ALBERT SZENT-GYÖRGYI MEDICAL UNIVERSITY

CENTRAL LABORATORY FOR CLINICAL MICROBIOLOGY

SZEGED, HUNGARY.

THESIS

TROPICAL DISEASES : REVIEW PAPER

BY

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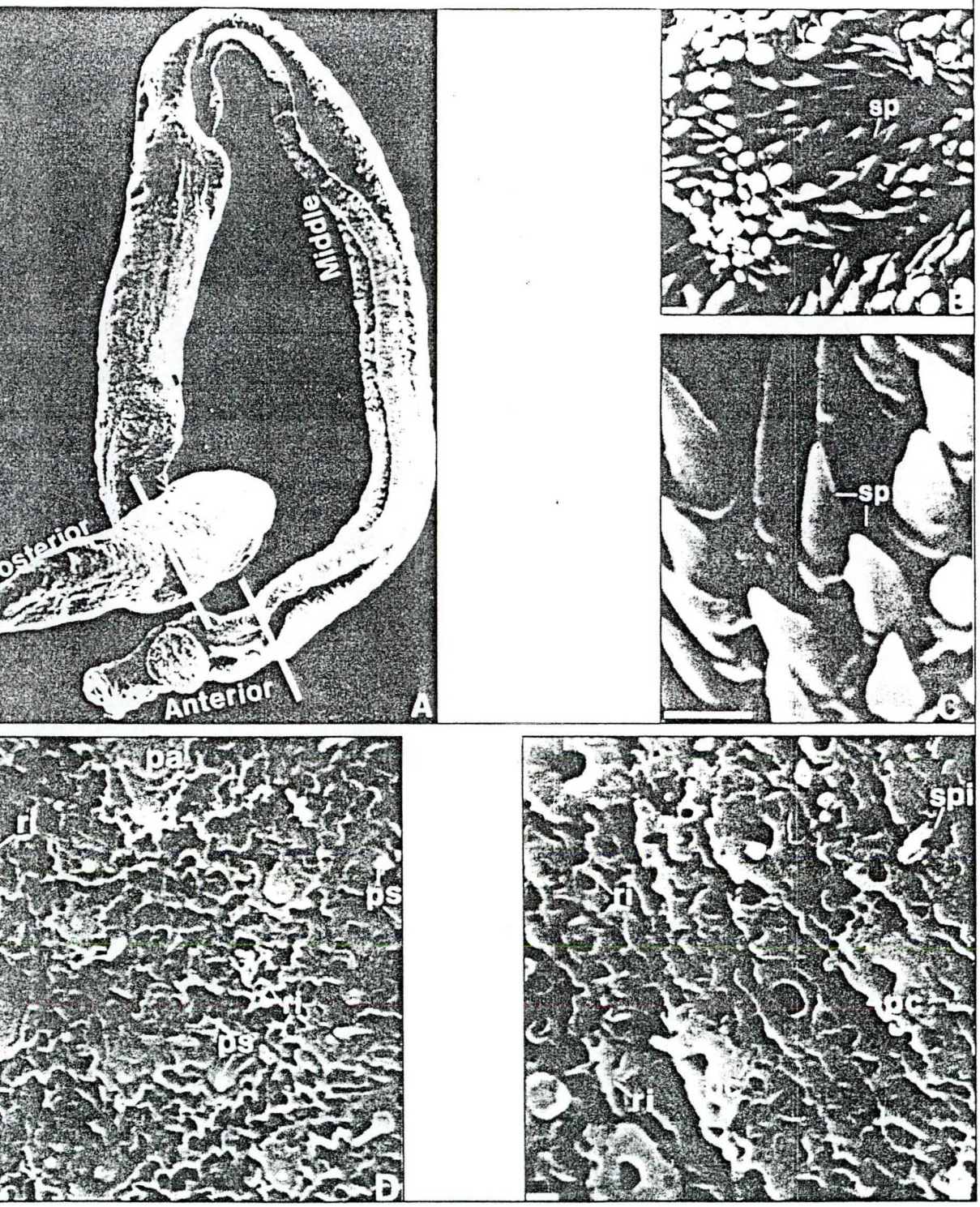
Signature
Maher Ayyad.



Male Schistosoma mekongi *indicating the division of the body into anterior, middle and posterior portions. × 43.*
A low-power micrograph of the ventral sucker exhibiting large sharp spines (sp) which are arranged in rows. × 2440.
A high-power micrograph of the spines (sp) in the ventral sucker. × 9930.
The dorsal and lateral aspects of the tegument of the anterior part of the body exhibiting round papillae (pa), sensory papillae or s (ps) and perforated ridges (ri). × 2510.
The ventral tegument of the anterior part showing papillae with crater in the centre (pc), papillae with cilia (pc'), ridges (ri) and a ory pit (spi). × 3000.
(A) = 500 microns; (B-E) = 2 microns)

PLATE XXXVIII

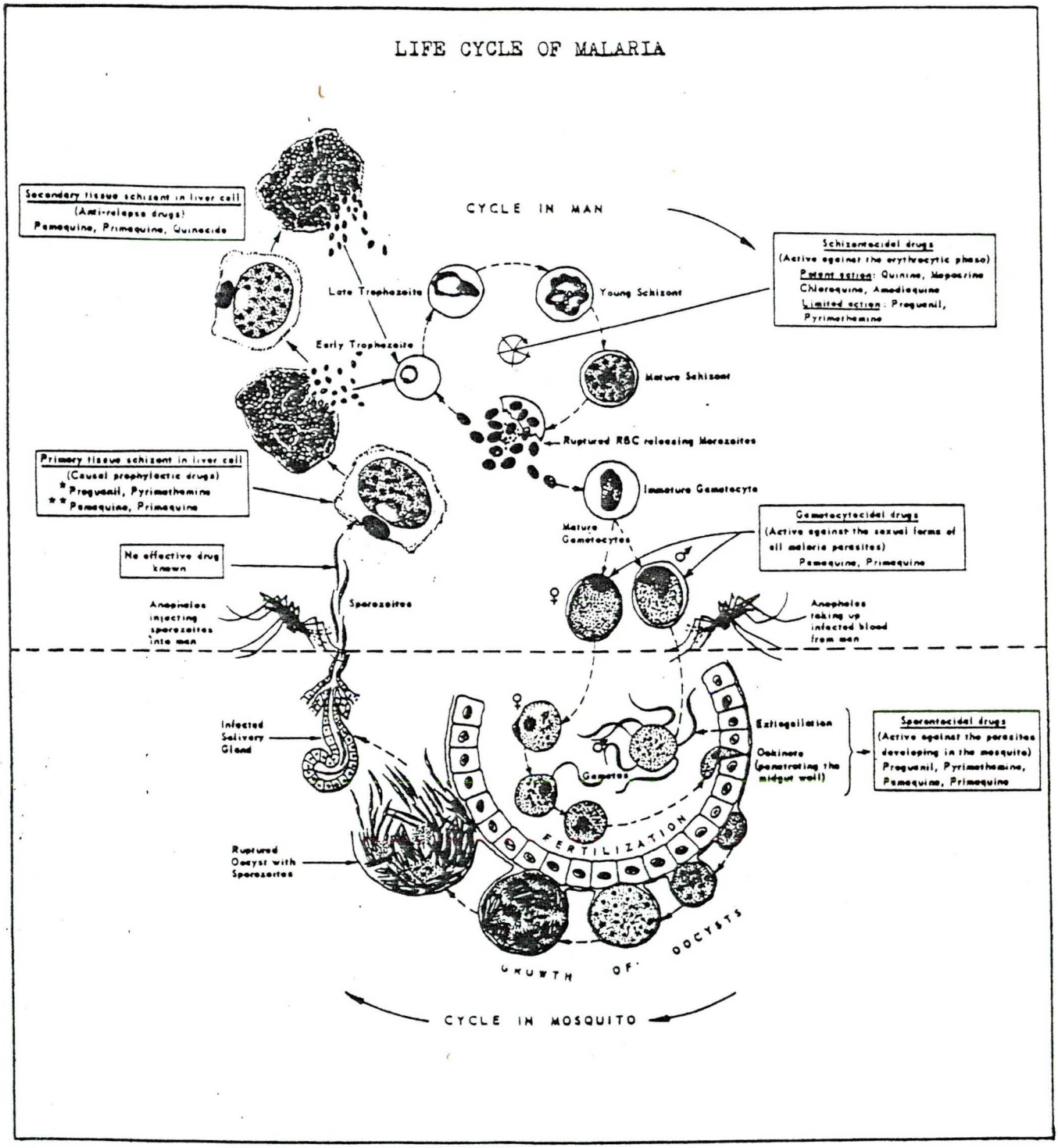


PLATE XXXIII

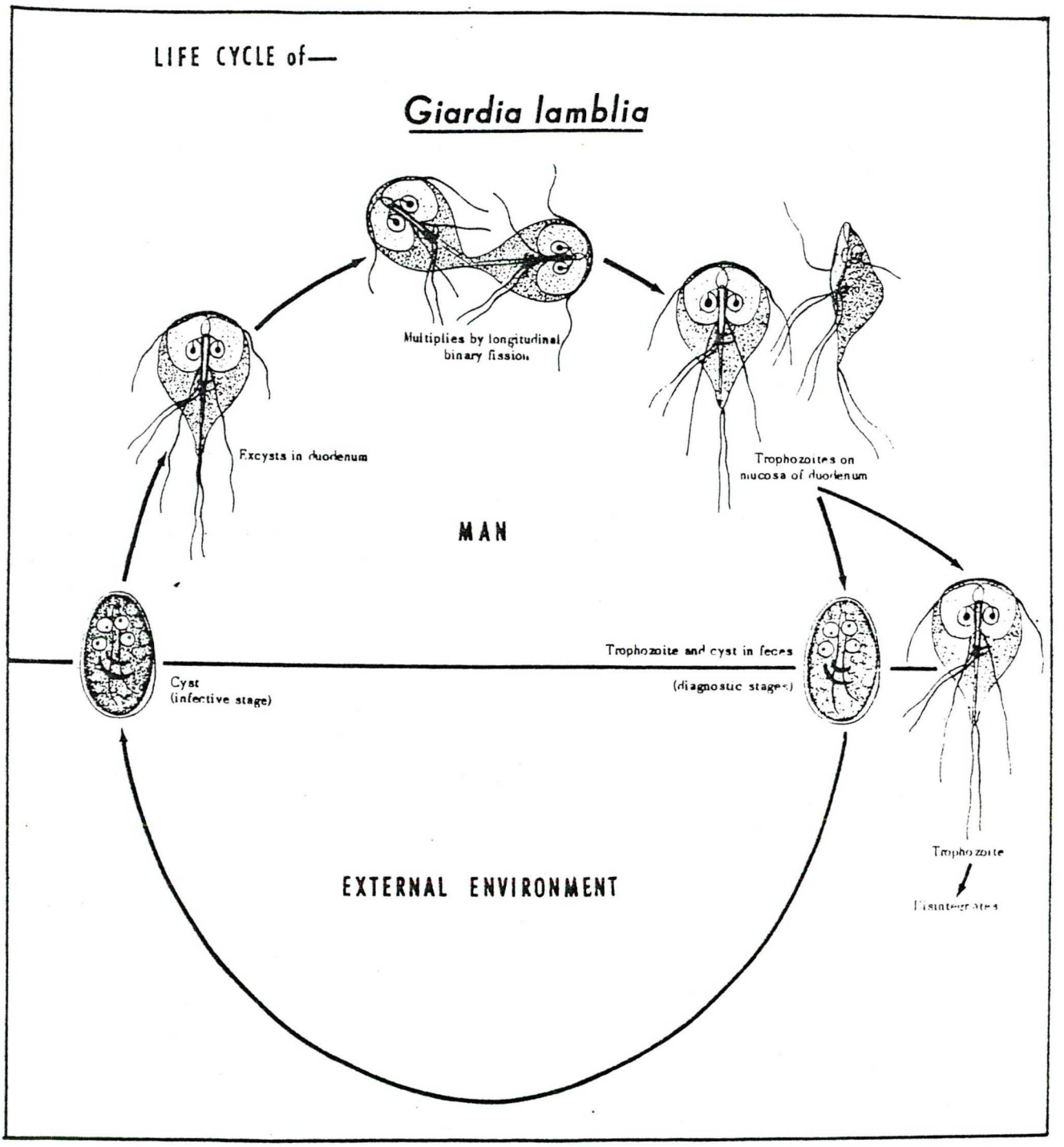


PLATE XXXI

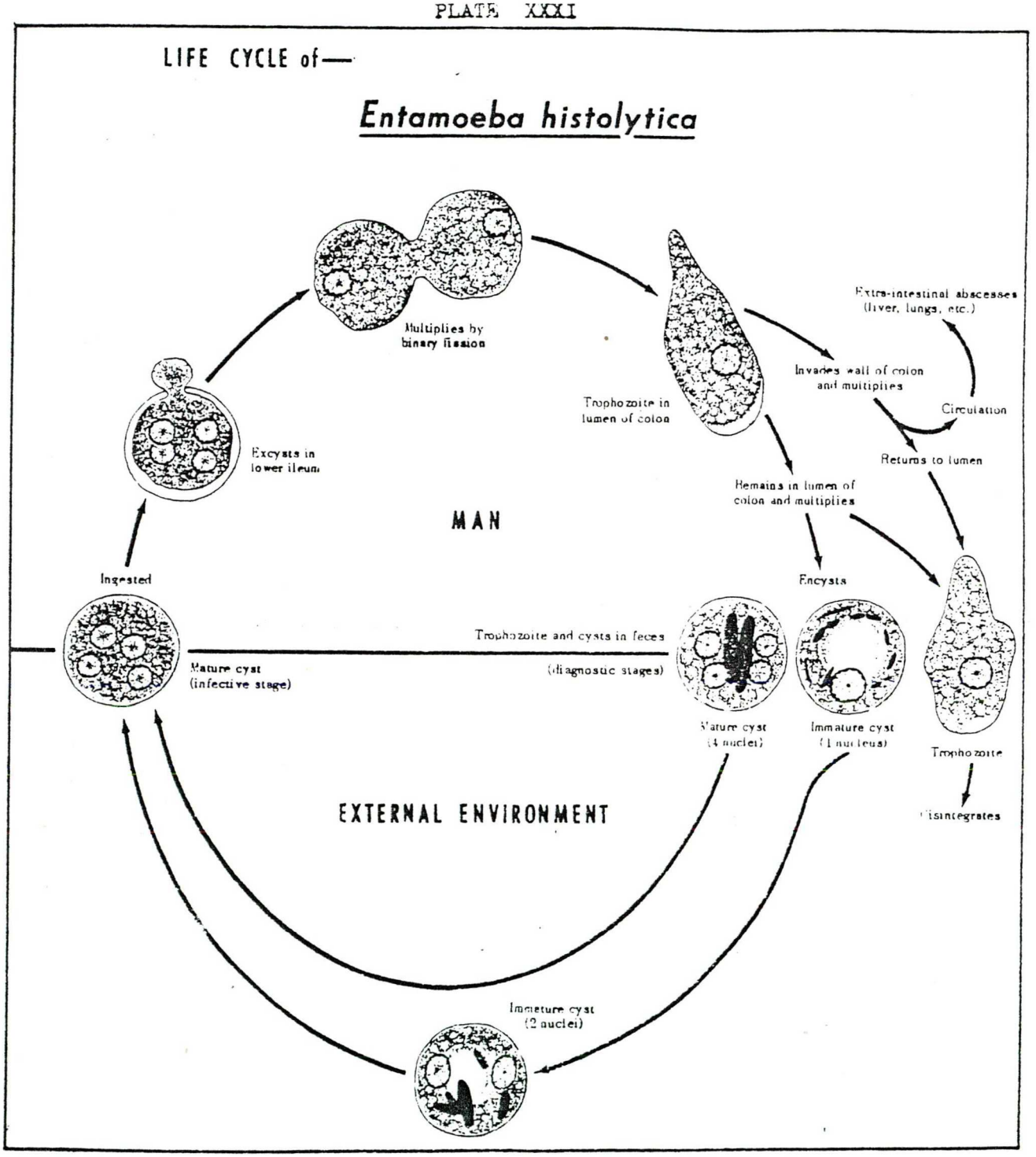

LIFE CYCLE of—
Entamoeba histolytica
Multiplies by binary fission
Trophozoite in lumen of colon
Extra-intestinal abscesses (liver, lungs, etc.)
Invades wall of colon and multiplies
Circulation
Returns to lumen
Remains in lumen of colon and multiplies
Encysts
Excysts in lower ileum
MAN
Ingested
Trophozoite and cysts in feces
(diagnostic stages)
Mature cyst (infective stage)
Mature cyst (4 nuclei)
Immature cyst (1 nucleus)
Trophozoite
Disintegrates
EXTERNAL ENVIRONMENT
Immature cyst (2 nuclei)

