam district, a place previously supposed to be free from the disease.

2. Fallacies in the diagnosis of kala-azar in non-endemic areas and the probable method of transmission in these cases are discussed.

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The most recent Advance in the Antimony Treatment of KALA-AZAR

UREA STIBAMINE

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(PARA-AMINOPHENYL-STIBINIC ACID IN COMBINATION WITH UREA.)

Remarkably beneficial results obtained by its use within the shortest time.

Its advantages are :—

(1) The short course occupying two to three weeks for a complete cure.
(2) The rapidity with which the symptoms of the disease disappear.
(3) The absence of symptoms of intolerance after its administration.
(4) It is most valuable in the treatment of relapses or in the cases resistant to sodium antimony tartrate or tartar emetic.
(5) Observations have shown that early cases are cured after 4 or 5 injections and sometimes even after fewer injections.

Extensively used with remarkable success in Calcutta Hospitals, Outdoor Dispensaries of the Calcutta Medical College (Kala-azar Research Enquiry), Pasteur Institute, Shillong, Tea Estates Dispensaries under the Medical and Public Health Departments, Assam, Bengal, Behar and Orissa, etc., etc.

Pamphlet on Urea Stibamine with details about its use, and booklet containing published reports (1922-1925) of cases treated with Urea Stibamine by workers in the institutions and places quoted above, sent post free on application.

Stocks of UREA STIBAMINE (Brahmachari) can be obtained from

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THE INDIAN MEDICAL GAZETTE

The three fruits were then invaded with *B. pyocyaneus* and the vibrio could not be recovered after 24 hours.

2nd Experiment:—

The vibrio was recovered and proved to be pure in the melon after 120 hours and in the cucumber and tomato after 72 hours. The reaction of the fruit remained acid except that of the melon, which at the end of the time was invaded by a spore-bearing organism (from the rind) and the reaction changed to alkaline. The vibrio then died out.

3rd Experiment:—

The skin was carefully sterilised before section. Vibrios in pure culture were found to be present in luxuriance after 168 hours in the case of the melon. The reaction of the fruit was still acid.

It was not easy to say whether the vibrio had increased or decreased, but the growth on agar at the end of a week was as luxurious as after 24 hours. The fruit was then invaded by a spore-bearing organism like that in experiment 2. The reaction became alkaline and the vibrio could not be recovered.

In all cases the identity of the vibrio was proved by all available laboratory tests including the agglutination with high-titre serum. A variant of the above experiment was made by squeezing out juice from a melon, tubing it and sterilising it at 100 degrees C. for 2 or 3 successive days and using this fluid medium, in one case without changing its acidity, and by alkalinising it in another.

The vibrio did not appear to flourish in the medium, the alkaline medium became acid after two days' growth, and the vibrio could only be recovered up to 48 hours, after which it died out in both kinds of medium. The medium may have been modified adversely by heating, as a smell of caramel was detected suggesting that the process of steaming had decomposed the fruit sugar.

If sugar is the nutrient property on which the cholera vibrio supports itself, it would explain why it died out in the heated medium.

CONCLUSION.—*Despite the natural acidity of the fruit, the cholera vibrio is able to live and probably to increase in numbers on the cut surface of a melon for as long as a week. This makes the danger of exposing cut or ruptured melons to the dust and flies of the bazar to be a real one.*

(*e*) *Experiment to ascertain what bacteria are to be found on the surface of cut or ruptured melons exposed for sale in the bazar.*—This experiment needs to be done before one can say whether the facts we have produced artificially are ever found under natural conditions. It is probable even in epidemic times and in infected neighbourhoods that a very large number of experiments would have to be done before one would be lucky enough to find an infected melon.

This and the departure of the senior writer on leave prevent this part of the enquiry being carried out.

Further experiments on similar lines might be done using *B. coli* as an index of fæcal contamination (by dust or flies or human handling) and the behaviour of other intestinal pathogens, *e.g.*, the enteric and dysentery group bacilli on the pulp of fruit, but as far as this paper goes, a few final conclusions are warranted.

GENERAL CONCLUSIONS.

1. The inside of fresh unruptured fruit is sterile.
2. The reaction of melons and tomatoes is strongly acid and of cucumbers is mildly acid at all stages of ripening.
3. The temperature of these fruits is lower than that of the external atmosphere by—

13.89 F. (7.7 C.) in the case of the melon.
15.98 F. (8.8 C.) in the case of the cucumber.
6.01 F. (3.34 C.) in the case of the tomato.

4. The cholera vibrio can be recovered from melons 7 days and from cucumbers and tomatoes 3 days, after they have been inoculated. Melon pulp appears to be a particularly suitable medium for the growth of cholera germs.

These few experiments justify the following advice to troops :—

(1) *Undamaged melons, cucumbers, and tomatoes may be eaten with safety.*

(2) *Ruptured or damaged fruit, and especially sliced melons which have been exposed in the bazar, should be strictly avoided.*

A NEW FORM OF CUTANEOUS LEISHMANIASIS—DERMAL LEISHMANOID.

