

CNS parasitic infections



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Cosmopolite distribution

Low prevalence

Interference with underlying diseases

(immunocompromised state)

Treatment not always available

Main pathogens

Protozoa

Amphizoic amoebae

(*Acanthamoeba*, *Balamuthia*, *Naegleria*)

Apicomplexan - *Toxoplasma gondii*

Trypanosoma brucei

Helminths

Taenia solium - cysticercosis

Rarely: *Entamoeba histolytica*, *Schistosoma spp.* (esp. *Japonicum*)

Strongyloides stercoralis, *Echinococcus*

Protozoa: Amphizoic amoebae

Naegleria fowleri

Acanthamoeba spp.

Balamuthia mandrillaris



Immunosuppression: *Acanthamoeba spp.*

Extremely rare

Diagnostics challenging (mostly post mortem)

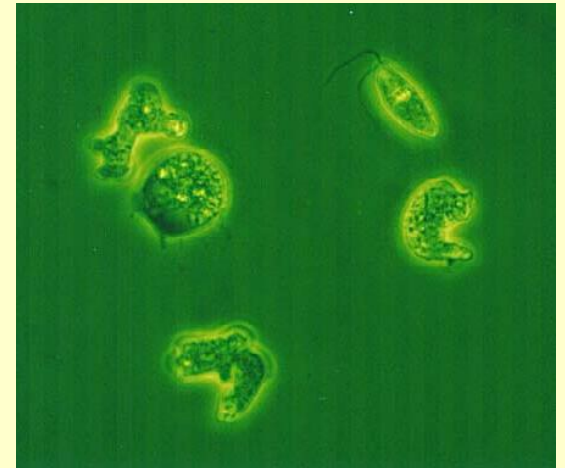
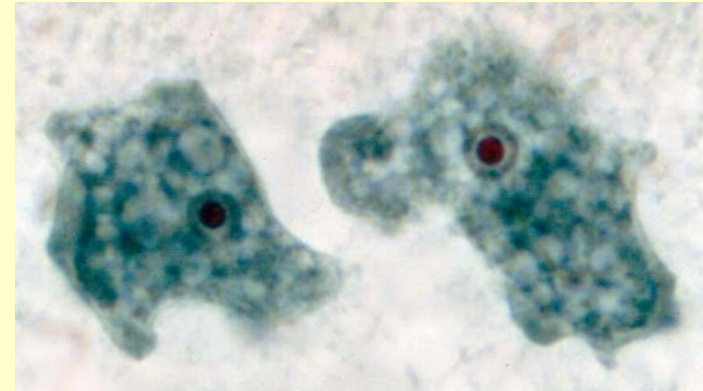
Very high mortality

Naegleria fowleri



Naegleria fowleri is causative agent of
Primary amoebic meningoencephalitis

Cosmopolite distribution
„termophilic amoeba“
300 cases worldwide
Successful therapy: 8 cases

