History of Kala-azar

Professor C. P. Thakur, MD, FRCP (London & Edin.)
Emeritus Professor of Medicine, Patna Medical College
Member of Parliament, Former Union Minister of
Health, Government of India
Chairman, Balaji Utthan Sansthan,
Uma Complex, Fraser Road – Patna–800 001, Bihar.
Tel.: +91–0612–2221797, Fax:+91–0612–2239423
Email: info@bus.org.in, cpthakur1@rediffmail.com,
thakurcp@gmail.com

Website: www.bus.org.in
“History of kala-azar is older than the dated records. In those days malaria was very common and some epidemics of kala-azar were passed as toxic malaria. Twining writing in 1835 described a condition that he called “endemic cachexia of the tropical counties that are subject to paludal exhalations”. The disease remained unrecognized for a fairly long time but the searching nature of human mind could come to a final diagnosis, though many aspects of the disease are still unexplored”
Synonyms

- Leishmaniasis
- Internal leishmaniasis
- Visceral leishmaniasis
- General leishmaniasis
- Kala-azar of adults
- Indian kala-azar
- Black Fever
- Black Sickness
- Cachexial Fever
- Catechetic fever
- Dum-Dum Fever
- Burdwan Fever
- Sirkari Disease
- Sahib’s disease
- Kala-dukh
- Kala-jwar
- Kala-hazar
- Assam fever
- Leishman-Donovan Disease
Synonyms

- Tropical leishmaniasis
- Tropical cachexia
- Tropical Kala-azar
- Tropical Splenomegaly
- Non-malarial remittent fever
- Malaria Cachexia (in error)
- Ponos (Greece)
- Haplopoianacon (Cephalonia)
- Semieh (Sudan)

Infantile Kala-azar (Nicolle)
Infantile leishmaniasis
Mediterranean Kala-azar
Mediterranean leishmaniasis
Febrile splenic Anaemia (Fede)
Anaemia infantum a leishmania (Pianese)
Leishmania anaemia (Jemme and Dicristina)
Marda tal biccia (Malta)
Malatia de mensa (Sicily)
Febrile pseudo leukemia infantum
Naming kala-azar

- Word kala-azar consists of “Kala” (in Hindi means “Black”) & “azar” (in Hindi means “Fever”)
- Fever associated with dark complexion
- “Black Sickness” would have been appropriate
- “Kala” or “Kal” in Hindi also means “fatal” just as “kala-swarp” means “deadly snake”
- Kala-azar means “Fatal Illness”
- Ross pointed out that black death signifies plague, a fatal illness.
- It indicates terrifying effect of the disease on the imagination of the people rather than the actual reality of disorder
- This explanation applies here also – some cases of kala-azar do not show great pigmentation of the skin
History—Before the year 1903

• Jwar–Vikar – a peculiar fever (1824–25) – also called kala–azar in Jessore
• Burdwan Fever (1854–1875) Dr. French, the Civil Surgeon of Bardwan. He observed a contagious fever with enlargement of spleen, diarrhoea, anasarca, liver+, in some patients cancrumoritis.
• Kala–azar or black sickness (1882) in Assam– Clarke McNaught, a Civil Medical Officer of Tura, headquarter of Garo Hills district in Assam called it “Kala–hazar”
• Hindley (1984) described a disease in Jalpaiguri in Bengal as “Pushkara” – different from Malaria. It was kala–azar.
History—Before the year 1903

- Giles (1889) – It is caused by Ankylostomiasis – Dobson strongly opposed this theory.

- Rogers (1896) – A malignant form of malaria

- Harold Brown (1898) – investigated “Kala-dukhu” in Purnia district of Bihar—similar as “kala-azar” of Assam

- Ross (1898) investigated “kala-jwar” of Darjeeling district in Bengal which was same as “Kala-azar”
Manson believed it was not malaria because of absence of periodicity in the febrile attacks and non-amenability to "Quinine" – suggested it was not malaria, might be caused by trypanosomes

Leishman reported the discovery as early as 1900, of peculiar bodies in the spleen pulp of a soldier who died of Dum-Dum Fever at Netely Hospital

Later on he published his work in British Medical Journal in 1903 “On the Possibility of the Occurrence of Trypanosomiasis in India”
The Royal Victoria Hospital, Netley (by permission of the Illustrated London News).
ON THE POSSIBILITY OF THE OCCURRENCE OF TRYPANOSOMIASIS IN INDIA.