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THE following paper on a "New Form of Cutaneous Leishmaniasis" was read by me at the meeting of the Medical Section of the Asiatic Society of Bengal held on 8th February, 1922.

The various forms of cutaneous and muco-cutaneous leishmaniasis are divided by Castellani and Chalmers as follows :—

(1) Cutaneous.
(2) Muco-cutaneous.
(3) Oro-pharyngeal.

The cutaneous forms are divided by them into :—

(*a*) The common variety—The oriental sore.
(*b*) The verrucose variety.
(*c*) The keloid-form variety.
(*d*) The framboesiform.
(*e*) The Papillomatous variety.
(*f*) The deep ulcerative variety.

Laveran describes the following forms of cutaneous leishmaniasis :—

(*a*) The oriental sore.
(*b*) American leishmaniasis.
1. The cutaneous ulcerating form.
2. The cutaneous non-ulcerating form which may be either

(1) Papillomatous or (2) macro-tuberculous.

The variety of cutaneous leishmaniasis described in the present paper is of extreme pathological and clinical importance. It differs from any form of cutaneous leishmaniasis described in the literature and appears to afford the missing link between cutaneous and visceral leishmaniasis or kala-azar and leads one to conclude that the special pathogenic properties of the parasites of kala-azar may be so modified after antimonial treatment that it may subsequently give rise clinically to a form of cutaneous leishmaniasis, thus proving the identity of the parasite of kala-azar and that of cutaneous leishmaniasis.

Among the multitude of kala-azar patients treated by me with intravenous injection of antimony, I met with four cases which, within six months to two years after completion of treatment, came to me with a peculiar form of cutaneous eruption which at first sight gave an impression of tuberculous leprosy. In none of them, however, could any lepra bacilli be found. When they came to me with these eruptions, there were no clinical symptoms of kala-azar.

The appearance of these cutaneous eruptions in patients who have apparently recovered from kala-azar after antimonial treatment made me suspect that they might be due to a cutaneous infection of these individuals in whom there was not a complete sterilization of the organs against the leishmania, though their virus had been attenuated by repeated antimonial injections. This led me to examine the scrapings from the cutaneous nodules of these cases with the help of Dr. Surendra Nath Ghose, Bacteriologist, Presidency General Hospital, Calcutta. The examination of the scrapings led to the remarkable discovery that the eruptions were due to cutaneous infection by the parasites of kala-azar.

During the antimonial treatment of kala-azar, the following results may follow :—

(1) Cure.
(2) Apparent cure followed by a relapse.
(3) No improvement.

A fourth result may follow, and this is what happened in the four cases mentioned above. The visceral leishmaniasis may be cured, but a few leishmania may be left behind with their virus so attenuated that they gave rise to a milder disease, namely, cutaneous leishmaniasis.

I give here the full history of the last case in which this transformation of a case of visceral leishmaniasis (kala-azar) into one of cutaneous leishmaniasis took place. The case was seen by Dr. Surendra Nath Ghose and myself.

Patient, aet. 31, an inhabitant of Barisal, gave a history of fever coming on with rigors from February, 1917, which was not benefited by quinine. In May, 1917, he had an attack of pneumonia. His fever persisted and there was progressive enlargement of the spleen. He was again treated with quinine which was given intramuscularly in doses of 10 grains for 6 days. He states that after this he was free from fever till the end of June 1917. In July, he again had an attack of intermittent fever, the temperature ranging between 99 degrees F. to 105 degrees F. He was again given intramuscular injections of quinine but with no benefit.

In January 1918, he came to Calcutta and was seen by Dr. Ghose and myself. When we examined him for the first time, his spleen was found enlarged, extending 6 inches below the costal margin and the liver extended 3 inches below the costal arch. The fever was of an intermittent type. He was at first given a course of treatment with soamin. The results of blood examination before treatment of soamin were R. B. C. 3,000,000, W. B. C. 3,500, Hb. 30 per cent. and differential count showed polymorphonuclears 60 per cent., lymphocytes 24 per cent., large mononuclears 14.8 per cent., and eosinophiles 1.2 per cent. The treatment with soamin was not followed by any improvement. Spleen puncture was made and the smear showed the presence of Leishman Donovan bodies. A few L. D. bodies were also found in peripheral blood. The patient was now treated with intravenous injection of tartar emetic given twice a week in doses of ½ to 10 c.c. He had altogether thirty injections. The fever stopped after 10 injections. When he left the treatment, there was marked improvement in his general condition, the spleen and the liver could not be felt below the costal margin and the blood condition was :—

R. B. C. 4,000,000.
W. B. C. 7,500.
Hb. 70 per cent.

No parasites could be found on spleen puncture.

He has had no fever since his treatment with antimony was stopped.