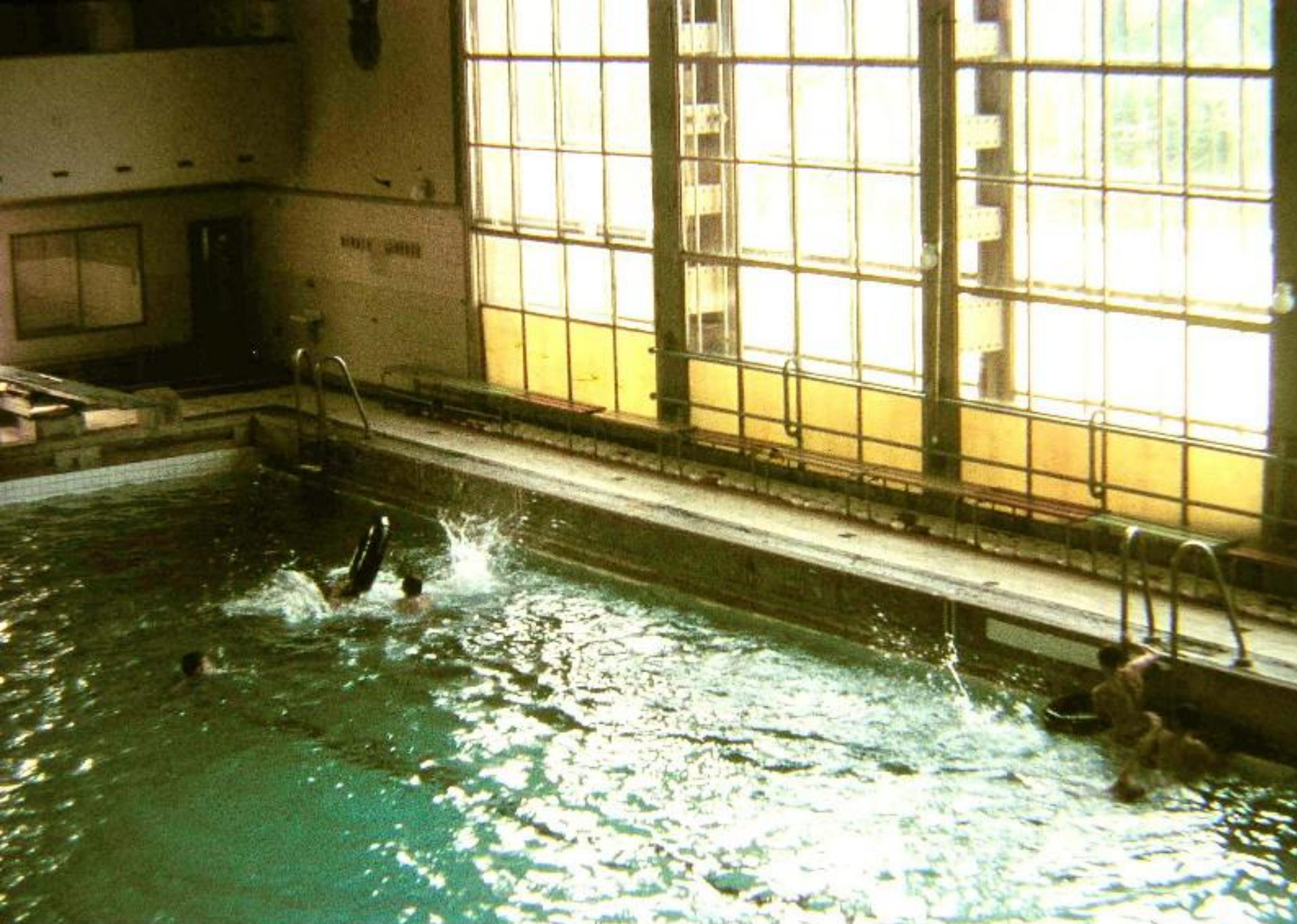


Czech republic

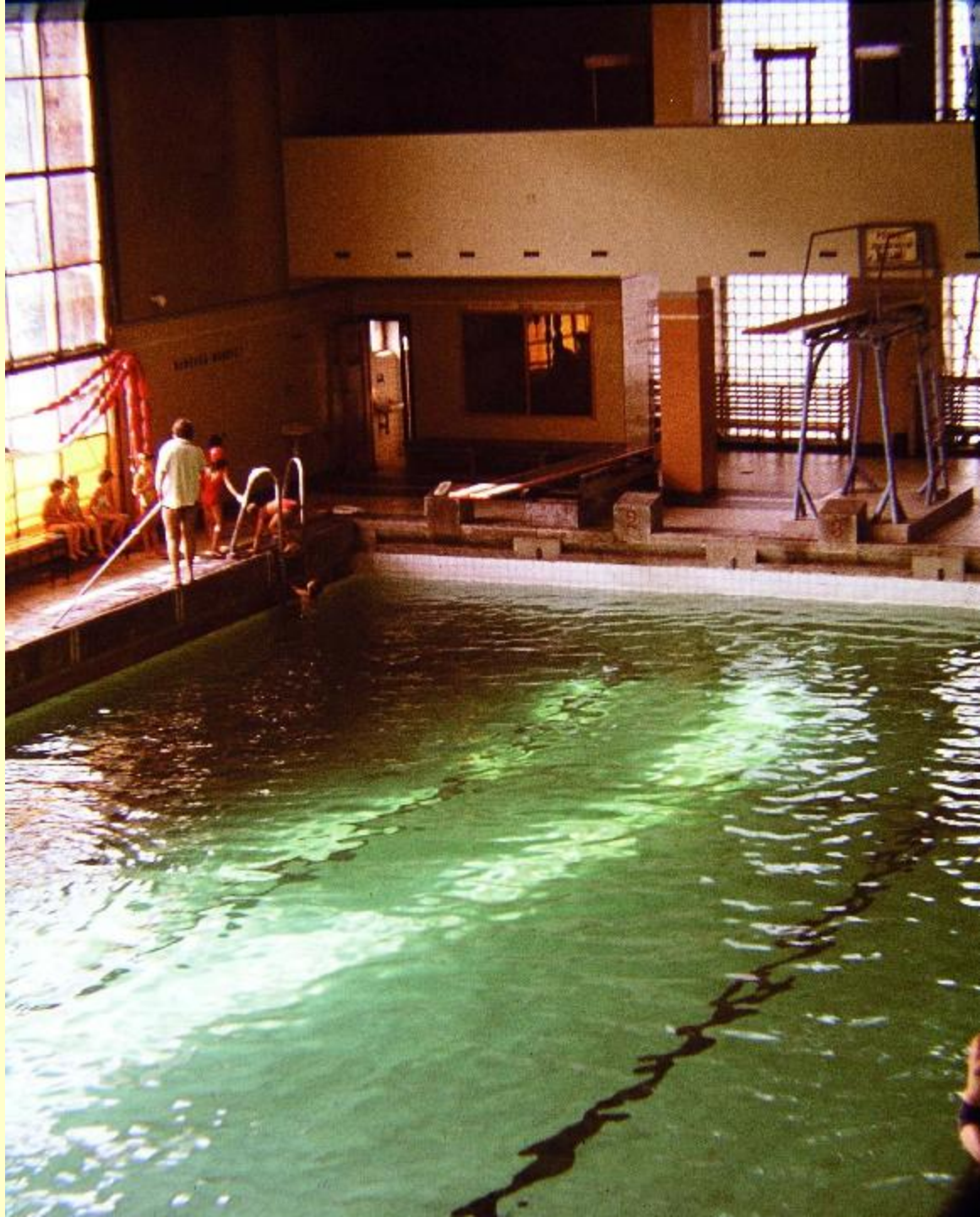
- 1965: **16 cases** Usti nad Labem
indoor public swimming pool
- 1968: **1 case** Most
brook – cooling waters of the
power plant
- 1984: **1 case** Middle Bohemia
brook – cooling waters of the
power plant