BY MAJOR W. B. LEISHMAN, M.B., R.A.M.C.,

Professor of Pathology, Royal Army Medical College.
[From the Pathological Laboratory, R.A.M. College, Victoria Embankment.]

The recent discovery of trypanosomiasis in man by Dr. Dutton and Dr. Forde, and the report of further cases by Dr. Manson, naturally lead one to question the possibility of the occurrence of this disease in other parts of the world than those originally reported-viz., the Congo and the Gambia. In the following remarks I hope to show that there is at least some ground for the belief that it may occur in India, and that a species of trypanosoma may be the cause of one of the indigenous fevers originally diagnosed as malaria. The disease, if it exist, is, however, more rare and is, more rarely, its immediate neighbours, Calcutta and Barrackpore—which gave rise to the belief that we were dealing with a specific type of fever, grave and commoner for the fever, grave and commoner features died away. The chief symptoms being irregular atrophy and gradual extension of the latter often in the form of fit. In none of the cases of malaria parasites found in the blood, nor were there any records of their having been found at an earlier stage of the disease.

The difference, then, between these cases of dum-dum fever and other cases of tropical cachexia, associated with a low form of fever was this form of fever, grave and commoner features died away...
• In July 1903, Donovan reported the finding of similar bodies from the spleen of patients suffering from prolonged fever with splenomegaly in Madras (now Chennai). He contested Leishman’s view that they were degenerate trypanosomes.

• Laveran and Mensil (1903), after examining the specimens sent by Donovan, concluded that the organisms were ‘Piroplasmata’.
A Professor of the Madras Medical College, Charles Donovan had already been working on the cause of Kala azar.

He had made observations similar to Leishman’s in Splenic aspirates of patients.

Donovan concluded that the Leishman bodies are a new parasite distinct from Trypanosoma. He published his findings in the same year, 1903, in the same Journal, BMJ, as a ‘memorandum’ to Leishman’s paper.

S. Roy
The greatest authority on Parasitology at the time, Ronald Ross took up investigations on the parasite of Kala-Azar in Calcutta.

In 1903, he ended all controversy by jointly accrediting Leishman and Donovan for the discovery of the parasite.

He named it: “*Leishmania donovani*”
Marchand (1903) observed identical bodies in sections of spleen, liver and bone-marrow from a Chinaman.

Manosn (1903) found similar bodies in a patient suffering from kala-azar in Darjeeling (Bengal), and showed that these bodies were not endocorpuscular bodies as supposed by Mensil and Laveran.

Christophers (1904) wrote a paper “On a Parasite found in Persons suffering from enlargement of the spleen”. He concluded that many cases of malarial cachexia and kala-azar of Assam were one and the same disease after examining the smears of spleen blood.

Bentley (1904) and Castellani (1904) observed parasites in kala-azar patients in Assam and Ceylon respectively.
Confirmation of Leishmania parasites

- Rogers (1904) published a paper “Leishman–Donovan Bodies in Malarial Cachexia and Kala–azar” described development of the parasite of cachexial fever and kala–azar into a flagellate stage – kala–azar of Assam and many cases of so–called “malarial Cachexia” were one and the same disease.


- Brahmachari (1906) described kala–azar in his paper ‘On a Contribution to the study of Fevers due to Leishman–Donovan Bodies”
Sir William Leishman, F.R.S.
(1865–1926)

The pictures opposite are from an article by W. Leishman and J. C. B. Statham on “The Development of the Leishman Body in Cultivation” (J. roy. Army med. Cps, 1905, 4, 327. By permission). They were drawn by Leishman himself. (Portrait by Bassano.)
Marchand (1903) observed in a case from China. Basset-Smith among sailors in the same year. Aspland (1910) showed wide spread in North China. Cochran (1911) reported from other parts of China. Saville found in Tientsin andJerusalem in Hoang Ho district. Jeffreys and Maxwell in Formosa (now Taiwan). Cardarelli (1880) followed by Fede, Somma and other workers showed presence of Kala-azar in Italy where two clinical varieties of disease existed – the febrile form was infectious. Pianese and Gianturco (1905) concluded that the disease was caused by *Bacterium coli*. Pianese (1905 to 1908) observed few cases in Italy.
History of VL Global