In the beginning of 1919, he noticed faint whitish patches on his face. These gradually spread. These patches were neither anæsthetic nor hyperæsthetic. They gradually spread over the whole body in front and behind in about six months. He was at first treated with arsenic internally. The patches became worse during cold weather. Subsequently, papillomatous nodules appeared over the face, the trunk and the extremities.

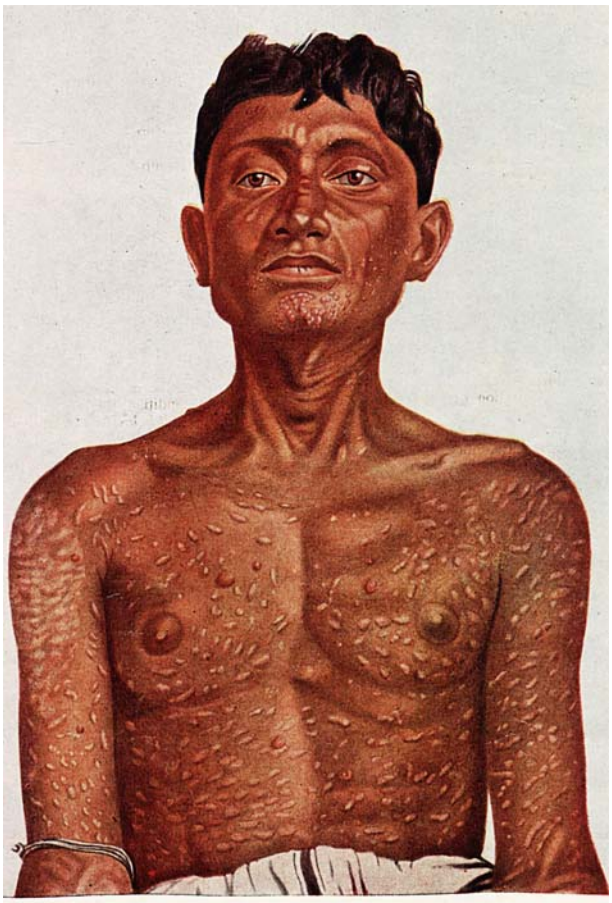
Patient was seen by me very recently. I asked Dr. Ghose to make a very careful examination of the scrapings and the juice from the papillomatous nodules for the presence of L. D. bodies. The smears showed a very large number of L. D. bodies in some of the slides.

Description of the present rash.—The whole of the body is covered with eruptions which are described as follows :—

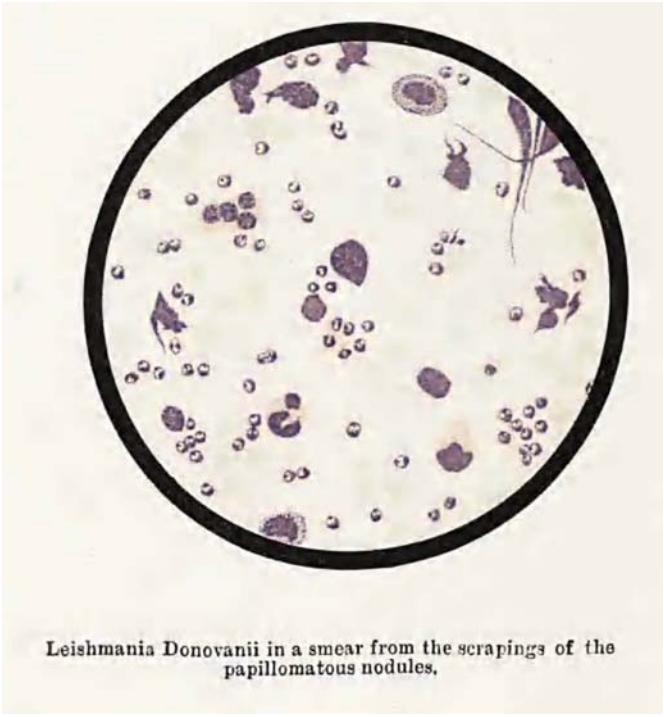
(1) On the face there are papillomatous nodules somewhat resembling small leprotic nodules.

(2) There is a slight erythematous appearance on the cheeks and the forehead.

(3) On the trunk, the upper and the lower extremities, there are slightly raised brown



Dermal Leishmanoid—showing the eruptions in the upper half of the body.



Leishmania Donovanii in a smear from the scrapings of the papillomatous nodules.

patches which are extensively spread over the whole body. A few papules are also present in these parts.

(4) There are some erythematous patches in the extremities, especially the lower.

(5) No ulceration or scab formation in any part of the body. Other features—no anæsthesia, no loss of knee-jerks, no thickening of the nerves. No eruptions in the mucous membrane of the mouth and nostrils.

Liver and spleen normal. On examination of the splenic body by spleen puncture, no L. D. bodies were found. No rise of temperature. The patient complains of no other trouble, except the ugly appearance of the body due to the eruptions.