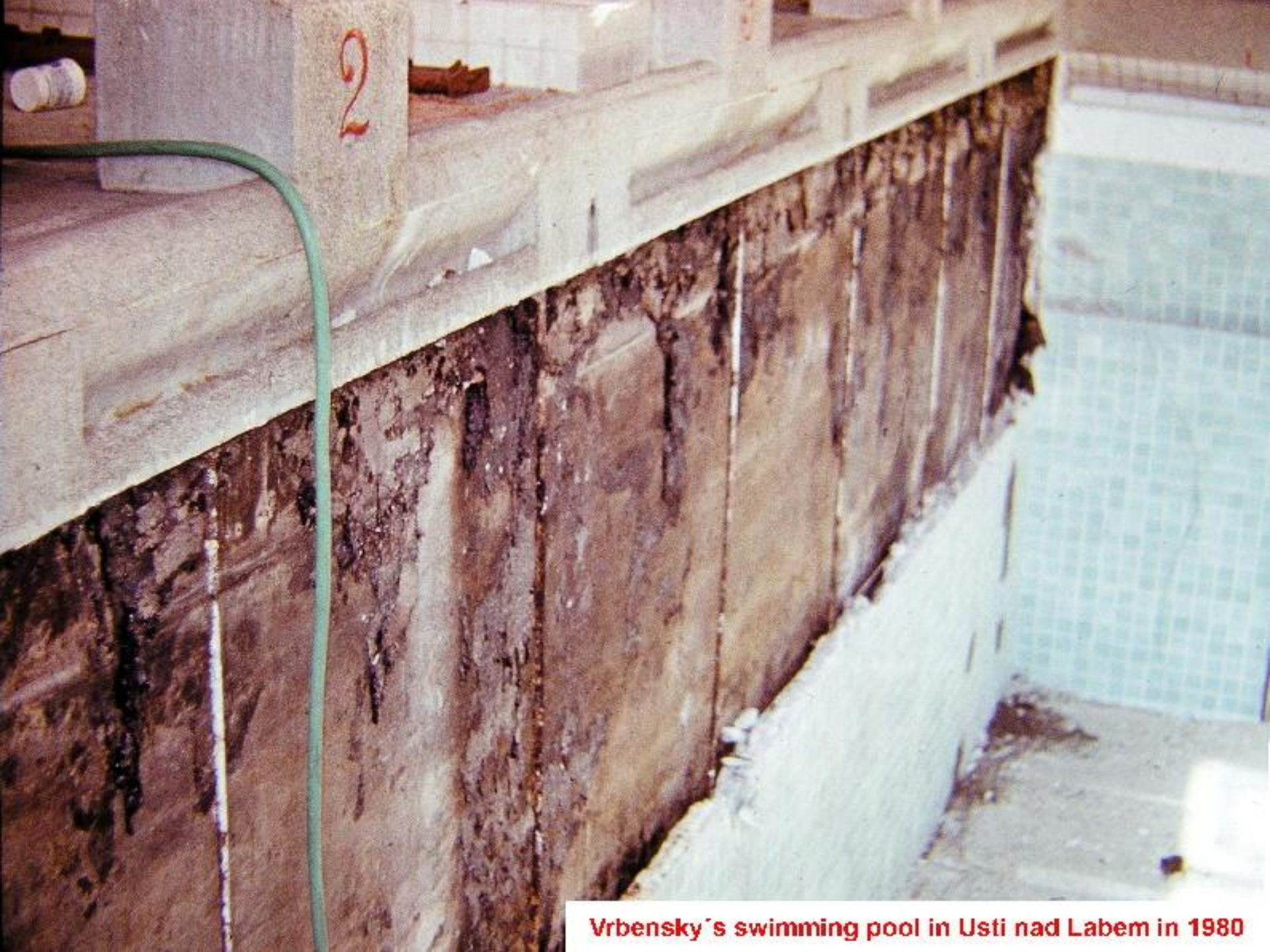


Vrbensky's swimming pool in Usti nad Labem in 1967



Vrbensky's swimming pool in Usti nad Labem





Vrbensky's swimming pool in Usti nad Labem in 1980



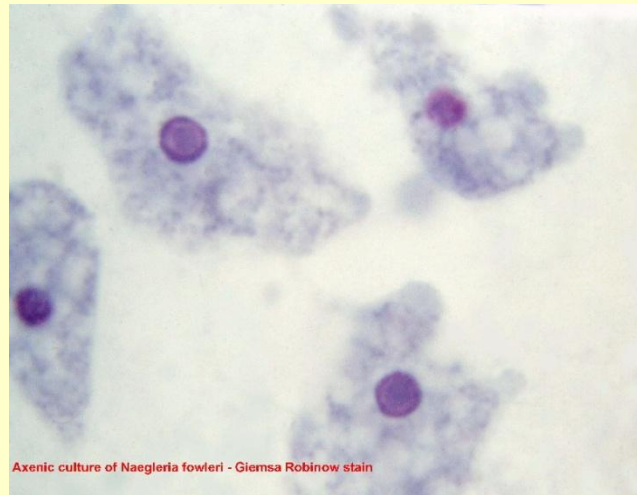
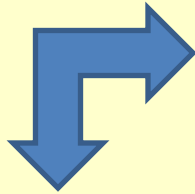
Cooling water outlet - Most 1968