- Gabbi (1908) observed similar disease in Sicily and Calabria
- Mya and Trambusti found Micrococcus tetragenus present in the apyretic form of the disease
- Neave (1904) discovered in Anglo-Egyptian Sudan in Africa
- Philips (1904) in Arabia, Cathoire (1904) in Tunisia subsequently recognized by Laveran as *Leishmania donovani*
- Pirrie (1907) in Sudan who himself died of VL
Cummins (1908) discovered at Sniga on the Blue Nile
Thomson and Marshall found 41–new cases in children and adults along the Blue Nile towards Abyssinia
Nicolle and Cassuto (1907) observed parasites in the spleen of a child in Tunis with irregular fever and splenomegaly
Nicolle during 1908 to 1914 treated 38–cases in Tunis
During 1908 to 1913, kala–azar was widespread in Calabria, in Sicily and round Naples, and isolated cases occurred in Fiumicino (Rome) and Trieste.
History of VL Global

- Disease also observed in Mediterranean Regions
- Archer (1907) reported occurrence in Cyprus
- Critien and Babington (1910) in Malta
- Gabbi (1910) in Spetza (Greek Archipelago)
- Tashinbbbey (1910) in Tripoli
- Alvares (1910) in Lisbon
- Christomanos (1911) in Greek mainland
- Pittalgua (1911) and others in Spain
- Marzinowsky and others (1912) in Russia (Taschkent), and in Moscow
Geographical Distribution of VL in India in 1903

Map of India showing the distribution of Kala-azar infection.

Heavily infected areas...

Areas from which a few indigenous cases are reported...
Kala-azar in 1903
Distribution of Kala-azar in Asia in 1900
Transmitting

- Giles (1889) suggested that it was caused by ankylostomiasis
  - Dobson strongly opposed this theory
- Rogers (1904) suggested that a vector C.lectularius was transmitting agent but Donovan opposed this theory
- Patton (1912) in Indian Science Congress suggested Bed Bug Theory, and excluded mosquito, flies, lice and ticks on various grounds. However he failed to infect 384 sandflies which were allowed to feed on patients.
- Basile (1912) in Sicily incriminated fleas
- Sintori (1922) suggested the sandfly Phlebotomus as an insect vector
- L.E. Napier found that the topographical distribution of kala-azar cases and phlebotomus closely correlated.
Transmission

- F.P. Mackie supported sandfly theory, 11 years prior to Sintori, in 1911 in South America.
- C.B. Wenyan suggested that Phlebotomus was the transmitter of the parasites.
- In 1925, a team of staff consisting of RB Llyod, R Knowles, L.E. Napier, and R.O. Smith of Calcutta School of Tropical Medicine worked on this topic. Subsequently, this work was confirmed by S.R. Christophers, H.E. Shortt, and P.J. Barraud of the Indian Kala-azar Commission by means of different studies. Epidemiological (Napier), Serological (Llyod) and all four through experimental entomological research confirmed Sandfly Theory.
- The Kala-azar Commission of India in its first report confirmed Sandfly Theory.
W.S. Patton & E. Hinde (1927) incriminated *P. sergenti* and *P. major* in China.

The range of flight of this insect is limited and hence removal of the patient can prevent spread of disease.

We succeeded in doing the same experiment in one of the study areas in Goanpura experiment.
Marked increase in globulin content of the blood, and probably there is an easily perceptible globulin content in kala-azar serum

Globulin Ring Test – serum diluted 10 to 20 times with normal saline in a test-tube, and then a small amount of distilled water is gently poured over the serum – resulted in a distinct white ring forms over the surface of serum

Globulin Precipitation Test

Globulin Opacity Test

The Aldehyde Test

Direct Agglutination Test (Friged and dried)

rK-39 Test – latest–suitable for screening for

BM and Splenic aspirate – Gold standard
Interpretation of Results

Positive result  Negative result  Invalid result

Fig. 2
STUDIES ON METHODS OF TRANSMISSION OF KALA-AZAR.

NOTE ON THE INFECTIVITY OF THE FORMS OF LEISHMANIA DONOVANI FOUND IN PHLEBOTOMUS ARGENTIPES.

Dodds, Price and Rogers (1914) segregated all affected families from Golaghat-Tea Garden to other unaffected area. At the end of three years only one more case of infection among 40 removed families occurred.

We have repeated such experiment in Goanpura in 2003 by removing all patients from the affected village and treated them with AMB. In the mean time we treated patients from surrounding villages also. We managed to get one supervised DDT spray and kala-azar was eliminated from that village.
Leonard and Rogers (BMJ + Indian Medical Gazette – 1915) used intravenous tartaremetic 2% solution starting with 4 cc increased gradually to 10 cc.

Rogers (1918) used sodium antimony tartarate

Napier used pentavalent antimony compound amino stiburea with 9 total dose of 2–3 gm, got cure rate of 90%.