Result of blood examination on 1st February, 1922 :—

Hb. 75 per cent.
R. B. C. 4,500,000.
W. B. C. 10,000.
Polymorphonuclears 62 per cent.
Lymphocytes 24 per cent.
Large mononuclears 6 per cent.
Eosinophilis 8 per cent.

The blood report does not at all correspond to that of kala-azar. No L. D. bodies could be detected in the peripheral blood.

Examination of the scrapings.—L. D. bodies are found in very large numbers, especially in the juice expressed from the papillomatous nodules. A few have also been found from the brownish patches. No lepra bacilli.

In view of the fact that the eruptions are due to leishmania infection whose virus has been modified by antimonial treatment, I propose to call this form of cutaneous leishmaniasis *dermal leishmanoid* just as small-pox modified by vaccination is called varioloid.

I shall study the morphological character of the flagellate forms of these parasites after culturing them with the help of Major Knowles, I. M. S., Protozoologist, Calcutta School of Tropical Medicine.

This case, along with three others of a similar type that I have observed, is a remarkable one, as they appear to point to the identity of the parasites of visceral and cutaneous leishmaniasis.

It seems that the virus of the parasite of kala-azar was attenuated in these cases by the antimonial treatment and a case of deadly visceral leishmaniasis was converted into one of cutaneous leishmaniasis. We thus have a direct proof of the identity of the parasites of visceral and dermal leishmaniasis, which has been attempted to be proved indirectly by complicated inoculation experiments.

Of the three other cases met with by me, one resembled the present case in the rash being generalized over the whole body. The other two cases had less generalized rash, most of the papillomatous eruptions being present on the face, there being some brownish patches over the arms.

One of these cases was treated with further injections of antimony and he appeared to improve. The second one, a boy of 15 years, was given six intravenous injections of tartar emetic in doses of 3 to 5 c.c., but he left treatment before any improvement was noticed. I propose to treat the present case with combined treatment of intravenous injection of antimony and soamin and shall report the results in a future communication.

It has been suggested by Manson that the treatment of kala-azar with a vaccine made from the virus of oriental sore is worth trial. May it be further suggested that in places where kala-azar is very prevalent, the inhabitants should be vaccinated with the virus of oriental sore as a prophylaxis against kala-azar ?

Apart from the interest in the above case on account of its forming a new hitherto unknown clinical entity, it raises the following most suggestive questions :—

(1) Are the parasites of kala-azar in the process of destruction by antimonial treatment eliminated by the skin and are cases of kala-azar therefore more infective during antimonial treatment ?

(2) If the parasites are eliminated by the skin, do they also enter the system through the skin at the time of primary infection ?

The above case, after being exhibited by me at the meeting of the Medical Section of the Asiatic Society of Bengal, held on 8th February, 1922, was exhibited at the Calcutta School of Tropical Medicine on 9th February, 1922.

I append here a drawing showing the eruptions on the upper part of the patient's body. A drawing from the scrapings from one of the nodules is also appended herewith showing the presence of Leishmania donovani which mostly seem to be extra corpuscular in the smear. As stated before, I have met with four cases of dermal leishmanoid.

Perhaps such cases are more common than has been suspected and more cases will be met with by observers who are treating kala-azar with antimonial preparations.

I am indebted to the Editor, *Indian Medical Gazette,* for announcing my discovery of this new form of cutaneous leishmaniasis in the *Indian Medical Gazette* for March, 1922.

I suggest that workers in the field of kala-azar should look out for such cases of infection by Leishmania donovani *sine* kala-azar as a result of antimonial treatment.

Since the above paper was sent to the editor, *Indian Medical Gazette,* I have succeeded in developing flagellated forms of *Leishmania donovani* with the help of Major R. Knowles, I.M.S., on N.N.N. medium from the juice obtained from the eruptions by puncture. Blood cultures were negative.

Visceral Leishmaniasis (Kalazar)

Shyam Sundar[1], Eram Nahid[2]

Visceral leishmaniasis (VL, also known as kala-azar) a neglected tropical and fatal parasitic disease caused by a parasite belonging to the Leishmania donovani complex and transmitted by infected female Phlebotomusargentipes sand flies. The main target of parasite is reticuloendothelial system, with infiltration of the spleen, liver, bone marrow and lymph nodes causing organomegaly and pancytopenia. Confirmation of diagnosis relies on invasive procedures like spleen or bone marrow aspirate, but most cases, having typical clinical fearures, can be detected using serological testing. Treatment of VL is very challenging because of few treatment options, long duration of treatment and drug toxicity.Treatment of choice is chemotherapy with single dose of Liposomal amphotericin B (LAmB) ormultidrug therapy (LAmB + miltefosine, LAmB + paromomycin (PM), or miltefosine + PM) for patients of VL in the Indian sub-continent.About 5-15% develop skin eruptions as sequelae of VL, known as Post Kala-azar Dermal Leishmaniasis, and ~5% have HIV-VL coinfection. Both these conditions do not have satisfactory treatment regimens.

