A study material for M.Sc. Biochemistry (Semester: IV) Students
on the topic (EC-1; Unit IV)

Kala-Azar

The Black Fever

Vyomesh Vibhaw
Assistant Professor (Part Time)
Department of Biochemistry
Patna University
Mob. No.:- +91-9708381107, +91-8825217209
E. Mail: vyomesh.vibhaw@gmail.com

Kala-Azar

- Kala-Azar is a chronic and possibly deadly parasitic disease caused by the infection of a parasite called Leishmania Donovani.
- It mainly affects internal organs, such as the spleen, bone marrow, liver and lymph nodes.
- The major signs of the disease are weakness, lack of appetite, recurrent fever, anaemia, lymphadenopathy and swelling of the liver and spleen.
- Kala-Azar is widespread in rural areas of the tropical and subtropical countries in the world. The disease is transmitted to humans by the bite of the female Phlebotomus Sand-fly that is infected by the parasite.
- The incubation period is normally two to six months.

Introduction

- 1900 – Sir William Leishman discovered L. donovani in spleen smears of a soldier who died of fever at Dum-Dum, India. The disease was known locally as Dum-Dum fever or kala-azar.

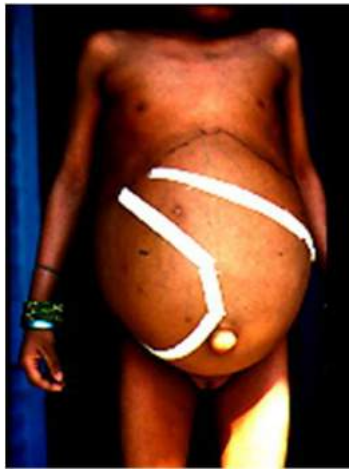
- 1903 – Charles Donovan found same parasite in a spleen biopsy.

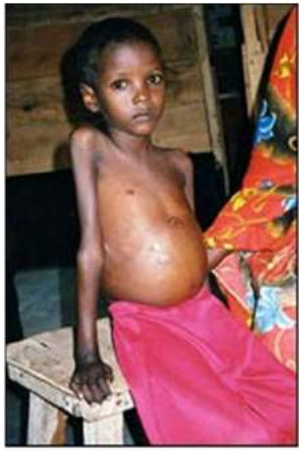
Morphology

- Amastigotes measure 2-3 micrometers, with a large nucleus and kinetoplast.
- Amastigotes mainly live within cells of the RE system, but have been found in nearly every tissue and fluid of the body.
- The RES is part of the immune system consisting of the phagocytic cells which accumulate in the lymph nodes and spleen.
- Also known as mononuclear phagocytic system or lymphoreticular system.
- Primary lymphoid organs – The sites where the RES cells are produced. The cells of the RES are produced in the bone marrow.
- Secondary lymphoid organs – Sites where the RES cells function. These sites include the spleen, liver, lymph nodes, and intestine.

Pathogenesis

- Infections range from asymptomatic to progressive, fully developed kala-azar.
- Incubation period is usually 2 – 4 months.
- Symptoms – Begins with low-grade fever and malaise, followed by progressive wasting, anemia, and protrusion of the abdomen from enlarged liver and spleen.
- Fatal after 2 – 3 years if not treated.
- In acute cases with chills, fevers up to 104 degrees Fahrenheit, and vomiting; death may occur within 6 – 12 months.
- Immediate cause of death is usually an invasion of a secondary pathogen that the body is unable to combat.





Hepatosplenomegaly and emaciation.

Global Distribution

- It affects as many as 12 million people worldwide, with 1.5–2 million new cases each year
- Difficult to determine because accurate public health records are not kept in some of these areas.
- Leishmaniasis-infected areas overlap with HIV-infected areas.
- One in every third of those patients die during their first visceral leishmaniasis episode.
- **India:** Currently, it is a main problem in Bihar, Jharkhand, West Bengal and some parts of Uttar Pradesh. In view of the growing problem planned control measures were initiated to control kala-azar.