Urea Stibamine of Dr. Brahamchari, a pentavalent compound of antimony also succeeded in achieving 90% cure rate

Shortt highly praised this drug during control of kala–azar epidemic in Assam
This compound was introduced by Kikuth and Schmidt as solustibosan. It contains 100 mg of antimony per ml.

Another salt Methyl Glucanttime Antimonial was used in French Speaking Countries.

Pentavalent antimon compound SAG was extensively used in Bihar and other endemic areas of India.

In Bihar it was used in increasing dose starting with $\frac{1}{2}$ ml and increasing $\frac{1}{2}$ ml daily till 6 ml dose was reached, and then daily or on alternate days for 10 days and after a gap of 10 days another course was repeated.

In 1977 epidemic 30% of patients were found unresponsive and hence incremental dose was removed.

After a sensitivity test, a regimen of 6ml daily for 20 days was given (WHO, 1982; Thakur, 1984); cure-rate – 90%
Epidemiological, clinical and therapeutic features of Bihar kala-azar (including post kala-azar dermal leishmaniasis)

C. P. THAKUR
Patna Medical College, Patna, India

Summary

This epidemic of kala-azar in Bihar, India, started from a small block and gradually spread to almost all of North Bihar. Vaishali was the district most affected, with the highest incidence rate of 5.9 per thousand in 1978. The epidemic spread more to the east than to the west. In 1977 there were 100,000 cases of kala-azar in Bihar and in Vaishali district the death rate was 28.7% of affected cases. It took five years to control the epidemic. 750 parasitologically confirmed cases of kala-azar were studied. The male:female ratio was 5.5:1. 63.4% of cases were aged 10 to 29 years. Clinical features were classical.

Sodium stibogluconate, used as a first line drug, was effective in 92.6% of cases. By increasing the course of antimonials therapy from 10 to 20 days the relapse rate was reduced to 0.5% compared with 15% in the previous epidemic. Kala-azar patients who also had tuberculosis were treated with the antimonial and antituberculosis drugs concurrently and all cases recovered. 86 cases unresponsive to sodium stibogluconate were given pentamidine, which was effective in 93.4%. Side effects with sodium stibogluconate were minimal, but were common and serious with pentamidine. The need for a safer drug effective in cases which do not respond to antimony was very evident. 20 cases of post kala-azar dermal leishmaniasis (PKDL) were reviewed: two had no previous previous history of kala-azar. The relapse rate was higher in PKDL than in kala-azar.

Again it was felt to increase duration to more than 20 days if necessary (Thakur et al., BMJ: 1984)
Comparison of regimens of treatment with sodium stibogluconate in kala-azar. CP THAKUR, MAHENDRA KUMAR, SATIS KUMAR SINGH, DILIP SHRAMA, UMA SHANKER PRASAD, RAMA SHRAY PRASAD SINGH, P S DHAWAN, VIJAY ACHARI

Abstract
One hundred and twenty six patients with kala-azar (visceral leishmaniasis) were allocated at random to one of the groups for treatment with sodium stibogluconate. One group was treated for 20 days treatment and treatment was continued if necessary. Both groups were followed up for six months. There was no significant difference in symptomatic outcome between the two groups at 20 days. At six months eight of the patients in the group treated for 20 days had relapsed and 54 were cured. Of the group given more than 20 days treatment if necessary, 62 were cured and none had relapsed (12 required more than 20 days treatment).
This difference between the two groups was significant. One patient in each group did not respond to sodium stibogluconate, but both were cured with pentamidine. Altogether 104 patients were cured after 20 days treatment; 20, including the eight who relapsed, were cured after more than 20 days treatment. There was no significant difference between the two groups in the side effects of the drug, which were minor. The longer courses of treatment (50 days in one patient) were well tolerated.

It is suggested that the traditional six day course of treatment with sodium stibogluconate for kala-azar is grossly inadequate and that a longer course is required to prevent relapse.
Introduction

- In the 1970s Bihar province in India experienced a massive epidemic of kala-azar (visceral leishmaniasis), and the disease is still endemic in some areas. Out of the 400,000 new cases of leishmaniasis in the world in 1977, a quarter occurred in Bihar. Sodium stibogluconate was used as a first line drug during this epidemic. Manson-Bahr’s regimen of six days treatment with sodium stibogluconate, still advocated in current editions of most textbooks, was the standard treatment in India.
A committee of Indian experts suggested that two courses of sodium stibogluconate lasting for 10 days each and interrupted by a break of 10 days should be adequate to treat Indian kala-azar. This was a modified version of Manson-Bahr’s regimen of treatment for Kenyan kala-azar. We had found Manson-Bahr’s regimen for Indian kala-azar grossly inadequate, and even with the regimen suggested by the committee of Indian experts the incidence of relapse was high. We started on some cases, new regimen of treatment daily for 20 days and the incidence of relapse (0.5%) was almost negligible. This encouraged us to compare in a randomised trial the efficacy, safety, and desirability of giving the drug for 20 days, or longer if necessary. We report the outcome of that trial.
CLINICAL RESEARCH


C P THAKUR, M KUMAR, P KUMAR, B N MISHR, A K PANDEY.