PLATE XXXV

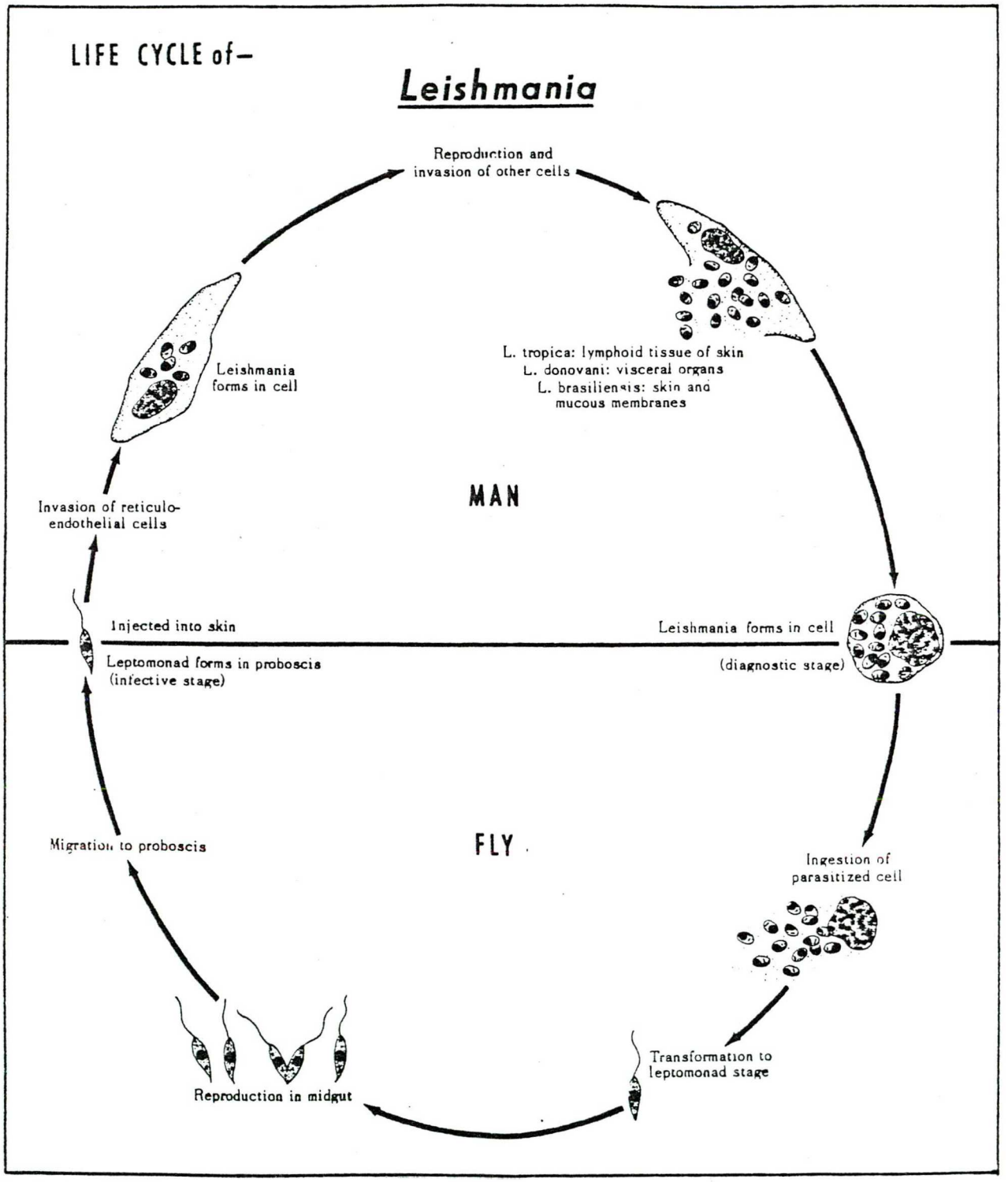

LIFE CYCLE of–
Leishmania
Reproduction and invasion of other cells
L. tropica: lymphoid tissue of skin
L. donovani: visceral organs
L. brasiliensis: skin and mucous membranes
Leishmania forms in cell
MAN
Invasion of reticulo-endothelial cells
Injected into skin
Leptomonad forms in proboscis (infective stage)
Leishmania forms in cell
(diagnostic stage)
FLY
Migration to proboscis
Ingestion of parasitized cell
Transformation to leptomonad stage
Reproduction in midgut

PLATE XXXII

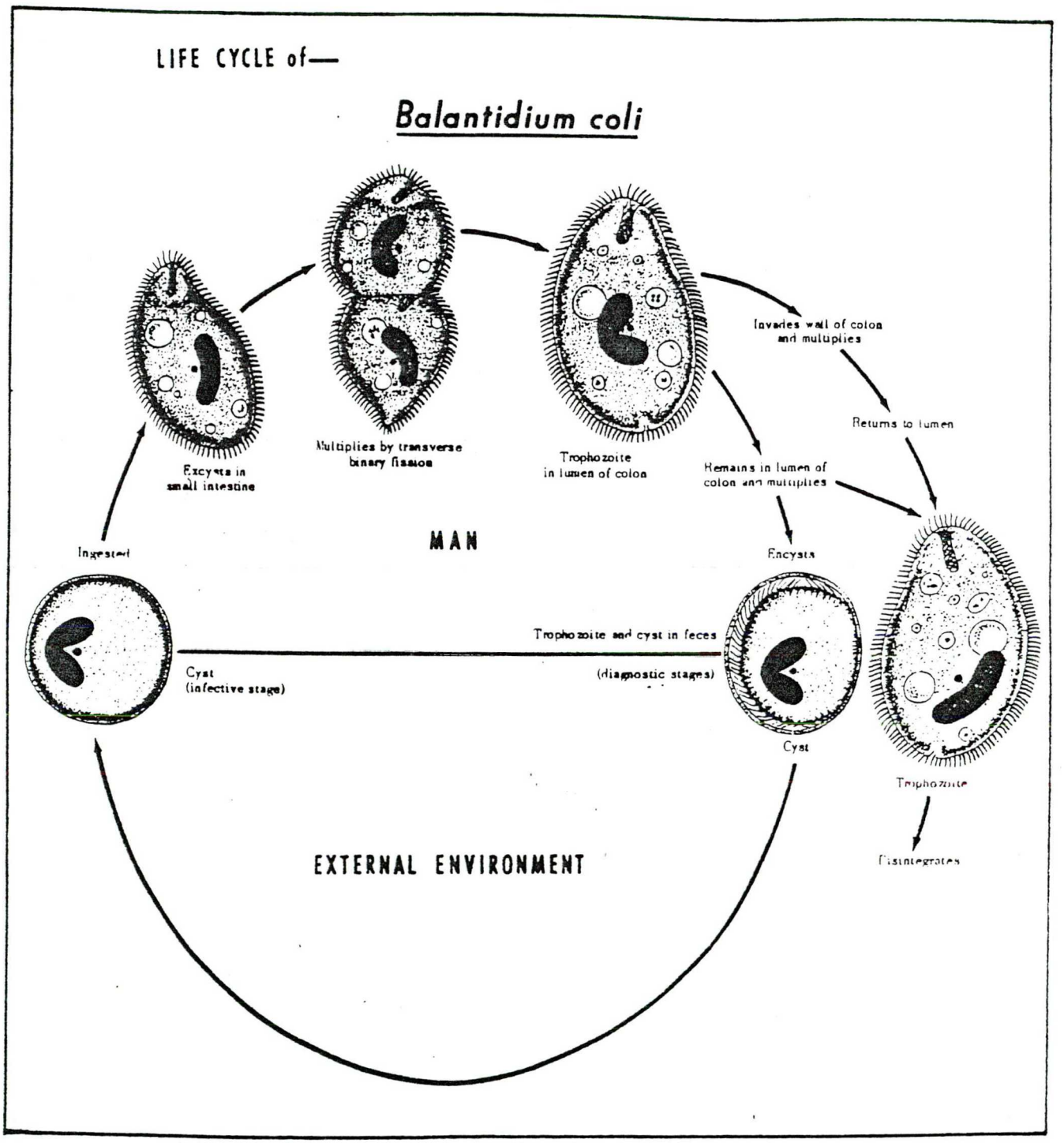

LIFE CYCLE of—
Balantidium coli
Excysts in small intestine
Multiplies by transverse binary fission
Trophozoite in lumen of colon
Invades wall of colon and multiplies
Returns to lumen
Remains in lumen of colon and multiplies
MAN
Ingested
Encysts
Trophozoite and cyst in feces
(diagnostic stages)
Cyst (infective stage)
Cyst
Trophozoite
Disintegrates
EXTERNAL ENVIRONMENT

PLATE XXXVII

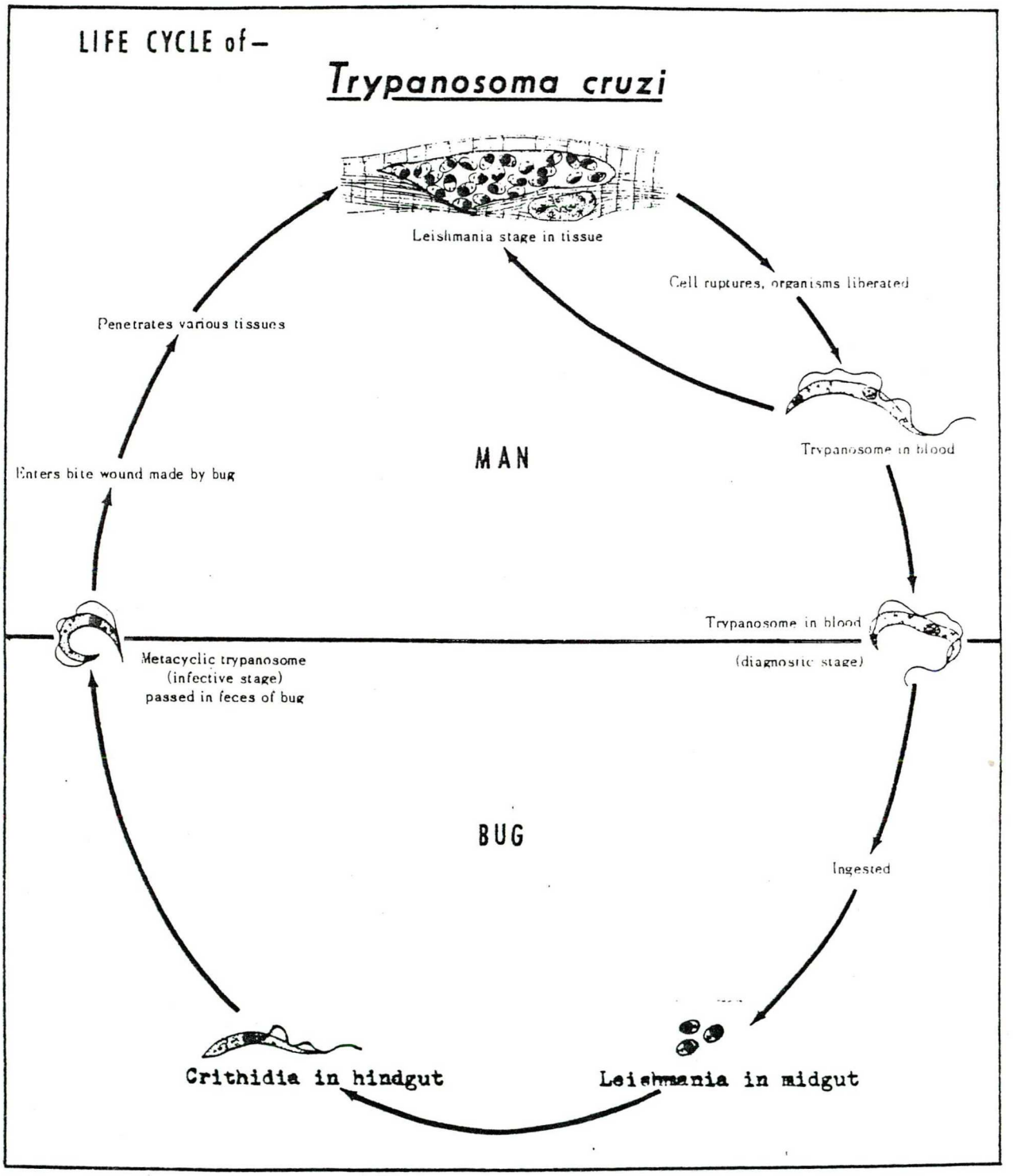
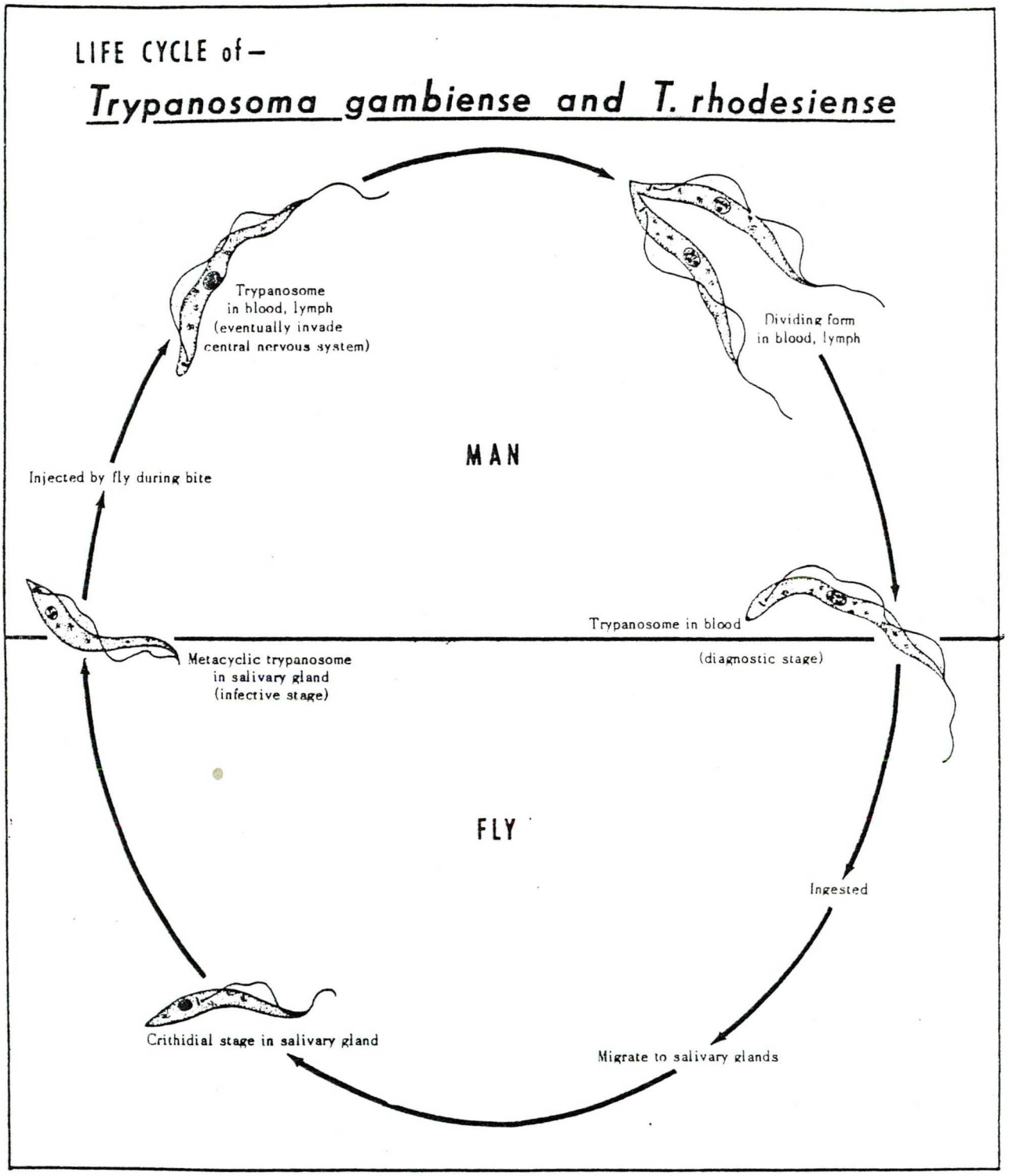