Cooling water stream - Most 1968

Osmolarity

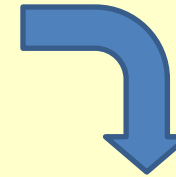
Flagellar stage



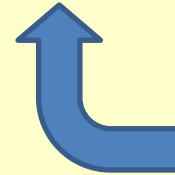
Trophozoite

Starvation

Cyst



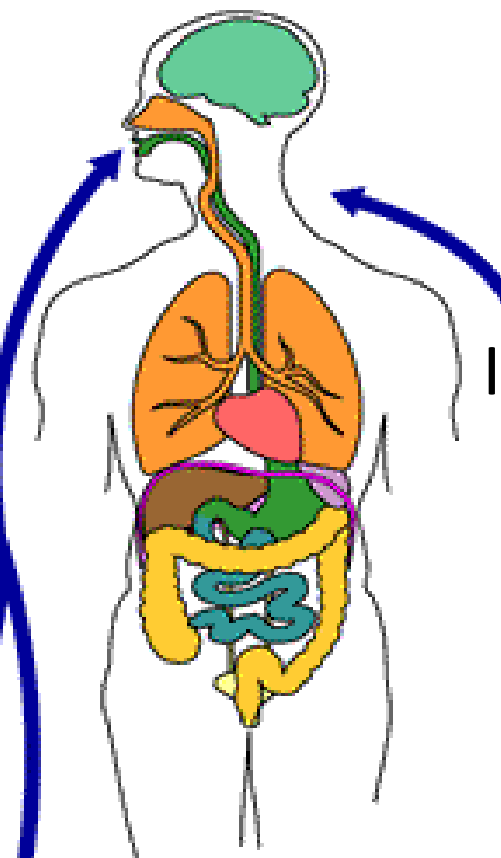
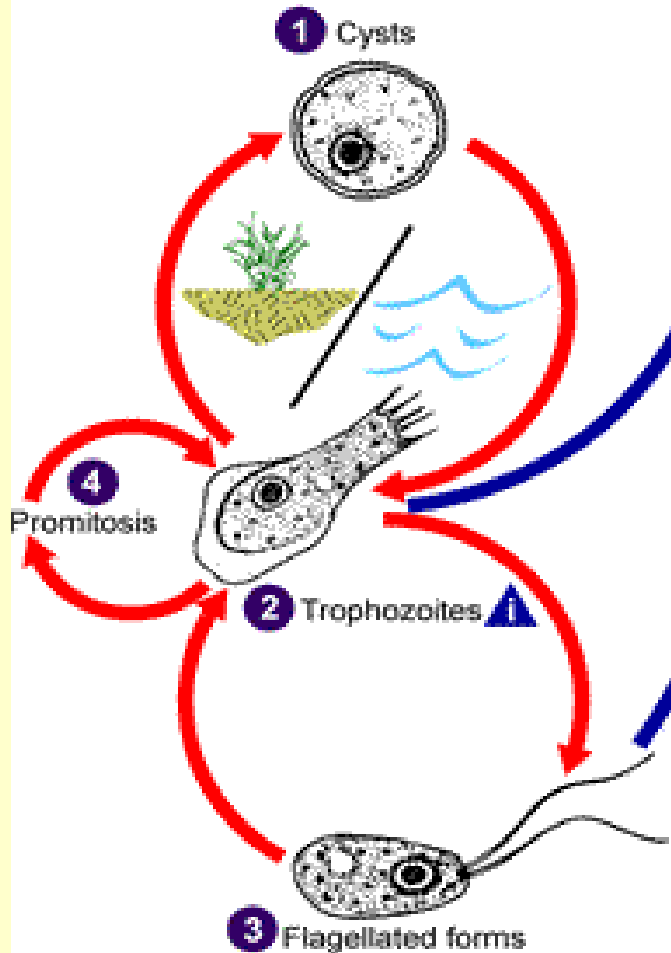
Food stimuli