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Key words **: Visceral leishmaniasis, L donovani and Leishmania infantum.**

Visceral leishmaniasis (VL) is one among the various neglected tropical diseases. VL is caused by the Leishmania donovani complex, which includes L donovani and Leishmania infantum. L. donovaniisthe causative organism of VL in the India[1].

It istransmitted in the Indian subcontinentby the bite of Phlebotomusargentipes (Sand fly). Persons of all ages can be affected by VL. The most common presentation of VL is an abruptonset moderate- to high -grade fever associated with rigor and chills which may continue for several weeks with decreasing intensity, and the patient may become afebrile for a short period before experiencing another bout of fever. The spleen may be palpable by the second week of illness and, may become hugely enlarged depending on the duration of illness. Hepatomegaly (usually moderate indegree) soon follows. In India, Lymphadenopathy is very rare. There is progressive anemia which may cause congestive heart failure , weight loss, hypoalbuminemia with edema, pancytopenia.Secondary infections such as measles, pneumonia, tuberculosis, bacillary or amebic dysentery and gastroenteritis arecommon. Herpes zoster, chickenpox, boils in the skin, and scabies mayalsooccur. It is fatal, if not treated.

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Editor's Comment :

- **With the introduction of rK39 rapid diagnostics, diagnosis has become simpler.**
- **In the Indian subcontinent single dose of liposomal amphotericin B (L-AmB) and multidrug therapy (L-AmB + miltefosine, LAmB + paromomycin [PM], or miltefosine + PM) are the preferred treatment of visceral leishmaniasis (VL).**
- **PKDL and VL-HIV coinfection, have become increasingly important because of their potential to trigger resurgence.**
- **Vector control through IRS is one of the key components of the current VL control strategy.**

Epidemiology :

Although the disease is endemic in over 67 countries, 90% of all reported cases occur in just six countries: Bangladesh, Brazil, Ethiopia, India, Sudan, and South Sudan. Of all the cases reported from India, the majority are from the state of Bihar[1].

There was a dramatic decline in its incidence after extensive insecticide spraying in the 1950s by the National Malaria Eradication Programme but resurgence was noted from small area of North Bihar in the early 1970s and within next 10–15 years it spread to the entire state of Bihar, a few districts of Jharkhand and West Bengal, plus the eastern districts of Uttar Pradesh. In due course, Nepal and Bangladesh were also affected. Akala-azar elimination initiative was launched in 2005 jointly by the Governments of India, Bangladesh, and Nepal with target for elimination as annual VL incidence below 1/10,000 people at the upazilla level in Bangladesh, the subdistricts [block

public health center (PHC)] level in India, and the district level in Nepal by the year 2015 – a deadline that was later reset to 2020[2]. Though there has been a dramatic decline in number of cases in India, and elimination target has been achieved in most of the endemic districts, barring few districts of Bihar and Jharkhand.

HIV-VL co-infection remains a major threat for the control of the disease, as the risk of developing active VL increases by >100 times. Initially, most of these cases were from southwestern Europe, but the number of cases is increasing in sub-Saharan Africa especially Ethiopia, Brazil and South Asia[3,4]. In India, 1.8–5.6% of VL patients were HIV-positive[3] (Fig 1).

Diagnosis

[i] Serological Tests: Through the development of the rK39 rapid diagnostic test (RDT) which has a sensitivity and specificity of 98% and 95%, respectively, serodiagnosis of kala-azar can be carried out in 20 minutes from a drop of blood. In elimination initiative, antirK39 RDT has been adopted for the diagnosis in combination with a clinical case definition[5]. However, there are two limitations, as anti K39 antibodies persist after cure for a long time (several years) thus it cannot be used in the diagnosis of relapses, further a significant proportion (~10%) of asymptomatic individuals, living in the endemic region, are also positive for serologic tests.

[ii] Antigen Detection Tests: most studied test is the kala-azar latex agglutination test (KAtex), detecting a heat-stable leishmania antigen in the urine of VL patients. Its specificity was excellent but sensitivity was low (48%–87%). Attempts to improve the sensitivity and the format of the test are ongoing[6].

[iii] Molecular Diagnosis: Polymerase chain reaction (PCR)-based assays to detect parasite DNA are being increasingly used in high-income countries, particularly in Europe, but frequent demonstration of PCR-positive tests in asymptomatic infected individuals in disease-endemic regions hampers their sensitivity. Several modification of PCR like quantitative PCR or isothermal loop medicated PCR (LAMP) have been developed. This has been especially useful in the long-term monitoring of HIV-infected patients, as a way to reduce the need of invasive investigations for quantification of parasite burden[7,8].

[iv] Parasitologic Diagnosis: It is the gold standard for diagnosis, which is made by the visualization of the amastigote form of the parasites by microscopic examination of tissue aspirates (spleen, bone marrow, or lymph nodes) (Fig 2). Specificity of microscopy is high, but its sensitivity varies between spleen (93%–99%), bone marrow (52%–85%), and lymph node (52%–58%) aspirates[9,10] (Fig 2).