PLATE XXXVI


LIFE CYCLE of—
Trypanosoma gambiense and T. rhodesiense
Trypanosome in blood, lymph (eventually invade central nervous system)
Dividing form in blood, lymph
MAN
Injected by fly during bite
Trypanosome in blood
(diagnostic stage)
Metacyclic trypanosome in salivary gland (infective stage)
FLY
Ingested
Crithidial stage in salivary gland
Migrate to salivary glands

Differentiation of the malaria species.

	Plasmodium vivax	Plasmodium ovale	Plasmodium malariae	Plasmodium Palciparum
	Benign tertian	Ovale tertian	Quartan	Subtertian or Malignant
Preerythrocytic cycle(days)	6	9	12	6
Incubation period(days in average)	14	17	28	11
Paraerythrocytic cycle relapse.	present	present	present	Absent
No. of merozoites in liver schizont.	10,000	15,000	2000	40,000
Erythrocytic cycle(hours	48	48	72	36
Parasitized RBC				
size	enlarged	enlarged	normal	normal
shape	normal	oval	normal	normal
Stippling	Schuffner dots (fine pink dots)	Schuffner dots (fine pink dots)	Ziemann dots (fine pink dots)	Mauror dots (irregular red olefts)
Age infected	young	-	old	all ages
Multiple infection	-	-	-	common

1) M A L A R I A

Introduction:

Malaria is still the most important parasitic disease in the tropics. In 1982, the most recent year for which reliable figures are available, 365 million people- nearly one-twelfth of the world's population- were living in areas, mostly in Africa, where malaria is still highly endemic and where no specific antimalaria measures are being applied. A further 2217 million- 46% of the world's population-were living in areas where malaria is still endemic but where control measures have reduced its level of endemicity to a certain degree.

This epidemiological picture (Fig. 1) has not changed significantly over the past decade and there is no reason to expect that it will in the near future, unless malaria is allowed to take root again in some parts of the world as a result of reductions or interruptions in control measures.

Excluding Africa south of the Sahara 7,8 million malaria cases were reported to WHO in 1981 as opposed to 8.0 million in 1980 and 7.0 million in 1979. The provisional figures for 1982 were 6.5 million. These data must be considered with caution, since screening, diagnosis and

notification efforts have declined over the past 15 years. Many countries have been forced to scale down malaria control measures, thereby reducing the availability of accurate information on the disease. The above figures may therefore not reflect a true reduction in global malaria incidence.

In areas other than tropical Africa the incidence of the disease is currently estimated to be around 20 million cases a year. In Africa south of the Sahara some million people are believed to be chronically infected and of these, about one-third suffer acute manifestations of the disease in the course of a year. Accurate figures are not available for the number of deaths caused primarily by malaria, although in Africa alone it is estimated that the disease in responsible for the deaths of one million infants and young children each year.

Malaria incidence varies widely from one part of the world to another. In North Africa it has been drastically reduced and in Tunisia, eradicated altogether. In southern Asia, where a new peak was recorded only a few years ago, the incidence has fallen again, but fairly slowly. By contrast, in central and south America there has been a steady, uninterrupted rise since 1974, whereas in tropical Africa a mainly hyper- or holoendemic area-

there has been little change, apart from an increasing involvement of urban and periurban areas. Europe, Australia and the United States have remained free of malaria transmission despite massive importation of cases from other countries.

The organisms:

Plasmodium falciparum is the parasite responsible for most cases of malaria(80% worldwide) and for the most severe, often fatal, forms of the disease. It is deeply entrenched in tropical Africa P. vivax is the commonest species in the Americas and in Asia. These two species account for most of the human suffering and economic loss due to malaria in the world today. In southern Asia, where renewed efforts at malaria control have shown recent successes, the incidence of P.vivax infection has fallen but that of P.falciparum has remained virtually unchanged. This is an ominous sign and apparently due to drug resistance and the impossibility of achieving radical cures in affected areas. Any relaxation of malaria control efforts in these areas could well cause an explosive upsurge in incidence.

Control:

The repertoire of tools and methods available for malaria control has not increased significantly over the past three decades, and has even steadily declined in efficacy.

In many areas, resistance of vector anopheline mosquitoes to insecticides has prompted a shift from chlorinated hydrocarbon insecticides, such as DDT and HCH, to organophosphorous compounds or the more expensive carbamides. Exophilic (outdoor)vectors, such as the Anopheles balabacensis mosquitoes in south -east Asia or the An.nuneztovari group in south America, are not amenable to control by intradomiciliary insecticide spraying, and the inaccessibility and wide-spread nature of their breeding places make larval control partically impossible.

Resistance:

Resistance of P. falciparum to drugs has probably become the most important threat to effective control of the disease. It has arisen largely through a combination of massive antimalarial drug deployment and a failure to combat transmission of the disease.
Population movements have also played a part in the occurrence and spread of resistance.

Resistance to the new antimalarial mefloquine has been experimentally induced in rodent malaria models and in P. falciparum in vitro. Naturally occurring P.falciparum populations are known to vary considerably in their relative sensitivity to mefloquine. However, primary resistance

to mefloquine (i.e. in patients not previously exposed to the drug) seems to be quite rare: to date, only two cases have been observed in two widely separated areas of the world. Current primary cure rates (up to 97% in some areas) for mefloquine treatment in falciparum malaria patients approximate those that were recorded for chloroquine shortly after its introduction as an antimalarial. Moreover, the majority of mefloquine treatment failure so far recorded have been associated with vomiting following administration of the drug and could therefore be attributed mainly to drug loss and inadequate treatment.

By the end of 1984(Fig.) chloroquine-resistant P. falciparum was present in 15 countries in eastern Asia and Oceania, 10 in South America and 15 in Africa(mostly south of the equator, where it had reached the Atlantic coast in three countries). Resistance to the second-line sulfonamide pyrimethamine combination is already widespread in the " hard-core " areas of South-East Asia and South America, and there have been recent reports of declining treatment efficacy in other areas, including East Africa, Although chloroquine and especially amodiaquine are still effective in most " semiimmune " individuals in tropical Africa, their ineffectiveness in an increasing number of non-immune patients poses a major threat to the lives of millions of infants and young children.

Apart from technical problems, malaria control has also suffered from inflationary increases in the costs of insecticides, drugs, equipment and fuel. In contrast, government budgetary expenditure on malaria control has either not increased or, in many countries, has even been cut back. All in all, the balance favours the malaria parasite.

Current efforts at malaria control hold only limited promise. New approaches are clearly required, and this is the goal of the three Scientific Working Groups (SWGs) on Malaria, whose activities in 1983 and 1984 are described in the following pages.

-GHEMAL, the SWG on the chemotherapy of Malaria, pursues the development of new antimalarial drugs. The recent registration of mefloquine and a mefloquine plus sulfadoxine pyrimethamine combination was achieved largely on the stength of clinical trials conducted under CHEMAL auspices. Other drugs, most with entirely new mechanisms of action, are under development and innovative approaches to drug design are being pursued.

-IMMAL, theSWG on the Immunology of Malaria , has made considerable progress in the development of "causal" prophylactic (acting directly on the cause of the disease) ,

clinically attenuating and transmission-blocking vaccines. Promising leads are expected to yield trial vaccines within the next few years and research on the mass production of vaccine antigens could lead to vaccines that are cheap enough for use even in the least developed countries.

-FIELDMAL, the SWG on Applied Field Research in Malaria, aims at the improvement of epidemiological and control technology and the validation and field application of new tools emanating from the work of CHEMAL and IMMAL. FIELDMAL spearheaded the establishment of a worldwide system for monitoring P. falciparum resistance to anti-malarial drugs and is exploring new ways of achieving community participation in malaria control activities and of incorporating these activities within primary health care infrastructures.

The life cycle passes in 3 stages:

Two in man: Excerythrocytic schizogony.
Erythrocytic schizogony.
One in mosquito: Sporogony.

Excerythrocytic schizogony(liver phases):

1. When an infective female Anopheles mosquito bites man, it inoculates saliva containing sporozoites(infective stage).
2. The sporozoite is a siokle-shaped organism with pointed ends and a central nucleus. It is about 10 u in length.
3. Sporozoites reach the blood stream and within 30 minutes enter the parenohyma liver cells, initiating a cycle of schizogony (preerythrocytic cycle or primary tissue phase).
4. The sporozoite on entering the parenchyma liver cell, becomes rounded (the trophozoite). The trophozoite feeds on the liver cell and enlarges.
5. The nucleus divides into a large number of pieces, each takes a piece of cytoplasm round it, resulting in the formation of a schizont containing thousands of merozoites.
6. The liver cell ruptures liberating the morozoites in the sinusoides.
7. The morozoites either invade the RBCs or other parenchyma liver cells:
   a) In case of Plasmoidum falciparum: all morozoites invade RBCs, without reinvading liver cells.

b)In case of the other species: some merozoites invade RBCs, and some reinvade liver cells initiating further excerythrocytic schizogony (Paraerythrocytic cycle or secondary tissue phase) which is responsible for relapses.

8.The period taken from entery of sporozoites in the liver till merozoites invade the RBCs is called the prepatent period or parasitic incubation period.

Erythrocytic schizogony(blood phase):

1. The erythrocytic cycle begins when a liver merozoite enters a RBC.
2. It assumes a ring shape: a small chromatin mass(nucleus) attached to a loop of cytoplasm enclosing a vacuole.
3. The ring form grows in size, feeding on the RBC and developing pigment (waste products). This is the trophozoite.
4. The parasite loses vacucles and the nucleus divides into a number of pieces, each takes a piece of cytoplasm round it, resulting in the formation of a schisent containing a certain number of merozoites. Pigment does not enter in the formation of merozoites, but remains in the center of the schizont.
5. The RBC ruptures liberating the merozoites and pigment.
6. The merozoites reinvade RBCs repeating the schizogonic cycles.

7. Some merozoites that invade RBCs develop into sexual stages(male or female gametocytes). Their cytoplasm is compact. In the female, the cytoplasm stains deep blue and the pigment is collected round a compact small peripheral nucleus, while in the male the cytoplasm stains pale blue and the pigment is distributed through it and the nucleus is diffuse and centra. These undergo no further development until taken by the mosquite.
8. Erythrocytic merozoites do not reinvade the liver cells. So malaria transmitted by blood transfusion reproduces only erythrocytic cycles.
9. The liberated pigment is phagocytosed.
10. Pigment is a degeneration product of haemoglobin(haematin or ferri-haemic acid).
11. The rutpure of the schizonts and liberation of pigment coincide with the malarial attack.
12. The interval between the bite of infecting mosquito and onset of symptoms (rupture of schizonts) is the clinical incubation period.
13. The erythrocytic cycle from invasion of RBCs by merozoites till next merozoite stage takes a fixed period for each species.
14. The parasitized RBCs show different changes in various species as change in size, colour and appearance of stippling.

Sporogony(Extrinsic cycle in mosquito):

1. When a female Anopheles mosquito vector bites infected man, it sucks blood containing the different stages of malaria parasite. All stages other than gametocytes are digested in the stomach.
2. The microgametocyte (male gamatocyte) undergoes exflagellation. The nucleus divides into 6-8 pieces which migrate to the periphery. At the same time, 6-8 thin filaments of cytoplasm are thrust out, in each passes a piece of chromatin. These filaments, the microgametes, are actively motile and separate from the body of the gametocyte.
3. The macrogametocyte(female gametocyte) by reduction division becomes a macrogamete.
4. Fertilisation occurs by entery of a microgamete into the macrogamete forming a zygote.
5. The zygote changes into a worm-like form, the ookinete, which penetrates the wall of the stomach to develop into a spherical cocyat between the epithelium and baement membrane.
6. The cocyata increase in size. Thousands of sporozoites develop inside the cocysts rupture and sporozoites are liberated in the body cavity and migrate everywhere particularly to the salivary glands. Now the mosquito is infective.
7. The sporogonous cycle in the mosquito takes 8-12 days depending on temperature.