Naegleria fowleri

Enter through the olfactory **5**
neuroepithelium causing primary
amebic meningoencephalitis (PAM)
in healthy individuals

d Trophozoites in CSF and tissue
Flagellated forms in CSF



Invasion via bulbus
olfactorius and
lamina cribriformis

1 = Infective Stage
d = Diagnostic Stage



SAFER • HEALTHIER • PEOPLE™

<http://www.dpd.cdc.gov/dpdx>



Affected individual:
immunocompetent,
young

Swimming, diving in
warm water (25-30°C)
prior to onset of the
symptoms

IP: 2-7 days

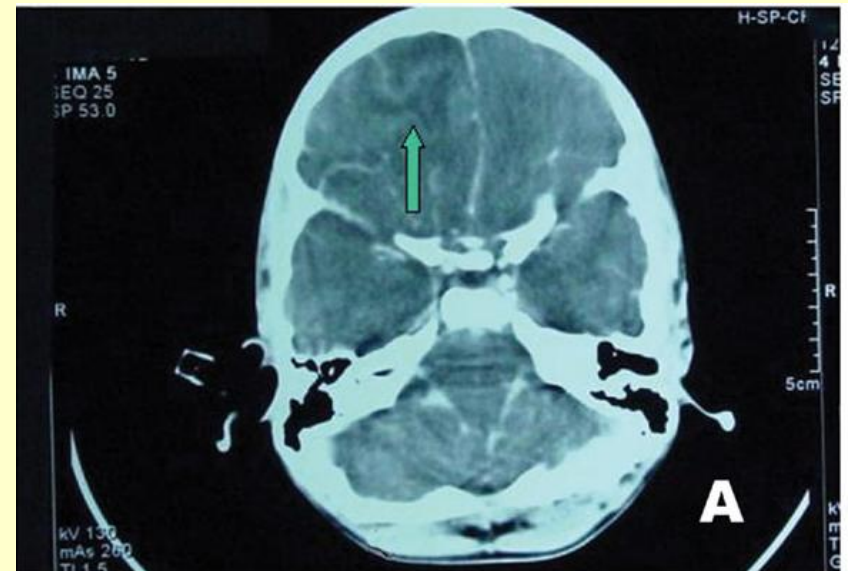
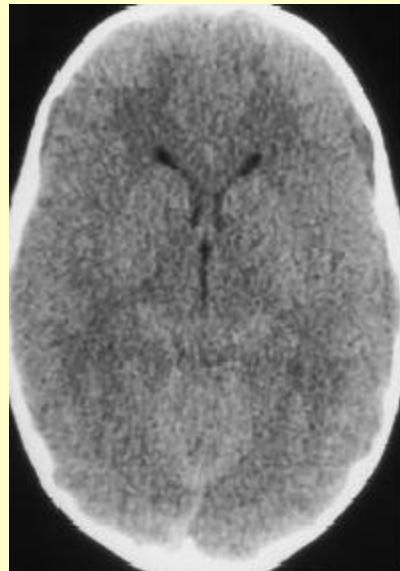
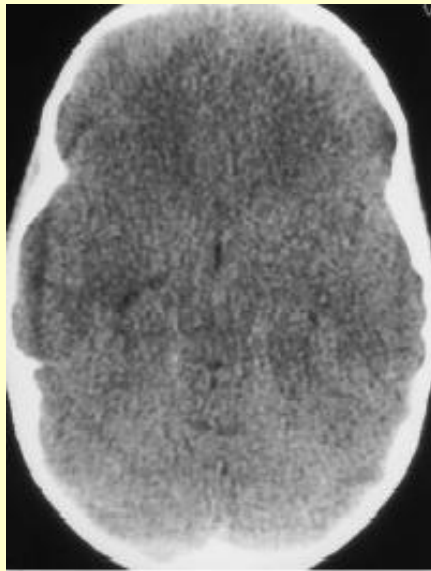
- Acute haemorrhagic and necrotic meningoencephalitis
- Very similar to acute **bacterial meningitis**
- **Acute disease**; death occurring 7 days after onset of symptoms (2-15 days)

- **Headache**
- **Fever** (pyrexia)
- **nausea, vomiting**
- pharyngitis,
- **meningeal signs**
(stiff neck)
- ataxy
- photophobia
- seizures
- lethargy, mental confusion, coma