Treatment

Pentavalent antimonials (SbV) :

Sodium stibogluconate (Sbv) and meglumine antimoniate (MA) are two forms available, given in a

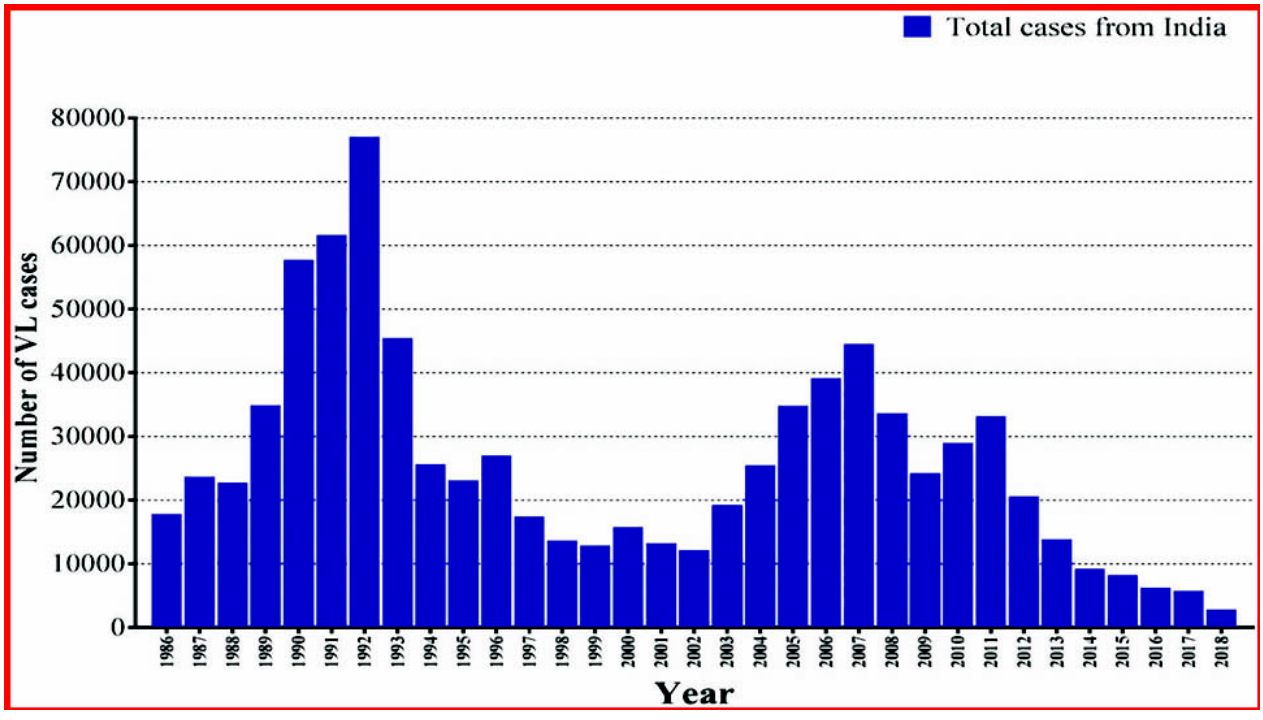

Fig 1 — Visceral leishmaniasis cases in India

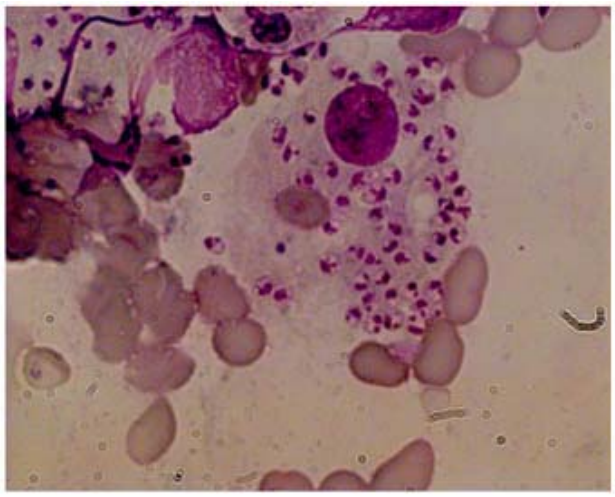

Fig 2 — Microphotograph showing intracellular and extracellular L. donovani bodies in splenic aspirate from a patient with visceral leishmaniasis

dose of 20mg/kg body weight for 28-30 days. But widespread resistance emerged in Bihar (India), and to some extent in adjoining Nepal, led to adoption of alternative treatment strategies for these regions. It's major limiting toxicities are cardiac arrhythmias, prolonged QT interval (QTc), ventricular premature beats, ventricular tachycardia, ventricular fibrillation and torsades de pointes. Other adverse effects include arthralgia, myalgia, increased pancreatic and liver enzymes[11].