Pathogenicity:

1. Rupture of blood schizonts results in destruction of RBCs and liberation of pigment and probably toxin leading to malaria paroxysm which entails 3 stages:
   a. The cold stage: The patient feels cold, shivers, and the temperature rises. Duration about one hour.
   b. The hot stage:There is fever, hot dry skin. Duration 1-4 hours.
   c. The sweating stage:There is profuse sweating and the temperature falls. Duration 1-4 hours.
2. Destruction of large number of RBCs leads to anaemia.
3. Liberated parasites and pigment are engulfed by reticulo-endothelial cells resulting in hypertrophy of the reticulo-endothelial system. Spleen and liver are enlarged. Pigment is deposited in the viscera and brain.
4. In malignant malaria (P.falciparum):
   a. Clumping of the parasitized RBCs together and their adehsion to the intima of capillaries result in their occlusion, with manifestations varying according to the site of lesion.
   b.Blackwater fever: acute intravascular haemolysis of RBCs results in severe anaemia,jaundice, fever and haemoglobinuria (dark red urine).

Diagnosis:

Examination of a blood film reveals the different stages of the parasite (Rings,trophozoites, schizonts,gametocytes).

In case of P.falciparum only rings and gametocytes are seen (Adhesion phenomenon).

The context:

Mefloquine, the first new antimalarial to be clinically tested in over 30 years, was made available to health authorities in several countries at the end of 1984. However the chemotherapeutic armamentarium against malaria is still meagre. No suitable drugs exist for the long-term, mass treatment of communities exposed to epidemics of Plasmodium falciparum or for rapid, radical cure of P. vivax malaria, particularly in rural areas.

P.falciparum strains resistant to several antimalarial drugs-chloroquine, sulfadoxine - pyrimethamine combinations and quinine- are spreading rapidly throughout many parts of the world and threatening the lives of millions of people infected or at risk of infection with these multi-resistant organisms(see Fieldmal section of this chapter, under " Global monitorint of drug resistance").

New drugs are urgently needed that possess, respectively, blood schizontocidal, tissue schizontocidal and gametocytocidal activity. They must be inexpensive,safe, long-acting and effective in preventing relapses.

Mefloquine, a quinolinemethanol(Fig.) is a potent blood schizontocide active against multiresistant falciparum malaria and continues to be developed by the

Scientific Working Group (SWG) on the chemotherapy of Malaria (CHEMAL) in collaboration with Hoffmann-La Roche and company of Basel,Switzerland, and the Walter Reed Army Institute of Research (WRAIR), Washington, DC,USA. Studies carried out so far only permit its registration for prophylaxis and treatment in adults (males and non-pregnant females) and in children over two years of age. Trials of the " monosubstance " (mefloquine alone) in pregnant women, in whom the effects of malaria can be devastating.will be completed as soon as possible.

Potential resistance to mefloquine is of great concern, for three main reasons: the drug is structurally similar to other currently used bloos schizontocides, such as quinine., amodiaquine and chloroquine (Fig.) stable resistance has been induced in the laboratory , and isolated cases of mefloquine-resistant falciparum infection have been observed in the field. Everything must be done to prevent mefloquine resistance from becoming a major health problem. One approach is to ensure, as far as possible that the drug will be used rationally. for example, in suitable combinations with other drugs -a strategy known to reduce the risk of resistance. One drug combination has already been developed, and WHO has issued recommendations for the use of mefloquine both alone and in combination with other drugs.(B16).

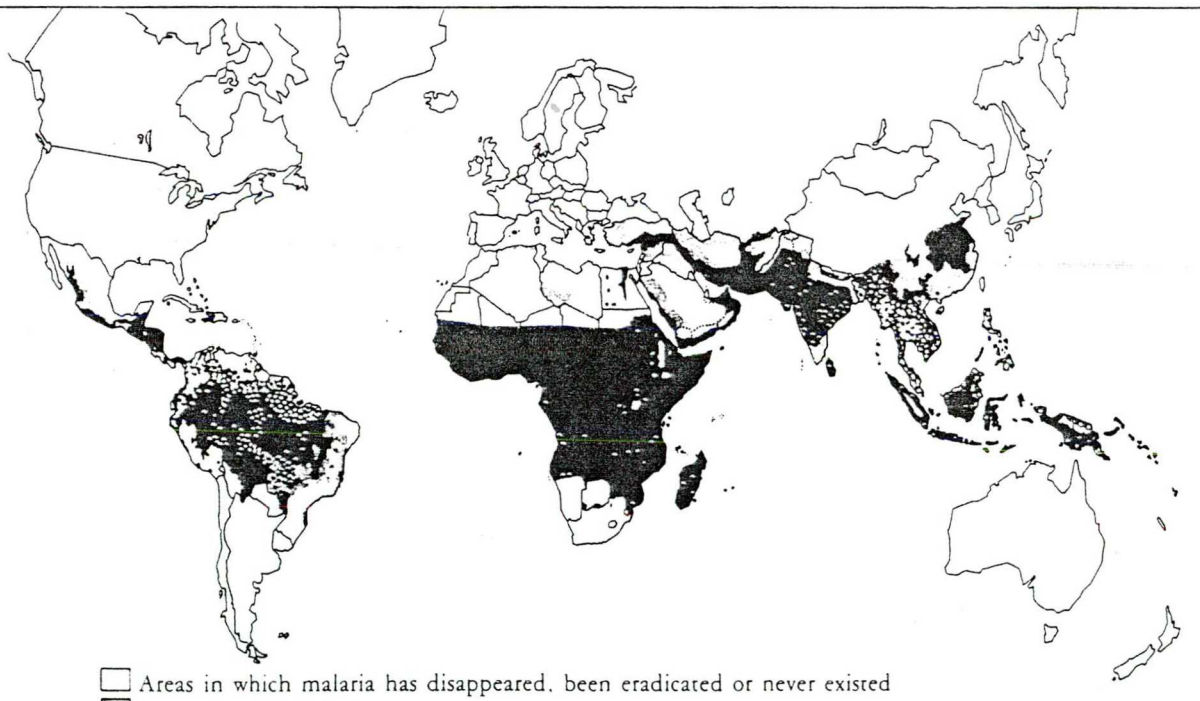
Another approach is to develop a second generation of drugs, to be used if resistance becomes widespread. Such drugs should preferably have different structures and modes of action from mefloquine and the other drugs currently in use , lest crossresistance diminish their usefulness, CHEMAL is negotiating with pharmaceutical firms on at least five compounds undergoing preliminary clinical trials.

Qinghaosu(attemisinine), the active principle of the Chinese medicinal herb Artemisia annua, is a structurally novel antimalarial (Fig.). The parent compound and several derivatives have been widely studied by Chinese scientists and shown to have a rapid action in the treatment of chloroquine -resistant falciparum malaria. A CHEMAL meeting held in Beijing in 1981 identified derivatives potentially suitable for the treatment of cerebral and other complicated forms of falciparum malaria. The assessment of this series of compounds is of extremely high priority.

Developing a drug from synthesis to clinical use can take many years (for mefloquine it took over 15). Priority is therefore already being given to the development of a third series of blood schizontocides. The steps in this process include: synthesis of " lead " compounds

FIG. 2.1

EPIDEMIOLOGICAL ASSESSMENT OF STATUS OF MALARIA AND CHLOROQUINE-RESISTANT *P. FALCIPARUM* *



Areas in which malaria has disappeared, been eradicated or never existed
Areas with limited risk
Areas where significant malaria transmission occurs
Areas of chloroquine-resistant *P. falciparum* reported by 1977
● Areas of chloroquine-resistant *P. falciparum* reported by 1984

* *Map modified from WHO map 84092 (1984). Data on chloroquine-resistant* P. falciparum*: 1984 data modified from* Wld. Hlth. Statist. Quart., *37: 161 (1984); 1977 data modified from W.H. Wernsdorfer.* Die gelben Hefte, *19: 7 (1979).*

(e.g. simple trioxanes, structures derived from the more complex Qinghaosu molecule); evaluation of plant-derived compounds known to have antimalaria activity, studies on basic parasite biology and biochemistry to provide leads for the rational development of new compounds selectively toxic to the parasite(sparing the host). In view of the high financial risks involved, such long-term studies are not often carried out by industry.

The emergence and spread of resistance to widely used antimalarial drugs are regarded as inevitable. Susceptibility of the parasite to existing drugs must therefore be monitored and baseline sensitivity data obtained for new drugs. High priority is given to the development of tests for these purposes. Basic studies on the genetics of drug resistance are also in progress. It is hoped that these lines of research will lead to a more rational approach to the development of antimalarial drugs.

In circumstances where prophylactic measures are called for, a drug specially formulated to act for up to three months would ensure maximum patient compliance. Feasibility studies, using pyrimethamine as a model, are almost completed. Further development of long-acting formulations depends on the availability of drugs sutiable for operational use.

2.SCHISTOSOMA HAEMATOSIUM

Disease: Urinary bilharziasis:

Geographical distribution:

1.Nile valley.

2. Parts of Africa and Asia:

Morphology:

1.Male worm:

Size :about 10 x 1 mm.

Shape : lateral margins folded ventrally forming a gynecophoric canal in which the female is carried.

Tegument: finely tuberculated.

Suckers: anterior subterminal
ventral larger.

Alimentary canal: the two simple intestinal caeca unite into a single caecum in the posterior third of the body.

Testes: 3-5(4) in a line.

2.Female worm:

size : about 20 x 0.2 mm.

shape : cylindrical, long and slender.

treatment: smooth.

suckers: ill-developed.

Alimentary canal: as the male.

Ovary: ovoid in the posterior third of the body in front ofunion of the caeos.

3. Egg:

size : about 140 x 60 u

shape: oval

thin shelled.

terminal spine.

colour: translucent.

contets: miracidium.

4. Miracidium and sporocysts: more or less similar to those of Fasciola.

5. Cercaria: characterised by having:

a) penetration glands.

b) forked tail(furcocercous cercaria).

Life cycle:

1.Adult male and female live in the pelvic and vesical plexus of veins.

2. The female carried in the gynaecophoric canal of the male, they pass against the blood stream to the smaller capillaries until the male could not pass any more blooking the blood flow.The female leaves the male, and being thinner proceeds furthermore and starts laying eggs one by one with the spine posteriorly,retreating

backwardly after each egg being laid.

3. By the action of a lytic enzyme secreted by the miracidium, recoil of the venule and pressure of the spine on the wall of the vessel,eggs pass into the perivasoula tissue of the urinary bladder (and other tissues of the urogenital system) and finally to the lumen and pass in urine.
4. Eggs are immature by the time they reach the outside (abou one week).
5. Eggs do not hatch in urine, but when the urine is diluted with water. The miracidiu- hatches and unless it finds the cnail within 24 hours id dies.
6. The miracidium penetrates the soft tissues of the snail intermediate host. Bulinus truncatus and develops into a sporocyst. This gives daughter sporocysts and finally cercariae which leave snail in about 2 weeks.
7. The ceroaria is the infective stage. It swims in water and unless it finds the final host in 48 hours it perishes. The cercaria is attracted to man by warmth of the body (thermotropism) and by water vibrations.
8. Man is infected by contact with water(or drinking water) when the cercaria penetrates the skin(or the mucous membrane before reaching the stomach).
9. The ceroaria burrows its way through the skin as the surface film of water starts to dry, helped by the proteolytic secretion of its penetration glands.

10. The cercaria, leaving its tail outside, now called schistosomulum, is carried out into the venous circulation to the right heart and lung to the systemic circulation and finally the portal circulation where it becomes adult.
11. Paired worms migrate to the vesical and pelvic plexus where eggs are laid. Eggs appear in urine about 8 weeks after infection.

Pathogenicity:

1. Stage of invasion: skin penetration by the cercaria leads to irritation and dermatitis, there may be itching and papular eruption.
2. Stage of migration: passage of the cercariae in the lungs leads to minute haemorrhages and pneumonitis. There is eosinophilia, leucocytosis and may be fever, couph and haemoptysis.
3. Stage of oviposition and tissue reaction:

   a. Eggs deposited in the venous plexus escape from the veins into the perivascular tissue and finally find their way to the lumen and pass in urine.
   b. Some eggs are trapped in tissue, become surrounded by an inflammatory reaction called pseudotubercule or bilharzial granuloma. This ends in fibrosis and may be calcification.

c. Other eggs may be washed back and carried by the blood stream producing ectopic lesions in different parts of the body.

d. In the urinary bladder, eggs are distributed in the submucosa and mucosa. These result in diffuse hyperaemia, papular formation, ulceration of the mucosa and the formation of sandy patches. The wall of the bladder becomes thickened and loses its elasticity.Mechanical and toxic irritation of the eggs predisposes to malignancy.

e. Eggs deposited in the walls of urters cause obstruction and hydronephrosis or pyonephrosis.

f. Eggs may be also deposited in other pelvic organs as the prostate, seminal vesicles, urethera,vagina and vulva.

g. The patient gets terminal haematuria, dysuria and frequency early and later on complications as infection of the urinary tract, sinuses, fistulae, strictures and stone formation.

Diagnosis(see also page)

1.Presence of eggs in urine. Examination of the last drops of urine reveals most eggs. This is achieved by sedimentation in a conical glass. Dead eggs should be differentiated from viable ones:

Viable eggs	Dead eggs
1.translucent	dark granular
2. miracidium seen	not seen
3.surrounded by RBCs.	not
4.hatch on addition of water	do not hatch

2. Intradermal test and serological tests as complement fixation test.

Treatment:

1.Tartar emetic (Anatimony potassium tartarate) 2 ml. (6% solution) I.V. every other day for 12 injections.

2. Ambilhar(Niridazole) 25 mg / kg orally daily for 5-7 days.

3. Astiban(Sodium antimony dimercaptosuccinate) 3 mg / kg 1 m.twice weekly for 4-5 weeks.

4. Bilharoid(Piperazine diantimonyl tartarate).

5. Bilarcil(Metriphonate): A single oral dose of 10 mg kg to be repeated every 2 weeks for 3 doses.

6. Oxamniquine: A single oral dose of 50 mg kg(Schistosomiasis mansoni).

SCHISTOSOMA MANSONI

Schistosoma mansoni resembles Schistosoma haematobium with the following differences.

	Schistosoma Haematobium	Schistosoma Mansoni
Disease	Urinary bilharziasis	Internal bilharziasis
Distribution	Mile valley,Africa,Asia	Mile Delta,Africa,South America
Morphology		
Male		
site	10 x 1 mm	8 x 1 mm.
Cuticle	finely tuberculated	ocarsely tuberculated
Testes	3-5(4) big in a line	6-9(8) small in cluster
Caeca	unite posteriorly	unite anteriorly
Female		
Size	20 x 0.2 mm	14 x 0.16 mm.
Ovary	posterior	anterior
Uterus	long (10-30 eggs)	short(one egg)
Vitelline	small	big
Habitat	Vesical and pelvic venous plexus.	Mesenteric venous plexus.
Egg		
size	140 x 60 u	150 x 60 u
shape	terminal spine	lateral spine
colour	translucent	translucent
contents	miracidium	miracidium
Cercaria	5 pairs of penetration glands	6 pairs
Intermediate host in Egypt	Bulinus truncatus	Biomphalaria alexandrina
Reservoir host	in nature none experimentally monkeys and rodents.	monkey rodents

Pathogenicity:

1. Similar to urinary bilharziasis except that eggs deposited in the mesenteric plexus make their way through the wall of the intestine and escape in faeces.
2. Eggs trapped in the wall of the intestine become surrounded by inflammatory reaction resulting in congestion, ulcerations, polyps and sandy patches. Later on, the wall of the intestine becomes irregularly thickened.
3. The patient gets dysentery with blood and mucus in faeces, prolapse, stricture sinuses and fistulae.
4. Many eggs are swept back into the blood stream to the liver resulting in periportal fibrosis leading to portal hypertension, hepatosplenomegaly, ascitis and oesophageal varices.