CT scan does not help with dg

normal scan

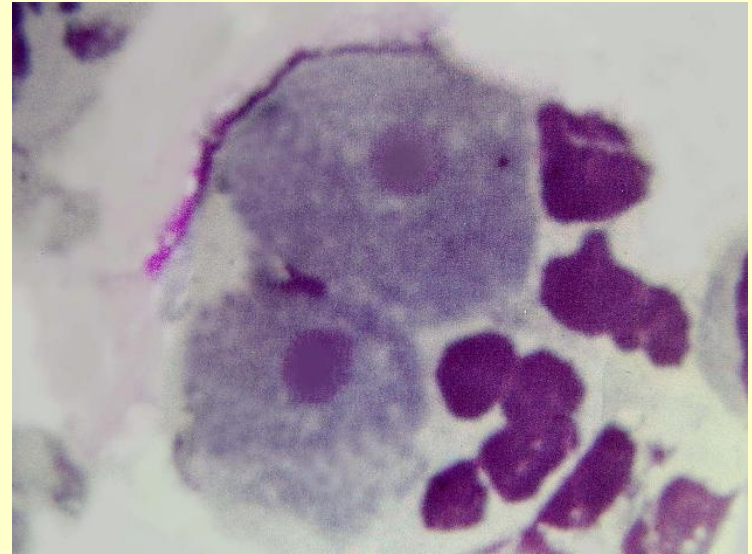
Brain oedema terminally



Haemorrhagic meningoencephalitis



Blood and biochemistry – normal



Cerebrospinal fluid:

elevation of the proteins

glucose normal or low

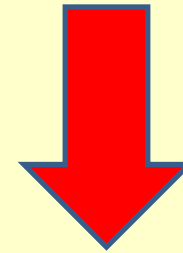
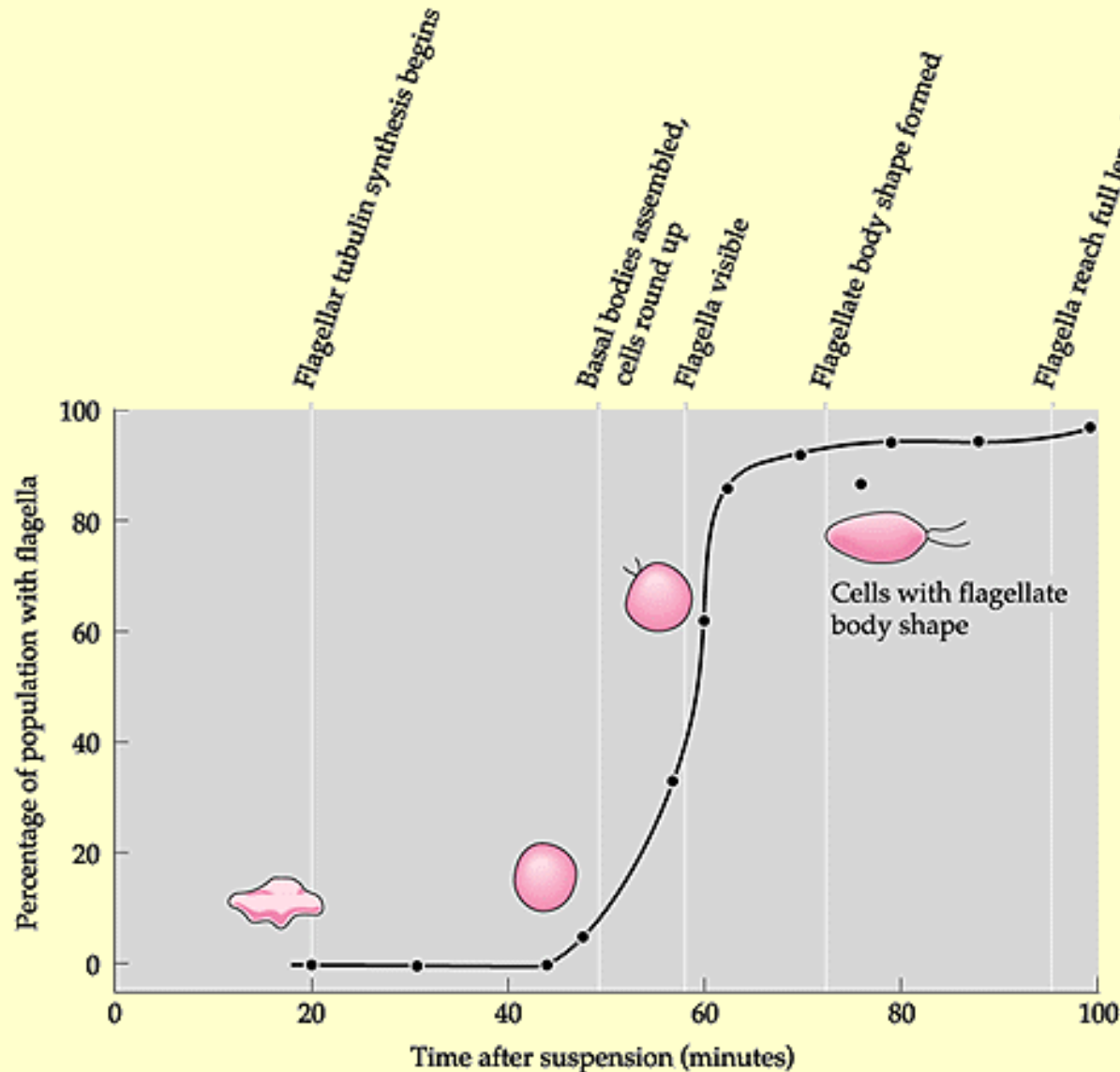
erythrocytes present