Abstract

The efficacy and safety of six regimens of treatment for kala–azar (visceral leishmaniasis) with sodium stibogluconate were evaluated in a prospective randomised study to ascertain the optimal treatment for Indian patients. Altogether 371 patients with kala–azar were randomised to receive sodium stibogluconate intramuscularly at a dose of 10 mg/kg body wt./day for 20 or 40 days (groups A and A1, respectively), 15 mg/kg body weight/day for 20 or 40 days (groups B and B1, respectively), or 20 mg/kg body weight/day for 20 or 40 days (groups C and C1, respectively).
Patients were examined blind before and at the end of treatment and every month for six months. The number of patients who were apparently cured that is, those whose temperature had returned to normal at the end of their regimen of treatment – was 45 (78%) in group A, 53 (87%) in group A1, 50 (81%) in group B, 60 (95%) in group B1, 58 (92%) in group C, and 62 (97%) in group C1. At six months 62 patients (97%) in groups C1, 51 (81%) in group C, 54 (86%) in group B1, 42 (68%) in group B, 45 (74%) in group A1, and 33 (57%) in group A had not relapsed and were cured as confirmed by a bone marrow aspirate free of parasites.
The differences between groups C1 and C, B1 and B, and A1 and A were significant. Logistic regression of the proportion cured with the dose and length of treatment showed that both factors were significant in improving the rate of cure; the highest dose for the longer time (group C1) had the best rate of cure. One patient in group C1, 12 in group A were cured with extended courses of 20 mg sodium stibogluconate. One patient in each of groups C1, B, A1, and A became unresponsive to antimony and were cured with pentamidine. One patient in each of groups C1, B, and A became unresponsive to both antimony and pentamidine. The patients tolerated the longer duration of treatment safely, and side effects were minor.
Sodium stibogluconate should be given intramuscularly in the dosage of 20 mg/kg for at least 40 days, when patients would be assessed for further treatment if necessary. Such a regimen should achieve the highest rate of cure with low toxicity and low rates of relapse and unresponsiveness.
Sodium antimony gluconate (SAG) or Sodium Stibogluconate (Pentostam)

- Rationalization of treatment on body weight (Thakur et al., BMJ:1988)
- 20 mg per kg. of BW for 40 days gave best result but we observed increased toxicity
- WHO recommended 20mg/kg BW with a maximum of 850 mg for 30 days (WHO,Tech. Series Report 1990)
- Even with this dose the unresponsiveness to the drug increased and also toxicity
Increasing the dose to 30mg/kg BW killed 3 out of 4 patients (Thakur C.P., 1986)

Transactions of the Royal Society of Tropical Medicine and Hygiene (1986) 80
Pentamidine

- 4 mg/kg body wt. IM/ IV on alternate day for 15 days.
- Responsiveness 74%
- Side effects:
  - Diabetes (10%), Hypo & Hyper glycemia, Anaphylactic shock
  - Drug was abandoned due to production of severe toxicities of death.
Amphotericin-B

- 1 mg/kg BW IV infusion in 5% dextrose given slowly in 2–4 hours for 20 days
- Relapse < 1%
- For relapsed patients 5 infusions more than the last treatment or 5 infusions more after parasitological cure (C.P. Thakur et al., 1996a)
- Minimizing toxicity with low dose hydrocortisone
- Correcting dehydration and electrolyte imbalance
- Giving 10 days rest, if ECG changes suggestive of myocarditis caused by prior administration of SAG for minimizing thrombophlebitis and raising hemoglobin to 5gm/dl before giving AMB (Thakur et al., 1995b)
Liposomal amphotericin-B (Ambisome)
Amphotericin-B Lipid Complex

- 3 drugs in use, Ambisome®
- Dose: 3mg/kg BW for 5 days
- Single dose of 15 mg/kg: Cured all patients
- No toxicity
- Very Expensive
- Some studies have shown that the drug is effective if given as a single dose but large scale studies are required to make it standard treatment
- The drug is safe and side effects are uncommon
Efficacy and safety of liposomal amphotericin B (AmBisome) for visceral leishmaniasis in endemic developing countries*