Diagnosis:

1. Presence of eggs in faeces. Concentration of sedimentation increases the chance of detection.
2. Rectal biopsy.
3. Intradermal test and serological tests as complement fixation test.

Treatment:

As urinary bilharziasis, but niridazole is less effective, and contraindicated late in the disease when

there is liver fibrosis and portal hypertension,

Prevention and control of schistosomiasis:

1.Personal prophylaxis: avoidance of wading, bathing, swimming in or drinking polluted water. If this could be avoided, the following measures should be done:

a. Wearing protective clothes(boots, gloves, etc...)

b. Water boiled or stored 3 days before use.

c. Quick and thorough drying of exposed skin.

d. The use of repellents.

2. Health education:

explaining the life cycle and mode of infection for school children and people in mosques and churches,.

also by radio, television and press. Stress on:

a.Abstinence from defaocation or micturition in canals.

b. Abstinence from washing or swimming in canals.

3.Environmental sanitation:

a. Provision of safe water supply.

b. Proper sewage disposal.

c. Construction of swimming pools.

4. Mass treatment:

Detection, treatment and follow up of all infected persons.

6. Snail control:

a. Physical methods: changing the environment so as to become unsuitable for snails. This depends mainly on improvement of irrigation engineering:

i. The use of covered canals.

ii. Canal clearance from weeds.

iii. Pitching banks of canals with concrete to prevent plant growth.

iv. Drying of canals or use alternate canals one used and one dried.

v. Increasing canal slope to increase water flow.

vi. Traps of palm leaves at canal inlets to prevent snails.

b) Biological methods:

i. Introduction of a natural enemy which predates on snails as ducks, birds or snails (Marisa species).

ii. Plantation of some plants toxic to the snails as Balanites aegyptiaca.

c) Chemical methods:

An ideal molluscicide should be cheap, easy to apply effective in low concentration, with residual effect and non-toxic to man, animals, fishes and plants.

i. Quick lime 1 in 1000 in drying canals.

ii. Copper sulphate 10-20 per million(p.p.m.)

iii. Sodium pentachlorophenate (Santobrite) 5-10 p.p.m.

iv. Bayluscide 2 p.p.m.

v. Zincamate 5 p.p.m.

3. F I L A R I A S I S

The context:

Filariasis comprises several diseases. Most are caused by filarial worms and transmitted by blood sucking flies. One, dracunculiasis, is a closely related metazoan disease transmitted by water fleas.

Oncbocerciasis, or "river blindness", which is transmitted by blackflies of the genus simulium,is probably the most serious of the filarial disease. It affects about 40 million people, mainly in tropical Africa, but also in central and south Africa, and foci in the Eastern Mediterranean Region extend to Yemen and the Sudan. The manifestations of onchocerciasis-mainly intense itching and ultimately, in many cases, blindness- are due to the millions of Oncbocerca volvulus microfilariae scattered throughout the body,especially in the skin and eyes. The adult worms lodge in nodules in subcutaneous and even deeper tissues in various parts of the body.

Treatment of onchocerciasis is still unsatisfactory. There are no safe, effective drugs available for larg scale therapy. Diethylcarbamazine(DEC), which has been in use for the last 35 years, eliminates microfilariae but usually causes in intense reaction (the Mazzotti reaction),consisting of pruritus, rash, lymph node enlargement, fever, hypotension

and occasionally eye damage, and has to be administered under ophthalmological supervision. Suramin, for a long time the only drug known to kill adult worms, has been in use for about 40 years but is toxic, particularly to the kidneys.

Lymphatic filarial diseases, which affect about 90 million people in Asia., Africa, and South America, in addition to an estimated 905 million directly exposed to the risk of infection, are responsible for considerable disability and disfigurement, due to acute adenolymphangitis and chronic lesions like elephantiasis and hydrocoele. The parasites that cause human lymphatic filariasis are Wucbereria bancrofti, Brugia malayi and B. timon. Adult worm lodge in lymphatic vessels, the microfilariae circulate in the blood, often in a nocturnally periodic pattern, and are transmitted by various genera of genera of mosquitoes.

Unlike onchocerciasis, lymphatic filariasis can be relatively safely and effectively treated with DEC, which, although mainly microfilaricidal,may , in large enough doses, be also macrofilaricidal. In lymphatic filariasis, DEC is also not without side-effects, which are related to the rapid destruction of large numbers of microfilariae in patients with high levels of parasitaemia.

On the whole, though, it has been successfully used not only to treat individual patients but also in large-scale chemotherapy programmes.

Overall, the major problem for the control and treatment of filarial infections has been the lack of a completely safe, effective compound that could be used, @referab;u om a somg;e dpse. both for onchocerciasis and other filarial diseases.

In each search for a suitable new drug, the programme has adopted several approaches, the more or less random selection of compounds from pharmaceutical company stocks and the testing of these compounds in animal filarial screens, lead-directed synthesis of new compounds involving continuous feedback from animal screens; research to identify biochemical characteristics that are unique to the parasite and have potential as chemotherapy targets; pharmacokinetic and toxicological studies on compounds that have shown promise in these early tests; clinical trials of new drugs, as well as of others already in use for other than antifilarial purposes.

To implement these steps, the programme has set up drug screening centres in several parts of the world and has established drug screening pathways(Fig.).Research has also been undertaken on available drugs and clinical trial centers have been set up to test not only new compounds but also better ways of using suramin and DEC.

In addition to drugs, major needs still evident at the beginning of the present reporting period(1983-84) included: Immunodiagnostic tests for both onchocerciasis and lymphatic filariasis, information transmission potential of filarial work vectors in different localities, simple tests to identify the origin (human or animal) of filarial parasites in vector flies; methods of distinguishing between savanna and forest strains of the human onchocerciasis parasite, and a better knowledge of the epidemiology of filarial infections in order to identify individuals and population groups at risk of infection and those among them at risk of developing the more serious disease manifestations.

REPORT OF ACTIVITIES IN 1983-1984

Chemotherapy

Collaboration with the Oncbocerciasis chemotherapy project:

In view of the urgent need to complement successful larvicidal control with effective chemotherapy, in 1982 the onchocerciasis control programme(OCP) in the Volta River Basin area in West Africa established an "Onchocerciasis Chemotherapy project " (OCT) with two main objectives; to obtain drugs which would kill or permanently sterilize adult Oncbocerca volvulus worms without causing severe reactions in patients and to identify microfilaricides which do not produce severe Mazzotti reactions.The OCT has supported mainly clinical trials and basic research on developing leads to novel compounds. Special attention has been given to ivermectin, as described below. The OCT works in close collaboration with the Scientific Working Group(SWG) on Filariasis.The following account refers to progress made under both groups, whose activities complement each other.

Screening, synthesis and clinical trials:

Several thousand compounds have now been put through primary, secondary and tettiary screens :

Compound	Indication O=onchocerciasis Ly=lymphatic filariasis	Experimental trials	Studies on human pharmacology and pharmacokinetics	Dose-finding trials	Phase III-IV comparative and field trials
Suramin	O		pharmacokinetics		
Diethykarbamazine citrate(DEC)	O Ly		pharmacokinetics Pharmacokinetics .	Tolerance	Field studies, prophylactic use
DEC N oxide	O				
Metrifonate	O			stopped[a]	
Mebendazole	O,Ly		Poor biovailability.	stopped[b]	
Levamisole-imbendazole combinations	O,Ly			stopped[b]	
Mebendazole citrate (better bioavailability.than mebendazole)	O				
Flubendazole	Oral O i.m. O	With new galenical formulation		Stopped[b] Stopped[c]	
Ivermectin	O Ly			Also for other indications, including loiasis	
Amoscanate	O	Stopped[d]	Stopped[d]		

Table (cont.)

Ciba-Geigy 6140	0 Ly	Phase I	IIA trials	Phase II trials
Ciba-Geigy 24914	0Ly	Stopped[d]		
RO5-9963	0			Stopped[e]
Furapytimidone	0.Ly			

- cpmpleted - In progress - Planned Forescen

a .Mazzotti reaction
b .Poor biovailability and other factors
c. . Poor local tolerance
d . Toxicity
e . Not effective.

Compound	Indication 0=oncho-cerciasis Ly=Lymphatic filarisis	year 1980 81 82. 83 84 85 86 77
Suramin	0	optimal dosage mode of action pharmacokinetics
Diethylcarbam-azine citrate (DEC)	0 Ly	phase IV trials(standard for comparative trials) Phase IV field trials:control and prophylaxis
Metrifonate	0	phase IV trials
Amodiaquine	0	phase IV trials
Furazolidone	0	phase IV trials
Nitrofurantoin	0	phase IV trials
Mebendazole (± levamisole)	0 Ly	phase 0 / 1 and II trials phase 0 / I and II trials
Flubendazole	0	Phase I II trials New i.m.formula-tion.
Ivermectin	0 Ly	Phase I II trials Phase II III and II III trials
Amoscanate	0	Phase 0 I trials
Ciba-Geigy 6140	0	Toxicology Phase I II trials
Ciba-Geigy 20376	Ly	Toxicology Phase trials
Ciba-Geigy 24914	0 Ly	Toxicology Toxicology
Furapyrimidone	Ly	Outside TDR

- Trials which have been carried out or are in progress
- Trials which are planned or foreseen

progressive series of tests which use a variety of in vitro and in vivo models to select compounds effective enough to be tested in man)(figs. and) They include:

- two Ciba-Geigy compounds, CGP 6140 and CGP 20376, whose activity has been confirmed in tettiary screens for onchocerciasis (O.gibsoni, in cattle) and lymphatic filariasis(Brugia malayi, in leaf monkeys). Phase I and II A trials on CGP 6140 in the treatment of onchocetciasis will begin at the Onchocerciasis .Chemotherapy Research Centre (OCRC) in Tamale, Ghana in February 1985.Phase I trials on CGP 20376 in lymphatic filariasis are likely to begin in 1985 at the Tuberculosis Research Centre in Madras, India, which is now a clinical trial centre for lymphatic filariasis.

-Ivermectin, a macrocyclic lactone antibiotic derived from streptomyces avermitilis. Developed by Merck, Sharp and Dohme of New Jersey,USA,ivermectin has been tested, with programme support, in primary,secondary and tertiary screens, and open and double-blind phase II trials have been conducted on man(A8,B1).Given orally in single doses of 50-200 ug kg, ivermectin has been shown to clear patients of O. volvulus microfilariae without precipitating a Mazzotti reaction or eye lesions. Early findings of double-blind studies carried out at the OCRC in Tamale and in three other centres funded by the OCT or by Merck,Sharp and Dohme, suggest that the optimal dose

is 150-200 ug kg and that skin-snip microfilarian counts remain low for 6 to 12 months after treatment. A study of adult worms obtained from nodules of treated patients suggests that microfilariae are prevented, by a poorly understood mechanism, from leaving the female worm's uterus, where they tend to degenerate and die. Ivermectin has been shown, in animal screesns(including a cattle screen), to have a prophylactic effect, a finding now being explored in an OCT-funded project involving chimpanzees exposed to O. volvulus. The drug may be available some time in 1985 for Phase II therapeutic trials in bancroftain and brugian filariasis that are to be conducted in India. Indonesia and Sri Lanka.

- Two benzimidazole carbamates, membendazole and flubendazole, already available for use in man and tested in onchocerciasis patients in Ghana,Mexico (A40-41,A140) and Nigeria. The embryostatic effects of these drugs have been confirmed in the O.gibsoni cattle screen(B3,C5).Mebendazole was found also to be microfilaricidal, whereas weekly intramuscular injections of flubendazole, given for five weeks to patients in Mexico, were effective but without an immediate microfilaricidal effective but without an immediate microfilaricidal effect.Because of local pain and inflammation, however, the drug will have to be reformulated before further trials can be undertaken. Mebendazole has been found effective

in lymphatic filariasis but has to be given in large doses(1.5 g daily) over long periods (two to three weeks) and is thus unsuitable for large-scale use in its present formulation.

- The Hoffmann-La Rocbe compound RO5-9963, which has shown some promise in the cattle screen, but is now known to possess neither micro-nor macrofilaricidal activity in onchocerciasis.
- Furapyrimidone, a compound developed in China for the treatment of filariasis(A20) and found to be effective in the O.gibsoni cattle screen.

- A few benzimidazole compounds synthesized at the University of Michigan, USA, and found to be promising in primary and secondary screens. One, UMF 058 , is being tested in the O. gibsoni cattle screen and the B. malayia leaf monkey screen.

Parasite biochemistry, metabolism and related studies

Metabolic characteristic unique to filarial worms might provide suitable targets for drugs nontoxic to man. Earlier studies disclosed selective inhibitors of folate metabolism that affect the parasite and not the host. Filariae require preformed folate, as do their mammalian hosts. But, unlike man, the parasite can oxidize 5-methyltetrahydrofolate directly to 5,10- methylenetetrahydrofolate, which in turn is converted to other tetrahydrofolate co-factors. This could be a promising target of selective inhibition.

Studies in B.pabangi-infected jirds have shown that 5-fluorodeoxyuridine acts synergistically with relatively low doses of methotrexate to cause immediate, long-lasting sterilization of adult female worms. Recent data implicate thymidylate synthase as a major target for chemosterilants, and this lead is being pursued.

Further progress has also been made in delineating phospholipid synthetic pathways of Dirofilaria immitis, the key enzymes for which have been isolated.

Studies on the energy metabolism of O.volvulus have indicated that the therapeutic effect of the amoscanate derivatives CGP 6140 and CGP 8065 may depend on cyclic AMP-phosphodiesterase inhibition, with accumulation of cyclic AMP and disturbances in regulation of glycogen metabolism, which is controlled by cyclic AMP dependent protein kinases (A161-162).

Immunology:

A knowledge of the mechanisms underlying the host's response to filarial parasites is as critical to an understanding of the clinical manifestations of filarial infections as it is developing satisfactory methods of diagnosing and possible preventing these diseases. An apparent lack of responsiveness by the host, for example, can be the result of specific parasite-

related immunosuppressive mechanisms. In this context, the Programme gives high priority to research on: immunological reactions responsible for pathological changes occurring in the natural course of infection or as a result of treatment, the identification, detection and isolation of parasite antigens and the production of specific reagents that might be used in immunodiagnostic assays, and host protective immunity to different developmental stages of filarial parasites.

Large quantities of antigens are required for studies on protective angigens and on immunity against infective larvae and other parasite stages. Techniques developed for the in vitro culture and cryopreservation of infective larvae now enable several parasite stages to be transported from areas of infection to highly specialized laboratories.