Though pentamidine was used for a brief period, however, its use was abandoned due to frequent serious toxicities like Insulin Dependent Diabetes Mellitus, unexplained hypotension and shock[12].

AMPHOTERICIN B :

Amphotericin B deoxycholate (AB) was recommended as primary drug in patients hailing from SbV resistance region, later it was used for all patients. AB is recommended at doses of 0.75–1.0 mg/kg given for 15–20 intravenous infusions. Main toxicity are infusion reactions (in most patients), nephrotoxicity, hypokalemia, myocarditis and occasional death. Thus its infusion mandates close monitoring. Prolonged hospital stay limits the treatment to available beds and escalates the cost of therapy. To circumvent frequent and severe adverse events of AB, lipid formulations of amphotericin B have been developed with minimal side effects, and has made possible delivery of large daily doses of the drug[13]. Various trials on liposomal amphotericin B (LAmB) in India are shown in Table 1.There is considerable geographical variation in the total LAmB dose. In the Mediterranean region and South America, 18–21 mg/kg administered in various regimens, has been recommended , but in India single dose of 10 mg /kg has been shown to cure >95% VL cases[14] and it is the recommended drug in the elimination program in three countries of the Indian subcontinent.

For HIV-VL co-infection, LAmB is given at doses of 4 mg/kg for 10 doses (days 1–5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/ kg. Secondary prophylaxis is important and found to be effective in HIV-VL co-infected patients[15]. Better and shorter regimens for HIV-VL coinfection, are under clinical trials.

MILTEFOSINE :

It is an alkyl phospholipid (hexadecylphosphocholine) and the first oral antileishmanial agent registered for use following a Phase III trial in India from March 2002 at dose of 50 -100 mg/ day for 28 days, and resulted in a long-term cure rate of 94%[16].

Table 1 — Liposomal Amphotericin B trials in VL in India

Study (year)	Trial arm and drug dosage	Apparent cure	Definitive definitive cure	95% CI for definitive cure (95% Confidence Interval)
Thakur (2001)[24]	L-AmB single dose 15 mg/kg	17/17 (100%)	17/17 (100%)	17/17–100
	AmB deoxycholate 1 mg/kg per day for 20 days	17/17 (100%)	77.1 (100%)	77.1–100
Sundar (2004)[25]	AmB deoxycholate 1 mg/kg per day for 15 days (every other day)	49/51 (96%)	49/51 (96%)	85.4–99.3
	L-AmB 10 mg/kg (2 mg/kg × 5 days)	50/51 (98%)	49/51 (96%)	85.4–99.3
	AmB lipid complex 10 mg/kg (2 mg/kg × 5 days)	51/51 (100%)	47/51 (92%)	80.2–97.4
Sundar (2010)[14]	L-AmB 10 mg/kg (single dose)	304/304 (100%)	291/304 (96%)	92.6- 97.6
	AmB deoxycholate 1 mg/kg per day for 15 days (every other day)	106/108 (98%)	104/108 (96%)	90.2-98.8
Sundar (2014)[26]	AmB lipid emulsion 15 mg/kg (single dose)	354/376 (94%)	317/376 (84%)	80.1–87.8
	L-AmB 15 mg/kg (single dose)	122/124 (98%)	120/124 (97%)	91.4–99.0

Because of its high cure rate and ease of administration, miltefosine was adopted by VL elimination programme in India, Nepal and Bangladesh. The recommended therapeutic regimens for patients on the Indian subcontinentare a daily dose of 50 mg for 28 days for patients weighing <25 kg, a twice-daily dose of 50 mg for 28 days for patients weighing >25 kg, and 2.5 mg/kg for 28 days for children 2-1 1 years of age.These regimens have resulted in a cure rate of 94% in India. After a decade of its use, the efficacy decreased and there was doubling of relapse rate[17], further its efficacy from Nepal and Bangladesh was lower than observed in India. Main limitations of miltefosine are its relatively high cost, need for monitoring of gastrointestinal side effects and occasional hepatic toxicity and nephrotoxicity. It is teratogenic with a half life of >150 hours, so women of child-bearing potential have to observe contraception for the duration of treatment and for an additional 3 months. In 2014, use of miltefosine was stopped in the kala-azar elimination programme in favour of single dose LamB.

PARAMAMOMYCIN :

It is an aminoglycoside antibiotic, acts by interfering with protein synthesis in the ribosome of the target organism and also inhibit the respiration. In India, in a phase II study of VL patients, PM at a dose of 16 mg kg day-1 for 21 days led to cure in 93%[18]. In a Phase III trial PM at a dose of 15 mg kg-1 (11 mg base) for 21 days showed 95% cure rate [19]and was approved by the Indian government in August 2006 for the treatment of patients with VL This is the cheapest antileishmanial drug, and is produced in India. Its availability is an issue.