TYPES OF LEISMANIASIS

- VISCERAL LEISHMANIASIS
- (Bangladesh, Brazil, India, Nepal and Sudan)

- CUTANEOUS LEISHMANIASIS
- (Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria)

- DIFFUSE CUTANEOUS LEISHMANIASIS

- MUCO CUTANEOUS LEISHMANIASIS
  (Bolivia, Brazil and Peru)

- **Post kala azar dermal leishmaniasis** (Endemic to India and the Sudan)

Visceral leishmaniasis

Irregular bouts of fever
Substantial weight loss
Swelling of the spleen and liver and anaemia

Cutaneous leishmaniasis

Most common form

sore at the bite site which heals in a few months to a year

skin ulcers on the exposed parts of the body, such as the face, arms and legs.

This form can progress to any of the other three forms.

Diffuse Cutaneous leishmaniasis:

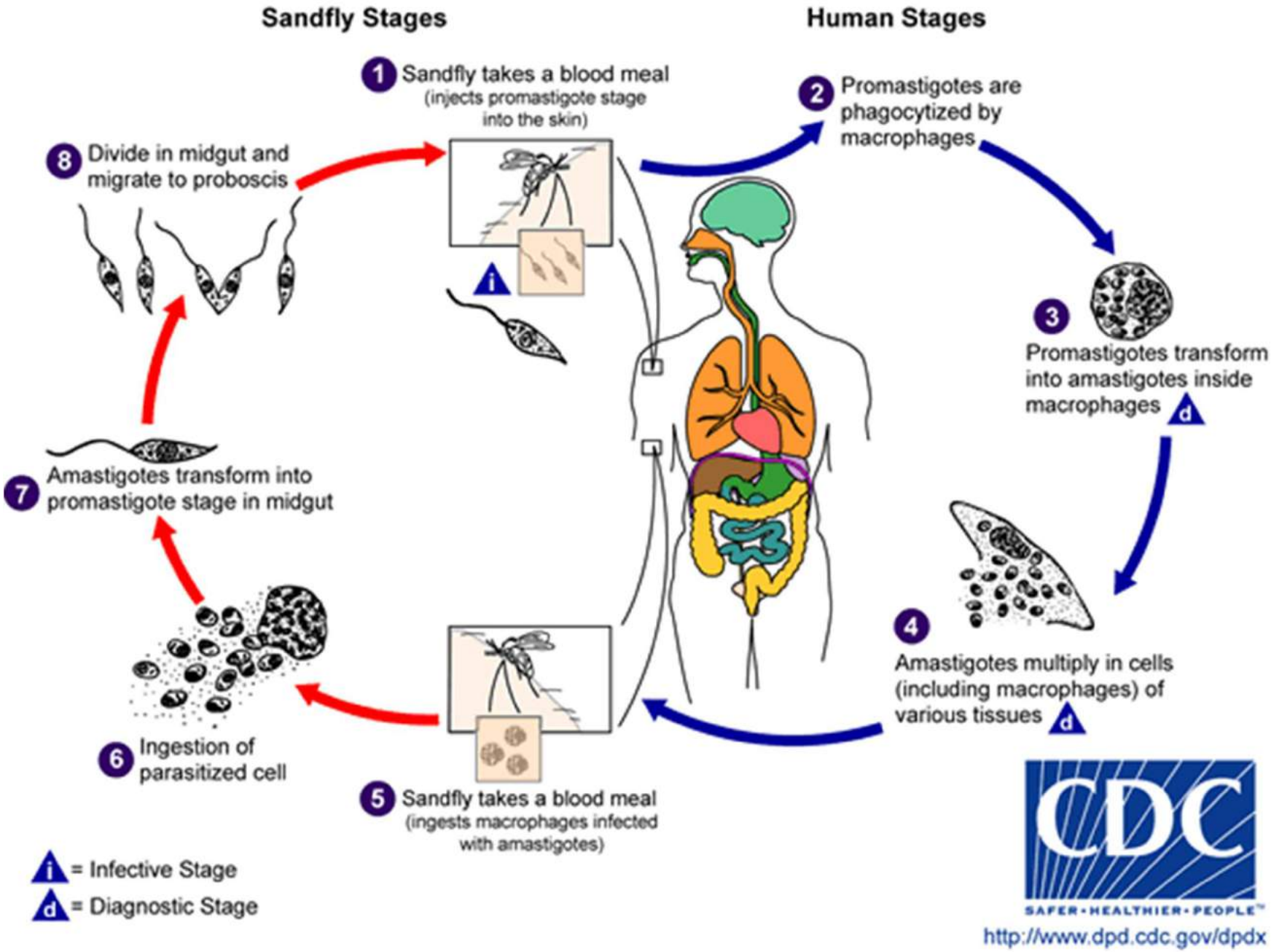
produces widespread skin lesions which resemble leprosy,