J.D. Berman,¹ R. Badaro,² C.P. Thakur,³ K.M. Wasunna,⁴ K. Behbehani,⁵ R. Davidson,⁶ F. Kuzoe,⁷ L. Pang,⁸ K. Weerasuriya,⁹ & A.D.M. Bryceson¹⁰

Reported are the results of a study to determine the efficacy and safety of liposomal amphotericin B (AmBisome) for treating visceral leishmaniasis (kala-azar) in several developing countries where the disease is endemic (Brazil, India, and Kenya).

At each study site, sequential cohorts of 10 patients each were treated with AmBisome at a dose of 2 mg·kg⁻¹·day⁻¹ (2 MKD). The first cohort received regimen 1: 2 MKD on days 1–6 and day 10 (total dose: 14 mg/kg). If the efficacy with this regimen was satisfactory, a second cohort received regimen 2: 2 MKD on days 1–4 and day 10 (total dose: 10 mg/kg); and a third cohort received regimen 3: 2 MKD on days 1, 5, and 10 (total dose: 6 mg/kg). In India, regimens 1, 2, and 3 (which were studied concurrently) each cured 100% of 10 patients. In Kenya, regimen 1 cured all 10 patients, regimen 2 cured 90% of 10 patients, but regimen 3 cured only 20% of 5 patients. In Brazil, regimen 1 was only partially curative: 5 of 13 patients (62%). Therefore, 15 patients were administered regimen 4 (2 MKD for 10 consecutive days; total dose, 20 mg/kg) and 13 patients were cured (83%).

These results suggest that for the treatment of kala-azar the following doses of AmBisome should be administered: in India and Kenya, 2 mg/kg on days 1–4 and day 10; and in Brazil, 2 mg/kg on days 1–10.
Short communication

A single high dose treatment of kala-azar with Ambisome (amphotericin B lipid complex): a pilot study

C.P. Thakur *

Patna Medical College, Balaji Utthan Sansthan, Patna 800 001, India

Received 3 March 2000; accepted 3 July 2000

Abstract

Thirty four patients with parasitologically confirmed visceral leishmaniasis were divided randomly into two groups of 17. Group A received Ambisome (amphotericin B lipid complex) at a dose of 15 mg/kg body weight infused over 2 h as a single dose; patients in group B received amphotericin B deoxycholate at a dose of 1 mg/kg body infused for 2 h for 20 days. All 34 patients had a clinical, parasitological and ultimate cure. Ambisome was much better tolerated than amphotericin B, and adverse events were fewer in the Ambisome group. It was concluded that, if the cost of Ambisome were reduced, it would be a suitable first line drug. A longer study comparing three regimes of Ambisome: 15 mg/kg body weight, 11 mg/kg body weight and 7.5 mg/kg body weight, should be undertaken. © 2001 Elsevier Science B.V. and International Society of Chemotherapy. All rights reserved.

Keywords: Ambisome; Single dose; Kala-azar
New Drugs – Aminosidine

- Dose: 16 mg/kg BW IM for 20 days (Thakur et al., 2000a)

- Cured > 90% of the patients

- Ototoxicity to be watched

- Aminosidine + SAG: Not much advantage (Thakur et al., 2000b)
Injectable Paromomycin for Visceral leishmaniasis in India.

Shyam Sundar, M.D., T.K. Jha, M.D. Chandreswar P. Thakur, M.D., Prabhat K. Sinha, M.D., and Sujit K. Bhattacharya, M.D.

CONCLUSIONS

Paromomycin was shown to be noninferior to amphotericin B for the treatment of visceral leishmaniasis in India. (Clinical Trials gov number, NCT 00216346.)
New Drugs – Miltefosine

- The first ever oral drug

- The drug is to be given orally in the following dose:
  - Adults >25 kg: 50 mg after food 2 times/day for 28 days
  - <25 kg: 50 mg once after food
  - Children 2–11: 25 mg after food 2 times/day
  - The medicine should be given for 28 days

- Responsiveness 95% (Phase IV)

- Side effects:
  - GI related like vomiting, diarrhoea etc., Raised AST & ALT, Nephrotoxicity

- Teratogenic effect: Not confirmed

- Easy to take but Costly
MILTEFOSINE, AN ORAL AGENT, FOR THE TREATMENT OR INDIAN VISCERAL LEISHMANIASI

T.K. Jha, M.D., Shyam Sundar, M. D., C. P. Thakur, M.D., Peter Bachmann, M.D., Juntra Karbwang, M.D., PhD., Christina Fischer, Dip., Andreas Voss, M.D., and Jonathan Berman, M.D., PhD.