MULTIDRUG THERAPY :

Rationale of multidrug therapy is to shorten duration of therapy with reduced doses by adding synergistic drugs which lowers the adverse events, resistance, hospital stay and treatment cost. therapy has been studied in the India. In a randomized, non-comparative, group-sequential, triangulardesign study, 181 subjects were assigned to treatment with 5 mg/kg of L-AmB alone, 5 mg/kg of L-AmB followed by miltefosine for 10 days or 14 days or 3.75 mg/kg of L-AmB followed by miltefosine for 14 days. When efficacy of all regimens was apparent, 5 mg kg of L-AmB followed by miltefosine for 7 days were given 45 additional patients. All groups had similar cure rates (>95%)[20].

Later a large Phase III study conducted in the India with three drug combinations: single injection of 5 mg/kg LAmB and 7-day 50 mg oral miltefosine or 10-day 11 mg/kg intramuscular PM; or 10 days each of miltefosine and PM, were tested for the treatment of VL. Each of the combination showed an excellent CR (> 97%)[21].

Current treatment guidelines for South Asia :

In 2010 WHO published the treatment recommendation based on the regional differences because the efficacy and required dosage of the antileishmanial agents vary in different areas[4].

1. VISCERAL LEISHMANIASIS

Single (10 mg/kg) dose of L-AmBor multi-drug combination therapy are the preferred treatment options for the Indian subcontinent.

2. HIV-Leishmaniasis co-infection

Lipid formulations infused at a dose of 3 -- 5 mg/kg/day or intermittently for 10 doses (days 1 -- 5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/kg are recommended. Antiretroviral therapy should be initiated and secondary prophylaxis should be given till the CD4 counts are > 200/µl (3 to 5 mg/kg every three week).

POST-KALA-AZAR DERMAL LEISHMANIASIS :

In Indian subcontinent and in Sudan and other East African countries, 2-50% of patients develop skin lesions concurrent with or after the cure of VL. Most common are hypopigmented macules, papules, and/or nodules or diffuse infiltration of the skin and sometimes of the oral mucosa or mixed macular lesions with other types of manifestations.In PKDL, parasites are scanty in hypopigmented macules but may be seen and cultured more easily from nodular lesions. Cellular infiltrates are heavier in nodules than in macules.The diagnosis is based on history and clinical findings, but rK39 and other serological findings are positive in most cases[22]. Treatment is three to four courses of AmB spread over several months - but it is expensive and unacceptable for most patients. Oral miltefosine for 12 weeks, in the usual daily doses, cures most patients with Indian PKDL[23].

Thus, VL is one of the major neglected and fatal infectious disease. There is emergence of drug resistance in disease endemic region, which is of concern and should be closely monitored. All suspect cases of kala-azar should be screened and diagnosed in an endemic area in an individual who has fever for more than 2 weeks, splenomegaly, and a positive serological rk39 test. There is increasing incidence of HIV-VL coinfection worldwide which further bring challenges to diagnosis and treatment. PKDL and HIV-VL coinfections pose a threat to the elimination of VL in this region, there is a need to develop simple and

effective regimens for these conditions. Vector control through IRS is one of the key components of the current VL control strategy. There is need of scientists, funding agencies, implementers for universal approach to diagnosis and treatment and elimination of VL.

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SIR UPENDRANATH BRAHMACHARI
— THE FORGOTTEN MAESTRO

Sir Upendranath Brahmachari, an Indian scientist and leading medical researcher and practitioner was born on 19 December 1873 in Sardanga village near Purbasthali, district Burdwan of West Bengal. After completion of MD & PhD, he was appointed as a teacher at the Campbell Medical School, Calcutta (Now Nilratan Sircar Medical College and Hospital), where he carried out his monumental work on Kala-azar. He made the path breaking discovery of urea stibamine which drastically reduced the deaths caused due to kala-azar and which for many years was mankind's only answer to the dreaded disease Kala-azar. Sodium stibogluconate, a newer form of this drug is still widely used globally for the treatment of kala-azar. In 1922, he discovered a new and deadly form of leishmaniasis, marked by the sudden appearance of eruptions on the face of the patient without fever or other complaints. It has been later termed as post-kala-azar dermal leishmaniasis.

Sir U.N Brahmachari was conferred with many awards including the prestigious Sir William Jones Medal of the Asiatic Society of Bengal, the Minto Medal from Calcutta School Of Tropical Medicine and the Griffith Memorial Prize from the University of Calcutta. He was awarded the title of Rai-Bahadur and was conferred the Kaisar-i-Hind Gold Medal. The British Government conferred him with the prestigious Knighthood in 1934.He was a nominee for the Noble Prize twice in 1929 and 1942 in the category of physiology and medicine.

He spent many nights working in a room lit by a single kerosene lamp in the ill equipped room of Campbell Medical College with no research chemist as assistant, no water basin to wash hands and no modern equipments. Even bigger handicap was that no Indian till date had distinguished himself/herself in medical research which was the domain of British doctors, pharmacists and chemists. His only humble goal was to find the answer to a disease which had killed millions of his countrymen.