Difficult to treat.

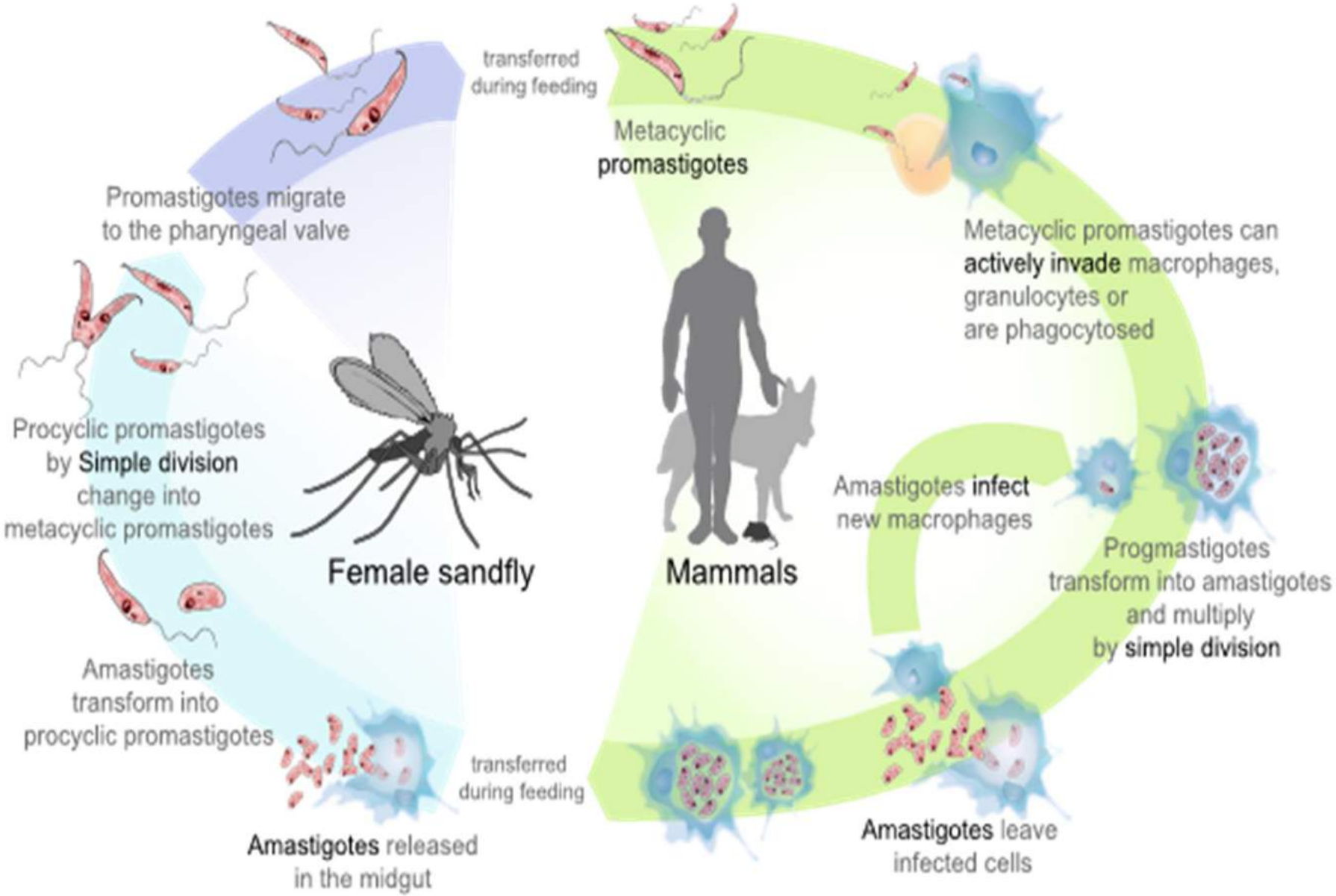
Mucocutaneous leishmaniasis or *espundia*