CONCLUSIONS
Orally administered miltefosine appears to be and effective treatment for Indian visceral leishmaniasis. (N Eng j med 1999; 341: 1795–800).
Paromomycin has been registered in India although phase IV trial results and a technical review are needed before it is recommended in the national program.

The recommended dose is 15 mg/kg IM for 21 days.

Paromomycin should be avoided in patients with severe anaemia (Haemoglobin less than 5 g/dl).

The medicine has minimal reversible ototoxicity and nephropathy as the side effects.
Is Resistant case of kala–azar caused by Leishmania Tropica?


- We worked hard to show that resistant cases of kala–azar were caused by Leishmania Donovani.

- Leishmania Species, drug unresponsiveness and visceral leishmaniasis in Bihar, India
  - C. P. Thakur, J. P. Dedet, S. Narain and F. Pratlong
Dr. U. N. Brahmachari first described a case of PKDL in a kala-azar patient in 1922 whom he treated with tartar emetic, a trivalent antimony compound; he termed the disease as dermal leishmanoid (Fig-1) and demonstrated LD bodies in skin snip (Fig-2).
PKDL (Post Kala-azar Dermal Leishmaniasis)

Fig.-1

Dermal Leishmanoid - showing the eruption in the upper half of the body

Fig.-2

Leishmania Donovani in a smear from the scrapings of the papillomatous nodules.
PKDL (Post Kala–azar Dermal Leishmaniasis)
PKDL (Post Kala–azar Dermal Leishmaniasis)

- Feeding experiment demonstrated that Nodules contain parasites leishmania donovani exactly like the parasites of kala–azar.
- Occurs as depigmented macules, erythematous papules and nodules.
- It was believed usually about two-thirds of the nodular and hypo pigmented macules are completely cured and marked improvement is noted in about \( \frac{2}{3} \) of remaining cases. In about \( \frac{1}{6} \) of the total cases no or slight improvement is noted. Relapse of dermal Lishmaniod after improvement is not very rare (Sen Gupta 1960).
PKDL (Post Kala-azar Dermal Leishmaniasis)

- We compliantly changed the criteria of cure of PKDL the disappearance of all lesions was adopted as criteria of cure (Thakur 1987).
- We cured all cases with SAG (Thakur BMJ 1987) and later with amphotericin B (Thakur et. al 1997).
- We saw that with fix duration of treatment many patient replaced and there fore we adopted this disappearance of all lesions as criteria of cure even with AMB.
- Effect of extensive use of AMB on the incidence of PKDL. (Fig–2)
- In 1980’s we and many other in Bihar left SAG and used AMB Extensively in the treatment of kala-azar. We saw that incidence of PKDL decreased remarkably. (Fig–2)
Figure-2: Incidence of Kala-azar and PKDL during 1970-2005
## Mistakes done in kala-azar Elimination Programme

<table>
<thead>
<tr>
<th>Years</th>
<th>Tools of control</th>
<th>Mistakes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953-64</td>
<td>DDT spray done for Malaria control killed more sandflies than mosquitoes, sandfly being more sensitive number of kala-azar cases decreased.</td>
<td>Chronic cases of kala-azar and PKDL- not taken care of. Haphazard use of SAG ½ ml increasing to 6 ml for 6-10 days In 1964 control programme was discontinued.</td>
</tr>
<tr>
<td>1977</td>
<td>Big epidemic of kala-azar 100,000 cases Survey done by Govt. of India Figures from Government Hospitals 18589, under reporting 5.37:1</td>
<td>Persisted with SAG in same doses, 30% of patients unresponsive to SAG (Peters 1978) No care of PKDL Programme discontinued only after 3 years leaving reservoir of infection at the level of 13620 (under reporting 5.37:1)</td>
</tr>
<tr>
<td>Year</td>
<td>Description</td>
<td>Details</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1991-92</td>
<td>Another big epidemic - 250,000 cases, (Survey of Govt. of India), reports from Govt. of Bihar’s figure 59614 (under reporting 4.19:1.) Again Control Programme started using, 2/3 Centre (21 crore) and 1/3 state (7 crore), SAG was used as main drug.</td>
<td>Again Control Programme discontinued after 3 years. (State reluctant to pay its share of money). SAG as a first line drug used when 50% of patients were found unresponsive to it, the programme was discontinued after 3 years only leavening the reservoir of infection at the level 11627 (under reporting 4.19:1). PKDL – Not taken care of.</td>
</tr>
<tr>
<td>2005</td>
<td>This time programme was taken over by the Central Govt. Amphoteracin B has been approved as a first line drug and in seven blocks Miltefosine.</td>
<td>Decline of the disease has started Erratic supply of medicine, the programme should be continued for 10 years to achieve elimination.</td>
</tr>
</tbody>
</table>
Table 1 shows the total number of cases of kala-azar in Bihar between 1977 and 2008 (Figures from kala-azar Department of Government of Bihar) & PKDL patients admitted to PMCH.