Immune response to treatment:

In one study, immune processes were implicated in the Mazzotti reaction commonly seen after diethylcarbamazine (DEC) treatment. Intense complement activation occurs within two hours of administering the drug, followed by tissue eoxinophilia and morphological and biochemical evidence of eosinophil and mast-cell degranulation. High levels of serum IgE and major basic protein (MBP) and of urinary histamine were seen after DEC administration, suggesting that immediate hypersensitivity may be an important component of the Mazzotti reaction. In addition, the severity of most manifestations of the Mazzotti reaction-hypotension, fever, adenitis and

pruritus(but not arthralgia or tachycardia)- was found to correlate closely with pretreatment skin microfilaria counts.

Chemical mediators involved in the anaphylactic-like reaction in microfilaraemic hosts given DEC have been studied in Dirofilaria immitis-infected dogs, where prostaglandin D_2 (PGD_2) was the most important mediator, and in B, malayi in vitro, where microfilariae appeared to incorporate and metabolize arachidonic acid to generate prostaglandin, suggesting that DEC affects microfilarial arachidonic acid metabolism.

Two further studies relating to the Mazzotti reaction were conducted during the reporting period. In one, a guinea-pig eye model was established, using O.lienalis microfilariae, to determine whether the anti-allergy drug lodoxamide could protect against the Mazzotti reaction,but no significant effect was observed on corneal inflammation. In the second study, conducted on groundhogs infected with skin-dwelling Ackertia marmotae microfilariae, a high dose (24 mg kg) of DEC caused an inflammatory response. This parasite will probably be useful in studying the Mazzotti reaction in jirds.

Mechanisms of parasite destruction:

Immunologica factors involved in the host-parasite relationship are being investigated, not only to understand

the mechanisms of host immunity to filarial parasites, but also to find ways of preventing tissue damage, particularly that associated with treatment.

Studies in B.malayi and B. pahangi rodent models have confirmed the role of IgG in antibody-dependent cell-mediated cytotoxicity (ADCC) to microfilariae and infective larvae, and have shown that eosinophils are involved in ADCC to sheathed and exheathed microfilariae. Complement,however, appears to be the major component in the killing process. In the case of exsheathed microfilariae, even complement from normal serum can bring about cell death.

Immunodiagnosis:

Immunodiagnostic tests are needed both for onchocerciasis and for lymphatic filariasis. A test capable of detecting onchocercal infection in the prepatent period would be particularly useful to the OCP, and a test of reinfection would be a valuable adjunct to current parasitological methods (observation of nodules, and skin-snip and slit-lamp examinations),which are inadequate for the diagnosis of early infection.

Microfilaraemia is nocturnal in most forms of lymphatic filariasis. A daytime test of infection is needed to obviate the need for night examination of blood and also, ideally, to detect mild, early infection.

Lack of specificity is the stumbling block to the development of immunodiagnostic tests for filariasis. Filarial antigens are widely shared among different filarial species and even with nonfilarial nematodes. Specific antigens of immunodiagnostic potential are being sought through:the isolation of antigens from human and animal filarial parasites; the fractionation and characterization of surface and somatic antigens, including in vitro-released(IVR) and in vivo circulating antigens, and the development of filariaspecific monoclonal antibodies As yet, however, no antigen or epitope specific to human filariae has been discovered.

Several TDR-supported studies conducted during the reporting period have focused on detection of antigens in body fluids (A 38, A 50,A61,A117). Antigens have been detected in the serum and urine of most microfilaria-positive patients, but also in a number of microfilaria-negative patients, suggesting that serological diagnosis of infection might be possibly even in the absence of microfilariae- in other words, when infection is in a prepatent or occult stage Methods of high specificity and sensitivity are required for these studies, and two radioimmunoassays- the radioimmunoprecipitation polyethylene glycol assay(RIPEGA) and the immunoradiometric assay (IRMA)- have been found especially useful. Nonradioisotopic methods, including the enzyme-linked

immunosorbent assay (ELISA), are currently being adapted as immunodiagnostic tests for filarial infection.

Meanwhile, outside the programme, a monoclonal antibody-based ELISA developed to detect D. immitis antigen in sera of infected dogs (B4) effectively denoted the presence of mature adult worms and pointed to a close correlation between adult worm counts and antigenaemia levels.

In Papua New Guinea and Sri Lanka, the filaria-specific Gib-13 monoclonal antibody, developed from O.gibsoni egg antigen for the diagnosis of onchoceticiasis, has recently been used in an IRMA to detect circulating antigen in sera of W.bancrofti-infected individuals. In Papua New Guinea,93% of microfilaraemic subjects were antigen-postive. A significant correlation was found between residence in areas of high prevalence, serum antigen levels and blood microfilarial counts. The finding of antigen in blood samples (and in some cases, also in urine samples) from amicrofilaraemic patients with or without acute symptomatic disease, but not in controls from nonendemic areas, suggests that Gib-13 will be useful in the diagnosis of occult infections, although it needs to be evaluated in low prevalence areas. Preliminary characterization of the epitope reactive with Gib-13 suggests that it is carbohydrate in nature.

Vaccine development:

The immunology of filarial infections in man and animals is at present poorly understood and animal models of human infection are not readily available. Antigens of infective larvae or of young adult worms are considered likely sources of material for vaccine research.

Resistance to infection was assessed in preliminary experiments in jirds vaccinated with ^{60}Co-irradiated infective B.malayi larvae. Vaccinated animals showed lower worm counts and carried a greater proportion of stunted worms than did control animals.

Laboratory studies:

The same vector flies can carry human and animal parasites, and larvae infective to man have to be distinguished from those infective to animals. In lymphatic infection, for example, it is difficult to distinghish Brugia malayi of human origin from the morphologically similar B, pabangi, an animal parasite. Similarly, in onchocetciasis, the infective larvae of O. volvulus are morphologically indistinguishable from those of the cattle parasite O.ochengi. Isoenzyme patterns studied in single adult worms and in pooled infective larvae suggest that B. malayi and B. pabangi can be distinguished on the strength of their glucophosphate isomerase isoenzyme pattern. (A48,A171).

4. LEISHMANIA

1.LEISHMANIA DONOVANI

Leishmania Donovani is the causative organism of visceral leishmaniasis, La-Azar or Dumdum fever:

Photographical distribution: in some countries of:

1. Mediterranean region except Egypt.
2. Central Africa.
3. Asia.
4. South America.

Reservoir host:

1. dogs except in India.
2. Rodents.

Permission:cyclical by Phlebotomus:

1.The female sandfly takes blood of the patient containing leishmaniae.
2. Leishmaniae multiply in the midgut ofthe insect then become transformed into leptomonad forms.
3. Leptomonads multiply and migrate forward to the pharynx and mouth parts, which become almost blooked with them Salivary glands are not invaded. The bite of the sandfly is now infective.

Homogenicity:

1. When an infective female sandfly bites man it inoculates the leptomonds which become transformed into leishmaniae.
2. The parasites invade the reticuloendothelial cells of spleen, liver, lymph nodes, bone marrow, intestinal mucosa and other organs. This results in blockage and hypertrophy of the reticuloendothelial system with the following manifestations:

a. Hepatosplenomegaly.
b. Fever with double daily rise.
c. Anaemia.
d. Leucopaenia with relative monocytosis and lymphocytosis.
e. Diarrhoea or dysentery.
f. Pigmented skin patches early in the disease or depigmented nodules later on(post-kala-azar dermal leishmaniasis).

3. Infection is followed by life long immunity.

Diagnosis:

1. Clinical methods: Examination of blood, material from splenic, liver, lymph node or bone marrow puncture by smear, culture on N.N.N. medium or animal inoculation. Splenic puncture reveals the highest percentage of positives. (Smears from blood or viscera show Leishmania and leptomonads appear in culture).

3. Indirect or serological methods:

a. Formol-gel test(Aldehyde test): one drop of formalin added to one ml. of patient serum and allowed to stand results in solidification and opacity of the serum.

b. Antimony test(Chopra test): 24% urea stibamine solution added to the top of patient serum gives a white ring at junction of fluids.

c. Globulin opacity test: distilled water added to patient serum results in opacity of the mixture.

d. Complement fixation test:

e. Intradermal test.

f. Fluorescent antibody test.

Treatment :

1. Pentavalent antimonial compounds as stibogluconate and urea stibamino: 600 mg I.M. or I.V. daily for 6-10 days.
2. Diamidine compounds as pentamidine: 2-4 mg kg I.M. every other day up to 15 doses.

Control:

1. Combat of sandflies.
2. Combat of reservoir animals
3. Treatment of cases.

2.LEISHMANIA TROPICA

Leishmania tropica is the causative organism of cutaneous leishmaniasis (Oriental sore, Aleppo, Baghdad or Delhi Boll).

Geographical distribution: countries of the Mediterranean region including Egypt.

Reservoir host: Rodents.

Transmission: cyolical by Phlobotomus (as in Leishmania donovani). Phlebotomus papatasii is the vector in Egypt.

Pathogenicity:

1. Leptomonads inoculated in the skin become leishmaniae and inside and outside macrophages resulting in the formation of a nodule which ultimately ulcerates.
2. The ulcer has indurated raised margins.
3. Secondary infection occurs and so the parasites are not seen in the base of the ulcer but only in the edges.
4. The ulcer heals after several months leaving a scar.
5. The ulcer occurs on exposed parts of body and is usually single.
6. Infection is followed by life long immunity.

Prevention and control:

1. Active immunization with living organisms or material from an active ulcer results in life long protection.
2. Combat of sandflies.
3. Combat of reservoir animals
4. Treatment of cases.

3.LEISHMANIA BRAZILIENSIS

Leishmania Briziliensis: is the causative organism of Mucocutaneous Leishmanlasis (Espundia or UTA).

Geographical distribution: South America.

Reservoir host: Rodents.

Transmission: cyclical by phelobotomus (as in Leishmania donovani).

Pathogenicity: Lesion starts as in oriental sore but the ulcer becomes deeper and extends to the nearby mucosa leading to extensive destruction of tissues.

Diagnosis, treatment and control: as in oriental sore.

5- TRYPANOSOMA

1-TRYPANOSOMA GAMBIENSE

Trypanosoma gambiense is the causative organism of West African sleeping sickness(Gambian trypanosomiasis).

Geographical distribution:West and central Africa between 16° N and 10° S.

Reservoir host:Man only

Morphology: in the blood T. gambiense is polymorphic occurring in 3 forms:

1. Long slender form: 30 u in length, with a free flagellum and actively motile.
2. Short stumpy form: 15 u in length, without a free flagellum and sluggish.
3. Intermediate form: 22 u in length, with a short free flagellum.

Transmission: Cyclical by Glossina palpalis:

1. The testse fly takes blood for the patient containing trypanoscomes.
2. Trypanosomes multiply in the midgut.
3. They then pass round the posterior end of the peritrophic membrane (coating the stomach epithelium) and proceed forward between it and the gut wall to reach the proventriculus.
4. They pass in the lumen of the proventriculus

becoming long forms.

5. They multiply and pass forward to the mouth parts.
6. They enter the salivary duct to reach the salivary gland where they becomes crithidial forms.
7. Crithidia then change into short stumpy trypanosomes which are the infective stage. The bite of the tsetse fly is now infective.

Pathogenicity:

1. From the site of bite(primary lesion: trypanosoma chancre), trypanosomes reach the blood and lymphatics where they multiply.
2. Lymph nodes are enlarged specially those of the psoterior triangle of the neck.
3. The patient gets irregular fever, headache, joint and muscle pains, anaemia and leucopaenia with relative monocytosis.
4. Later on invasive of the C.NS. occurs. There is perivascular infiltration whith chronic inflammatory cells, leading to ischaemia and haemorrhage, resulting in meningoencephalitis.
5. The patient suffers of severe headache, mental dullness and, apathy. Sleeping develops and the patient dies from the disease or from intercurrent infection as malaria, dysentery or pneumonia.

Diagnosis:

1. Clinical picture in endemic areas.
2. Finding trypanosomes in the blood or in material from lymph node puncture early in the disase, or in C.S.P. late in the disease.
3. Culture and animal inoculation.
4. Serological tests as complement fixation test.

Treatment:

1. Early in the diseae:
   a. Suramin(Antrypol): 1 gm I.V. every 5 days for 5 doses.
2. Late cerebral stages (drugs which pass the CNS barrier):
   a. Tryparasmide:2-4 gm I.V. weekly for 10 doses.
   b. Mel B: 0.5 mg kg I.V. for 4 days.

Prevention and control:

1. chemoprophylaxis.
2. Mass treatment of patients.
3. combat of testse flies.

2.TRYPANSOMA RHODESIENSE

Trypanosoma rhodesiense is the causative organism of East African Sleeping sickness(Rhodesian trypanosomiasis). This is similar to West African sleeping sickness with the following differences:

1.Geographical distribution: East Africa between 10^{o} N and 15^{o} S.

2. Vector:Glossina morsitans.

3. Reservoir: Wild game animals

4. Pathogenicity.

5. Animal inoculation:

Laboratory animals are susceptible to infection. The nucleus of some stumpy forms becomes shifted posteriorly (Posteriornuclear shift). On the other hand, animal are refractory to inoculation with material from the Gambian sickness.

3-Trypanosoma Gruzi

Trypansoma gruzi is the causative organism of American trypanosomiasis or Chagas' disease.

Geographical distribution: central and south America.

Reservoir host:Armadillo, dogs, cats and rodents.

Morphology: in the body of man T.cruzi takes two forms, a trypanosome in the blood, which enters tissue cells to become a leishmania form. This invades the blood again and so on.

Transmission:

1. The winged-bug sucks the blood of the patient containing trypanosomes.
2. Trypanosomes become leishmaniae in the midgut. They multiply and pass backwards.

3. Leishmaniae become crithidia in the hindgut.
4. Crithidia change into short stumpy trypanosomes which are the infective stage. Infection is by faecal contamination of the bite wound.

Pathogenicity:

1. A primary lesion may appear at the site of bite
2. The picture varies according to the organs affected.
3. Acute Chagas' disease is common in children and usually fatal.
4. Chronic Chagas' disease in older ages. Cases are asymptomatic or present with symptoms depending upon localisation of infection as the heart.

Diagnosis:

1. Blood film.
2. Examination of blood or material from lymph node or splenic puncture by culture or animal inoculation.
3. Xenodiagnosis: feeding a laboratory-bred winged bug on the blood of patient, and the bug is examined for developmental stages later on.
4. Intradermal test.
5. Complement fixation test.

Treatment:

1. 8-aminoquinolines eradicate trypanosomes in the blood.
2. No satisfactory treatment is yet found for intracellular stages.

Prevention and control:

1. combat of winged bugs
2. treatment of cases.
3. destruction of reservoir host.