commences with skin ulcers which spread,

causing tissue damage, particularly the nose and mouth


Sandfly Stages
Human Stages
1 Sandfly takes a blood meal
(injects promastigote stage
into the skin)
2 Promastigotes are
phagocytized by
macrophages
3 Promastigotes transform
into amastigotes inside
macrophages
d
4 Amastigotes multiply in cells
(including macrophages) of
various tissues
d
5 Sandfly takes a blood meal
(ingests macrophages infected
with amastigotes)
6 Ingestion of
parasitized cell
7 Amastigotes transform into
promastigote stage in midgut
8 Divide in midgut and
migrate to proboscis
i = Infective Stage
d = Diagnostic Stage
CDC
SAFER • HEALTHIER • PEOPLE™
http://www.dpd.cdc.gov/dpdx

Life cycle of *Leishmania*



1. Leishmaniasis is transmitted by the bite of female phlebotomine sandflies. The sandflies inject the infective stage, promastigotes, during blood meals.
2. Promastigotes that reach the puncture wound are phagocytized by macrophages.
3.They transform into amastigotes.
4. Amastigotes multiply in infected cells and affect different tissues.
5. Sandflies become infected during blood meals on an infected host when they ingest macrophages infected with amastigotes.
6. In the sandfly's midgut, the parasites differentiate into promastigotes.
7. They multiply and migrate to the proboscis.

Strategy for control

The strategy for kala-azar control broadly included three main activities.

1. Interruption of transmission by reducing vector population through indoor residual insecticides.

2. Early diagnosis and complete treatment of Kala-azar cases.

3. Health education programme for community awareness.

Control of the disease is based on control of the sand fly population.

Miltefosine has cured up to 98% of VL cases.

Diagnosis and Treatment

- Tests examine tissues or serums for L-D bodies.
- Most frequently used test is the enzyme-linked immunosorbent assay (ELISA).
- ELISA – Multi-step process of detecting if a person is infected by analyzing antibody-antibody interactions of the patient's serum.
- Direct agglutination test (DAT).

Research

- The capacity of the parasites to cause this wide range of disease manifestations depends upon their ability to evade the immune defence mechanisms by performing a well-tuned orchestra of host parasite interactions inside the macrophages.
- key role of cell-mediated immunity (CMI) in protection.
- The survival strategies of the parasites leads to the suppression of CMI which can further be aggravated by the co-infections with HIV, tuberculosis etc.
- Currently, no vaccines are in routine use. However, the genomic sequence of *Leishmania* has provided a rich source of vaccine candidates.
- Several potential vaccines are being developed, under pressure from the World Health Organization, but as of 2010 none are available.
- HIV protease inhibitors have been found to be active against *Leishmania* species in two *in vitro* studies in Canada and India. The studies reported the intracellular growth of parasites was controlled by nelfinavir and ritonavir in a human monocytes cell line and also in human primary monocyte-derived macrophages.
- Since September 2011 there exists a World Community Grid project called Drug Search for Leishmaniasis which has the goal to find new drugs against this disease.

Acknowledgement and Suggested Readings:

1. Medical Microbiology, A guide to Microbial Infections: Pathogenesis, Immunity, Laboratory Investigation and Control; Barber, Irving, Swann and Perera; Elsevier Publication
2. Microbiology, An Introduction; Tortora, Funke and Case; Pearson Publication
3. Microbiology; Prescott, Harley and Klein; The MacGraw-Hill Companies
4. Microbiology: Principles and Explorations; Jacquelyn G Black; John Wiley and Sons Inc.
5. Brock Biology of Microorganisms; Madigan, Martinko, Stahl and Clark; Benjamin Cummings (Pearson Publication)

Thanks