<table>
<thead>
<tr>
<th>Year</th>
<th>No of PKDL cases between 1970 &amp; 2008</th>
<th>Kala-azar cases in Bihar</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>13</td>
<td>100000 x (18589)</td>
</tr>
<tr>
<td>1978</td>
<td>15</td>
<td>41980</td>
</tr>
<tr>
<td>1979</td>
<td>27</td>
<td>25472</td>
</tr>
<tr>
<td>1980</td>
<td>28</td>
<td>13620</td>
</tr>
<tr>
<td>1981</td>
<td>27</td>
<td>14165</td>
</tr>
<tr>
<td>1982</td>
<td>28</td>
<td>11120</td>
</tr>
<tr>
<td>1983</td>
<td>30</td>
<td>11830</td>
</tr>
<tr>
<td>1984</td>
<td>35</td>
<td>12985</td>
</tr>
<tr>
<td>1985</td>
<td>48</td>
<td>13029</td>
</tr>
<tr>
<td>1986</td>
<td>52</td>
<td>14979</td>
</tr>
<tr>
<td>1987</td>
<td>50</td>
<td>19179</td>
</tr>
<tr>
<td>1988</td>
<td>55</td>
<td>19639</td>
</tr>
<tr>
<td>1989</td>
<td>59</td>
<td>34489</td>
</tr>
<tr>
<td>1990</td>
<td>14</td>
<td>54650</td>
</tr>
<tr>
<td>1991</td>
<td>20</td>
<td>250000 x (59614)</td>
</tr>
<tr>
<td>1992</td>
<td>22</td>
<td>75523</td>
</tr>
<tr>
<td>1993</td>
<td>10</td>
<td>44155</td>
</tr>
<tr>
<td>1994</td>
<td>17</td>
<td>24391</td>
</tr>
<tr>
<td>1995</td>
<td>18</td>
<td>21045</td>
</tr>
</tbody>
</table>
X1 - The figure shown is that of survey done by National Institute of Communicable Diseases, Government of India and figure in bracket was obtained from different blocks of Government of Bihar.

<table>
<thead>
<tr>
<th>Year</th>
<th>Value</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>14</td>
<td>25056</td>
</tr>
<tr>
<td>1997</td>
<td>14</td>
<td>15948</td>
</tr>
<tr>
<td>1998</td>
<td>14</td>
<td>12441</td>
</tr>
<tr>
<td>1999</td>
<td>12</td>
<td>11627</td>
</tr>
<tr>
<td>2000</td>
<td>5</td>
<td>12909</td>
</tr>
<tr>
<td>2001</td>
<td>15</td>
<td>10237</td>
</tr>
<tr>
<td>2002</td>
<td>10</td>
<td>9184</td>
</tr>
<tr>
<td>2003</td>
<td>5</td>
<td>13960</td>
</tr>
<tr>
<td>2004</td>
<td>4</td>
<td>17324</td>
</tr>
<tr>
<td>2005</td>
<td>4</td>
<td>21177</td>
</tr>
<tr>
<td>2006</td>
<td>1</td>
<td>29711</td>
</tr>
<tr>
<td>2007</td>
<td>17</td>
<td>31684</td>
</tr>
<tr>
<td>2008</td>
<td>7</td>
<td>28125</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td>7342 June</td>
</tr>
</tbody>
</table>

X2 - The figure was obtained by a survey done by an expert team of government of India. Figures in bracket was from PHC of Bihar.
Conclusion

- The continuous search by human minds to go at the depth of the problem has not only found the cause of kala-azar but its distribution and the treatment.

- The depressing part of the story is that the countries which were affected with it in 1903 are still affected except for few advance countries. With discovery of new tools kala-azar could be eliminated provided a proper environment is created for that. We hope that we will succeed in the elimination of kala-azar.
Thank You.