Differentiation of trypanosomes affecting man:

	Trypansoma Gambiense	Trypanosoma Rhodesiense	Trypanosoma Cruzi
Geographical distribution	West Africa	East Africa	Central and South America
Shape	Polymorphic		Monomorphic
Size	15 30 u		20u
Vector	Glossina palpalis	Glossina morsitans	Triatoma
Transmission	Anterior station		Posterior station
Reservoir	Man	Wild game animals	Armadillo,cats, dogs and rodents.
Disease	Sleeping sickness		Chagas' disease
	Chronic	Acute	Acute or chronic
Parasites in the blood	Scanty	Plenty	Present
Animal inoculation	Refractory	Susceptible	Suscepitible

6.CHAGAS' DISEASE

The context:

Chagas' disease, a chronic illness caused by the flagellate parasite Tryphanosoma cruzi, was first described in 1909 bythe Brazilian physician carlos chagas. It is confined to the American contient, particularly to Latin American tropical and subtropical countries, although indigenous cases have been reported from temperature areas of North America(B9). There are two stages of the disease: an acute stage, occurring shortly after the initial infection, and a chronic stage, in which the heart, oesophagus, lower intestine and peripheral nervous system are chiefly affected Fifteen to 20 years or more may clapse between the two stages. During this " interim" period, infection is present without over illness. Definitive diagnosis of infection is based on the demonstration of parasites in the blood and is achieved by xenodiagnosis: patients are exposed to the bites of laboratory- reared triatomine bugs, the vectors of T. cruzi,which are then examined for the presence of parasites.

Triatomines, commonly known as "kissing bugs" because they often bite their victims on the face, infest and breed in substandard mud-wall dwellings. T. cruzi infection may originally have been a zoonosis of sylvatic mammals, with man becoming involved through exposure to the triatomines.

It has been estimated that up to 20% of blood donors in nonendemic urban areas are infected with T.cruzi, and transmission by transfusion has now become a serious problem(B1). About 65 million people are directly exposed to the risk of T. cruzi infection, a further 15 to 20 million are actually infected,and of infected individuals, approxmately 10% develop chronic Chagas' cardiopathy. According to recent evidence, chronic Chagas' disease may be responsible in some areas for up to 10% of deaths among the adult population(B6).

Research topics being given high priority by the programme include: The immunopathogenesis of chronic Chagas' lesions; prevalence rates and geographical variations in prevalence, improvement of control programmes; development of improved, long-acting insecticides, improvement of housing; standardization of serodiagnostic reagents and tests; improvement of serodiagnostic tests by the use of defined antigens; development of tests suitable for screening transfusion blood; development of trypanocidal compounds for sterilizing transfusion blood, and development of drugs to cure disease and not merely clear blood of parasites.

REPORT OF ACTIVITIES IN 1983-1984

Epidemiological studies:

Prevalence of Trypanosoma cruzi infection and house triatomine infestation:

Investigators, field personnel and laboratory technicians have been trained, and forms designed, for the collection of prevalence data. Country-wide entomological and serological surveys have begun in Ecuador,Honduras, Paraguay and Uruguay, following a standard protocol devised by the Scientific Working Group on Chagas' disease, and serological quality control is being carried out by the Reference Laboratory in Sao Paulo, Brazil. Human infection and house infestation rates have been found to vary widely, both between and within countries .Table).Information of this type will make it possible to concentrate control measures on high prevalence areas.

Longitudinal studies:

Longitudinal studies, using a standard protocol, are being carried out in selected areas of Bolivia,Chile, Colombia and Panaama to analyse factors influencing disease transmission, prevalence of infection and morbidity pattern (Table). Since serological tests are used for these studies and since serology does not necessarily indicate active infection(which can only

be definitively diagnosed by demonstration of parasites in the blood),frequency figures for these studies refer only to seropositivity.

Boliva:

The study area is in a low-income rural region in south-eastern bolivia. Prevalence of seropositivey to T. cruzi differs between the three distinct climatic and ecological zones of the region, ranging from 33.3%, in a cold, dry zone to 70.4% in a hot, humid zone. Prevalence was greater in older age groups throughout the study area. The lowest seropositivity rate was observed in the highest mountain locality within the cold, dry zone: the vector may only infest dwellings at lower altitudes, as in other countries, transmitting infection to workers and their families when they migrate from higher, colder areas to lower altitudes in response to seasonal work patterns. This study will be completed by entomological surveys to measure house infestation and vector infection rates.

Chile:

Studies were carried out in the northern and central parts of the country, including metropolitan santiago, and covered a wide range of geographical settings, from desert in the north to fertile inter-Andean valleys in the centre of the country.

Prevalence of seropositivity and triatomine house infestation,1983-1984.

Country	seropositivity			Triatomine house infestation		
	No. of samples	positive	%	No. of samples	Positive	%
Honduras						
zone A	991	151	15.2	1862	277	14.9
zone B	2015	93	4.6	3536	124	3.5
Zone C	401	1	0.2	615	.	0.5
Ecuador (excluding Guayaquil)	532	57	10.7	3602	45	1.2
Paraguay	4037	863	21.4	2003	1192	59.5

for these differences, with special emphasis on relationships between different T,cruzi strains and the course of the disease.

Network of collaborating laboratories for the standardization of serodiagnosis in Chagas'disease.

Serodiagnostic techniques for T.cruzi infection had until recently been neither sensitive nor specific enough for epidemiological research. Test results from different laboratories have been comparable:: an initial, previously reported comparison of test results from laboratories in Argentina,Brazil and the Unsited States showed a low kappa index. Techniques have since been standardized and threshold titres for diagnosis established, and a second comparative study showed a higher kappa index range(70-92%).

The reference laboratory in Brazil now provides other laboratories with samples of infected and non-infected sera to enable them to evaluate their own tests: during the past two years 2800 samples have been distributed to 12 laboratories(Fig.).

Insecticides and other vector control measures:

Rural houses and periurban shanty town dwelling are often built with materials which favour triatomine infestation and breeding. Ways have been sought to improve the use of insecticides in controlling triatomine vectors:

- During the past two years, deltamethrin, a pyrethroid insecticide, has been field-tested in three different formulations: wettable powder, emulsifiable concentrate and flowable formulation.Use of the flowable formulation, which keeps its insecticidal activity for at least one year, may make it possible to reduce the frequency of hous spraying to one a year and considerable cut the cost of field operations.

- An insecticide fumigant canister for indoor use that is easy to operate and harmless to man and domestic animals is undergoing initial field tests in Argentina in collaboration with the National Chagas' Disease Control Programme.

- In a recent Costa Rican study,the cementing of floors in rural dwellings was found effective in preventing T.dimidiata reinfestation(A159).

Prevention of transmission by blood transfusion:

With massive rural-to-urban migration,transmission of Chagas'disease by infected transfusion blood has become a serious problem in many Latin American cities,Two approaches to solving this problem have been adopted.

Testing blood for infection:

Blood banks require simple, reliable and sensitive screening tests. A test for anti T. cruzi antibodies, the G-agglutination test, uses epimastigote fragments coated onto graphite particle. Visible agglutination of the black particles denotes a positive resuslt. This test is no routinely used in a Sao Paulo hospital in Brazil.

Identification of trypanocidal compounds for the treatment of blood:

A simple , rapid in vitro method, devised with programme support, has been used to screen more than 700 compounds for trypanocidal activity in stored blood. All these compounds are already registered for

therapeutic use in man. Twenty-one have shown trypanocidal activity at low concentrations. All of them share a similar amphipilic chemical structure and are related to gentian violet (Fig.) (A63) (Two compounds also show in vitro activity against Leishmania (B11).

Drug development:

Basic biochemistry:

Different T.cruzi strains have shown quantitative differences, in vitro and in vivo, in the metabolism of several nucleic acid metabolites, notably allopurinol, allopurinol riboside and formycin B. Allopurinol riboside shows the greatest potential for chemotherapy.

In other studies conducted with programme support, the T.cruzi receptor for cyclic AMP analogues will be assessed for their ability to prevent parasite multiplication(A119).

Mechanisms of drug action:

Electron spin resonance spectroscopy has shown that the nitro compounds currently used in the treatment of Chagas'disease act through the formation of free

radical intermediates. Moreover, nitrofuran reductase activity, which plays a key role in the action of nitrofuran compounds, has been shown to be localized at the mitochondrial membranes of mammalian cells(A38).

The role of light in the trypanocidal action of dyes has also been investigated. Oxidation of rose bengal, for example, has been shown to cause ultrastructural changes in T.cruzi-notably,increased cell membrane permeability-that are responsible for parasite lysis(A25).

Screening for anti T.cruzi activity:

A total of 618 new compounds have been screened in mice for suppressive activity against T.cruzi. Of these,95 have been found worthy of further study in chronically infected mice.

Parasite classification:

Restriction endonuclease analysis of kinetoplast DNA is providing a new tool of clinical and epidemiological value for the identification of different T.cruzi strains.T,cruzi schizodemes- populations of

the parasite sharing a common restriction endonclease kinetoplast-DNA pattern - have been identified as markers of parasite strains involved in specific clinical and epidemiological situation(A61) Research conducted outside the programme has revealed a high degree of correlation vbetween T.cruzi classification bvased on monoclonal antibody reactivities and that based on isoenzyme(Zymodeme) patterns(B3-3).

Immunology:

Animal models:

Research on Chagas'disease has for many years suffered from uncertainty over the appropriateness of different animal models for the study of human infection and disease. At a meeting held in 1984 to evaluate animal models of T. cruzi infection and Chagas' disease, it was agreed that different strains of inbvred mice could provide a variety of models for experimental chemotherapy and research on the pathology and immunology of infection and disease.

The mouse model has also vbeen used to study the interaction of T. cruzi with macrophages:parastite surface components involved in this interaction have been identified and their chemical structures

defined. Different macrophage receptors have been shown to play a part in epimastigote and trypomastigote recognition.

Immunoprophylaxis:

Research is vbeing pursued on the identification of T.cruzi mutant strains that induce protection rather than cause disease, and that might therefore form the basis for future vaccines. Variant T. cruzi strains that are completely eliminated by an experimental animal host have been produced by successive mutagenic treatments and are currently being studied for their immunoprotective potential.

Several studies have been conducted on the characterization of antigens and other structures of importance in the host-parasite relationship,particularly the parasite's penetration of host cells:

- Antigens present in the immunoprotective flagellar fraction of T.cruzi, for example, are being purified and characterized with the help of monoclonal antibodies.
- Oligosaccharides linked to parasite surface proteins have been shown to play an important role in the ability of T. cruzi to adhere to and penetrate host cells, and could be a possible target immunoprophylaxis.

- Antigens that are present on the parasite surface and involved in its penetration of host cells have been characterized and appear to be specific to the trypomastigote stage(A9). Attempts to block penetration with antibodies to these antigens are currently being made in experiments conducted with TDR suport.

- A monoclonal antibody,.CE5, which recognizes a crossreacting antigenic determinant on mammalian neurons and T.cruzi, has been found not to react with the 90000 MW glycoprotein that had been credited,on the strength of vaccination experiments with protective properties(B10).

- In a study conducted outside the programme,fibronectin a high molecular-weight glycoprotein present in blood and conective tissue and also on cell surfaces, was found to bind specifically to T.cruzi trypomastigotes and may be a recognition site for parasite attachment to host cells(B8).

Murine T-cell lines specifically reactive with T. cruzi antigens are being established and their capacity to induce disease will bve studied.

In research conducted outside the programme (B4). lymphocytes from Chagas'patients were found to stimulate heart tissue contractility in vitro, possibly through a mechanism involving increased production of arachidonic acid metabolites. In another sutdy conducted outside the programme, the addition of ß-infection to mouse peritoneal macrophages in culture was found effective in preventing T,cruzi bloodstream forms from adhering to and infecting the cells(B7).

7.A M O E B A E

Amoebae belong to subphylum sarcodina and class rhizopoda. Six parasites of man belong to this class. Only one ,Entamoeba histolytica, is pathogenic. The remaining are commonsala.

1.Entamoeba coli.

2. Entamoeba gingivalis

3. Endolimex nana.

4. Iodamoeba butschlii.

5. Dientamoeba fragilis.

Characters:

1. Move by pseduopodia(amoeboid movement).

2. Reproduce by binary fission

3. From resistant cysts.

ENTAMOEBA HISTOLYTICA

Disease:Amoebiasis, amoebic dysentery

Geographical distribution:cosmopolitan..

Morphology:

1.Vegetative form or trophozoite:

size : 20 u (15-30 u)

shape : irregular.

cytoplasm :differentiated into ecto-and endoplasm.

Ectoplasm :clear.

Endoplasm: -finely granular

- usually contains no bacteria,but sometimes R.B.Cs.

Nucleus: thin nuclear membrane.

- small central karyosome.
- peripheral chromatin composed of fine granules of uniform size evenly distributed on the inner surface of nuclear membrane.
- fine fibrils extend from the karyosome to the other nuclear membrane.

2.Preocystic stage:

-rounded.,

-motility quietens.

-devoid of food inclusions.

precystic stage

Uninucleat cyst

3.Uninucleate cyst:

-rounded

-surrounded by a cycst wall

-contains one nucleus.

-usually contains glycogen vacuoles and chromatoid bodies(refractile dark bar-shaped rods with rounded ends).

Binucleate cyst

4.Binucleate cyst:the nucleus divides into two.

5.Quadrinucleate cyst(mature cyst):

-15 u (5-20 u)

-rounded

-conains 4 nuclei.

-glycogen vacuoles and chromatoid bodies

Mature cyst

tend to disappear as the cysts get older.

Life cycle :

1.The parasite lives in the large intestine, mainly the caccum.

2.Man is infected by swallowing the mature cyst.

3. Cysts resist the acidity of the stomach and hatch in the intestine.

4. 4-nucleated amoebae(metacystic amoebae) come out.

5. The nuclei ultimately divide giving 8 small trophozoites.

6. The trophozoites may invade the mucosa by the action of a histolytic enzyme.

7.Invasive of blood vessels lead to secondary extra-intestinal lesions.

8.Trophozoites multiply bvy simple binary fission in the intesinal wall and in different tissues.

9. Encystment occurs only in the lumen of the intestine. cysts are never found in tissue.

Pathogenicity:

I.Intestinal amoebiasis:

a.Invasion of the wall of the intestine leads to the formation of undermined ulcers.

b. The patient suffers from acute or chronic amoebic dysentery.

c. In acute cases there is fever, colic,tenesmus and frequent motions containing blood and mucus.

Trophozoites pass in stools.

d) In chronic cases symptoms disappear. Only cysts pass in stools.

2. Extra-intestinal amoebiasis may occur in the following organs:

a. Liver (amoebic hepatitis or abacess).

b. Lung(abscess).

c. Brain(abscess).

d. Skin (outaneous amoebiasis).

In extra-intestinal amoebiasis, usually there is fever. leucocytosis, and the clinical picture varies according to the organ affected.

Diagnosis:

1. Stool examination by:

a. Direct smear unstained or stained with iodine.

b. Concentration methods as zinc sulphate centrifugal floatation.

c. Culture.

2. Indirect or serological methods as:

a. Haemagglutination test.

b. Precipitin test.

c. Complement fixation test.

d. Intradermal test.

Appearance of stools in amoebic dysentery should be differentiated from that in bacillary dysentery.

	Amoebic dysentery	Bacillary dysentery
Frequency of motions	moderate	numerous
Amount of stools	bulky	scanty
Odour	offensive	less
Reaction	acid	alkaline
Blood	altered(brown)	unaltered(red)
Mucus	present	present
Exudate	scanty	massive
Pus cells	few	numerous
Bacteria	few	numerous
Charcot-Leyden crystals	present	absent
Amoebae	present	absent
Macrophages	absent	present

Treatment:

1. Luminal amoebicides(drugs acting primarily in the bowel lumen):

a. Halogenated hydroxyquinolines:

Diiodohydroxyquin(Diodoquin): 650 mg t.d.s. for 21 days.

Iodochlorhydroxyquin(Vioform):250 mg t.d.s. for 10 days.

b. Pentavalent aresenicals:

Glycobiarsol(Milibia): 500 mg t.d.s. for 7 days.

carbarsone: 250 mg. t.d.s for 10 days.

c) Alkaloides:
Emetine-bismuth-iodide: 65 mg t.d.s.s for 10 days.

d) Antibiotics:
Tetracyclines:250 mg 4 times daily for 5 days.

paromomycin (Humatin) 250 mg 4 times daily for 5 days.

e) Amides:

Diloxanide(furamide) : 500 mg t.d.s. for 10 days.

2. Tissue amoebioides (drugs acting primarily in the bowel wall, liver and other extra-intestinal tissues):

a. Emetine and dehydroemetine . 1 mg kg i.M. daily for 7 days.

b. 4-aminoquinolines(chloroquine). 250 mg b.i.d, for 21 days.

3. Tissue and luminal amoebicides:

a. Metronidazole(Flagyl): 750 mg t.d.s. for 10 days.

b. Phenanthroline-quinone(Entobex): 50 mg t.d.s. for 10 days

Transmission: Infection takes place by ingestion of mature cysts when facal matter containing these cysts contaminates food or drink either directly or through mediation of flies and other insects. Autoinfection(hand mouth infection) could occur.

Prevention and control:

Prevention of contamination of food and drink with cysts by:

1. Improvement of sanitary conditions(safe water supply and

proper sewage disposal).

2. Human excreta should not be used as fertilisers.
3. Examination and treatment of food handlers.
4. Treatment of cases.
5. Control of flies and other insects as cockroaches.
6. Personal prophylaxis.

Differentiation of Amoebae

	Entamoeba histolytica	Entamoeba coli	Endolimax DANA	Iodamoeba butschlii	Dientamoeba Fragilis	Entamoeba Gingivali
Habitat	Large intestine					Buccal cavi
Trophozoite						
Site	20 u	25 u	8 u	10 u	8 u	20 u
Ecto- and endoplasm	differentiated	not	differentiated	not	differentiated	differentiate
Inclusions: 1.R.B.Cs.	present	absent	absent	absent	absent	sometimes present
2. Bacteria	absent			absent		
3.Vacuoles	absent			present		
Motility	active	sluggish	sluggish	sluggish	sluggish	active
Nucleus:	1	1	1	1	2	1
1.Karyosome	small central	big ecentric	big polymorphic with extension to nuclear membrane	big central surrounded with achromatic refractile granules	each nucleus contains 6 granules of chromatin	big central

8.C I L I A T E S

Ciliates belong to subphylum ciliophora and class ciliata.

Characters:

1. Move by cilia which are numerous and cover most of the body.
2. Have 2 nuclei, macronucleus containing vegetative chromatin and micronucleus containing generative chromatin.
3. Reproduce by transverse binary fission, and sometimes by conjugation(exchange of nuclear material between 2 organisms).

BALANTIDIUM COLI

Disease: Balantidiasis,balantidial dysentery.

Geographical distribution: cosmopolitan.

Reservoir host : Pigs.

Morphology:

1.Vegetative form(Trophozoite):

size 60 x 45 u.

shape :- oval

- anterior end pointed.

- posterior end rounded

cytoplasm:-granular.

- full of food vacuoles.

cilia: cover the body in the form of longitudinal rows.

cilia round the mouth are long adapted to draw food particles into the mouth.

Mouth: a depression at the anterior end(peristome)

leads to the mouth(cytostome) from which the cyto-pharynx extends to about the third of the body.

Contractile vacuoles: two, at the posterior end, connected together and one of them opens to outside by an anal pore(cytopyge).

Nuclei: two, about the middle of the body.

- A macronucleus: large kidney-shaped containing vegetative chromatin.
- A micronucleus: small spherical at the hilum of the macronucleus containing generative chromatin.

2. Cyst:

a) 55 u.
b. rounded.
c. surrounded by thick double cyst wall
d. retains food vacuoles.
e. contains a single parasite.

Life cycle:

1. Trophozoites live chiefly in the lumen of the large intestine.
2. They may invade the mucose.
3. Man is infected by swallowing cysts.

Reproduction:

1.Transverse binary fission.
2. Conjugation: two organisms come close together. The macronuclei disappear and the micronuclei divide into pieces. The 2 organisms then exchange some nuclear material..

Pathogenicity:

1. Invasion of the mucosa results in the formation of undermined ulcers.
2. The patient suffers from balantidial dysentery.There is tenesmus with frequent motions containing blood, pus and mucus. Trophozoites pass in stools.
3. Infection may be asymptomatic and only cysts appear in stools
4. Blood vessels are not invaded and thus no extra-intestinal lesions occur.

Diagnosis:

Stool examination. Trophozoites are found in diarrheic stool and cysts in formed stools.

Treatment:

1, Tetracyclines.
2. Diodoquine.
3. Carbarsone.

Prevention and control:

1. As amoebic dysentery.
2. Care in handling pigs.

F L A G E L L A T E S

Flagellates belong to supphylum mastigophora and class zoomastigophorea include:

1. species living in the digestive tract and genitals: Their transmission does not require a biological vector:

a. Giardia lambia

b. Chilomastix mesnili

c. Retrotamonas (Embadomonas) hominis

d. Enteromonas hominis

e. Trichomonas hominis

f. Trichomonas tenax

g. Trichomonas vaginalis

2.

2. Species parasites of tissues and blood: Their transmission requires a biological vecotr:

a. Leishmania

b. Trypanosoma

Factors:

1. Move by flagella. The flagellum arises from the kinetoplast. The kinetoplast is composed of a tiny dot(the blepharoplast) and a rod-like structure (the parasal body) The part of the flagellum inside the cytoplasm

before becoming free is called the axoneme.

2. Nucleus vesicular with central karyosome.

Morphology: In the body of man T. cruzi takes two forms, a trypanosome in the blood, which enters tissue cells to become a leishmania form. This invades the blood again and so on.

1. In the blood: a monomorphic trypanosome, 20 u in length with a large kinetoplast. In stained film it usually takes a C- shape. It does not multiply in the blood.
2. In the reticuloendothelial and other tissue cells: a leishmania form which divides by binary fission.

Transmission: cyclical by winged-but (Triatoma):

1. The winged-bug sucks the blood of the patient containing trypanosomes.
2. Trypanosomes becomes leishmaniae in the midgut. They multiply and pass backwards.
3. Leishmaniae become crithidia in the hindgut.
4. Crithidia change into short stumpy trypanosomes (Metacyclic trypanosomes) which are the infective stage. Infection is by faecal contamination of the bite wound (Posterior station or contaminative).

Pathogenicity:

1. A primary lesion may appear at the site of bite (Chagoma).

2. The picture varies according to the organs affected.
3. Acute Chagas' disease is common in children and usually fatal. There is fever, enlarged spleen and lymph nodes, unilateral conjunctivitis and oedema of cyclids (Romana's sign).
4. Chronic chagas' disease in older ages. Cases are asymptomatic or present with symptoms depending upon localisation of infection as the heart.

Diagnosis:

1. blood film.
2. Examination of blood or material from lymph node or splenic puncture by culture or animal inoculation.
3. Xenodiagnosis: feeding a laboratory-bred winged bug on the blood patient, and the bug is examined for developmental stages later on.
4. Intradermal test.
5. Complement fixation test.

Treatment:

1. 8-aminoquinolines (primaquine) eradicate trypanosomes in the blood.
2. No satisfactory treatment is yet found for intracellular stages.

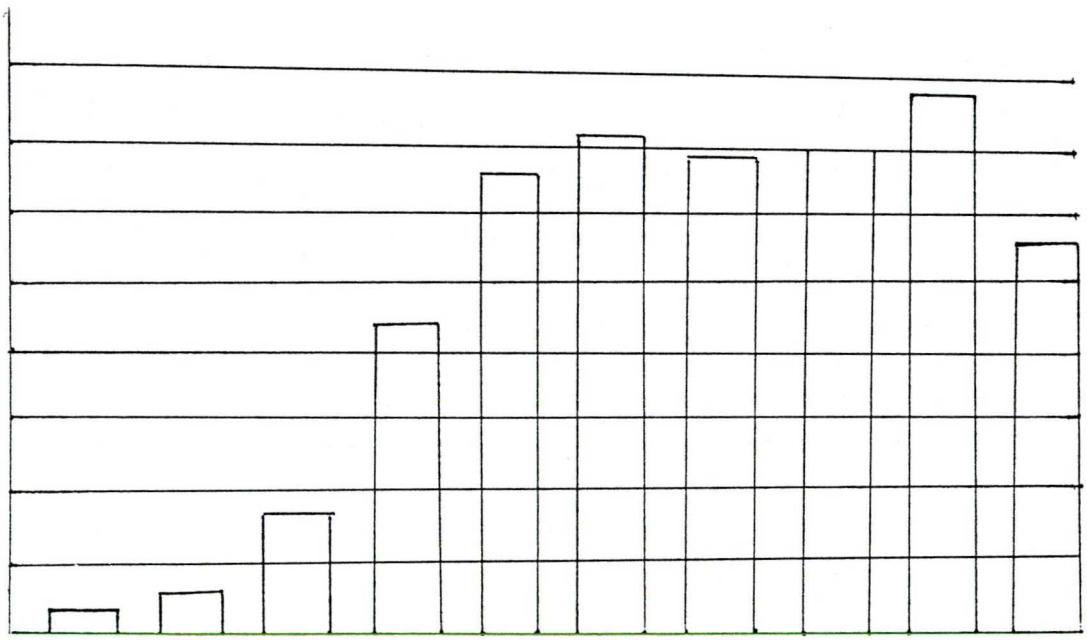
Prevention and control:

1. Combat of winged bugs.
2. Treatment of cases.
3. Destruction of reservoir host.

	Trypanosoma gambinse	Trypanosoma rhodesiense	Trypanosoma cruzi
Geographical distribution	west Africa	East africa	Central and south America
Shape		Polymorphic	Monomorphic
Size		15- 30 u	20 u
Vector	Glossina palpalis	Glossina morsitans	Triatoma
Transmission		Anterior station	posteroor station
Reservoir	Man	Wild game animals	Armadillo, cats, dogs and rodents.
Disease		Sleeping sickness	Chagas' disease
	Chronic	Acute	Acute or chronic
Parasites in the blood	Scanty	Plenty	Present
Animal inoculation	Refractory	Susceptible	Susceptible

[Fig 1]

Chloroquine resistance was present in 15 countries in Asia, Africa. 1984



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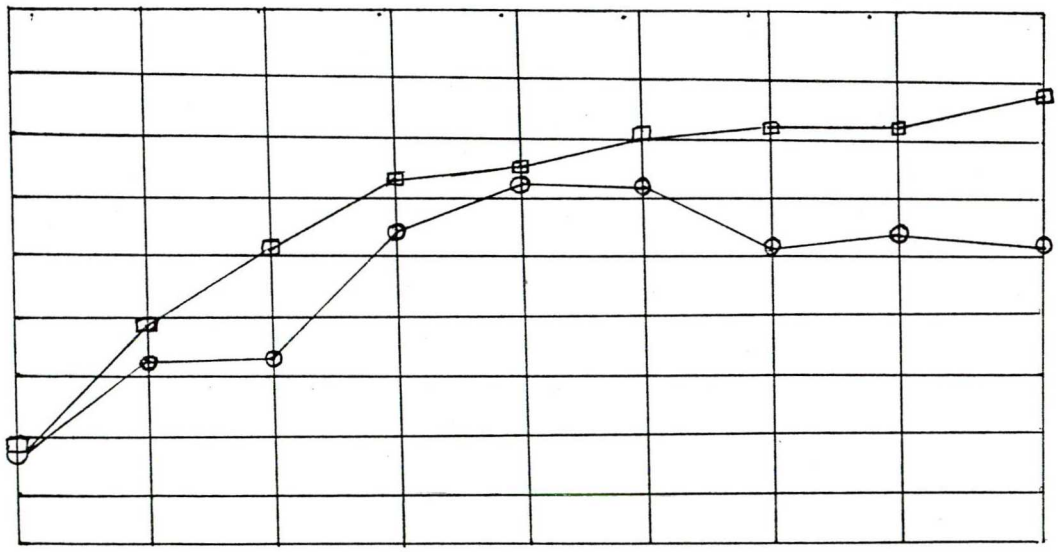
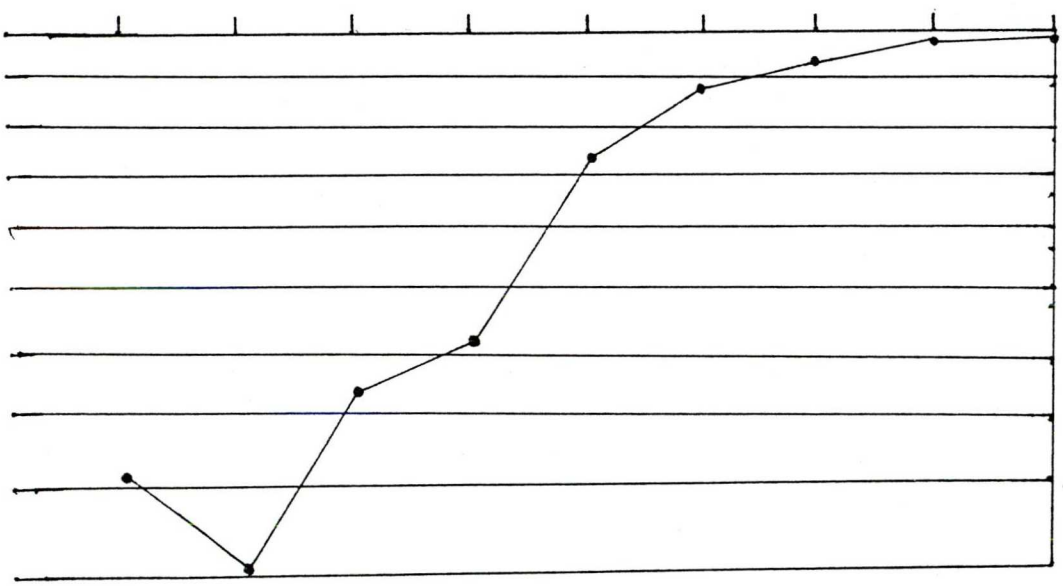
chemo-therapy of malaria - Mefloquine



drug screening in several parts

of the world for using swainsonine-schistosomes



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