pleocytosis with abundance of neutrophils

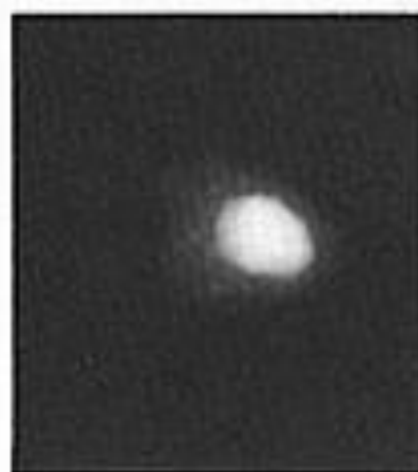
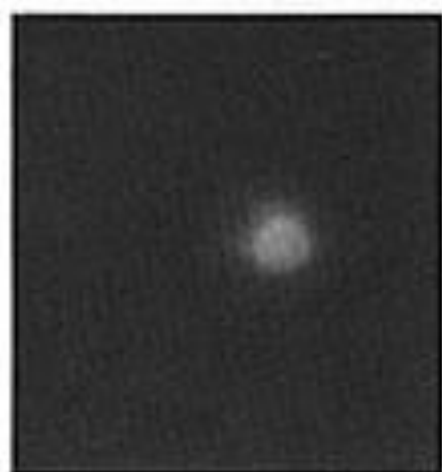
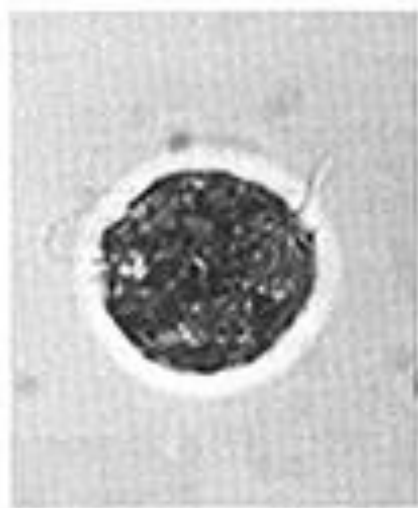
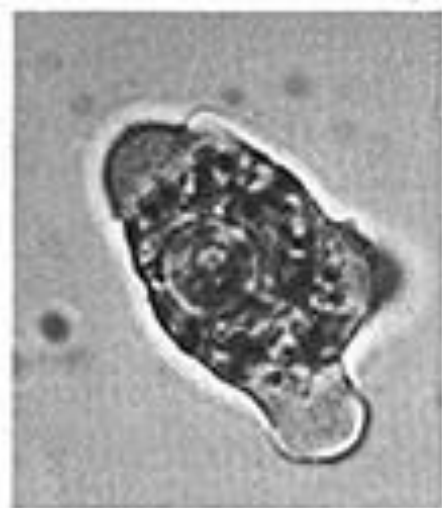
trophozoites of Naegleria fowleri

Flagellation test

Dilution of CSF 1:1
(with distilled water)



Lysis of the host cell,
flagellation of naegleria



(A)

(B)

(C)

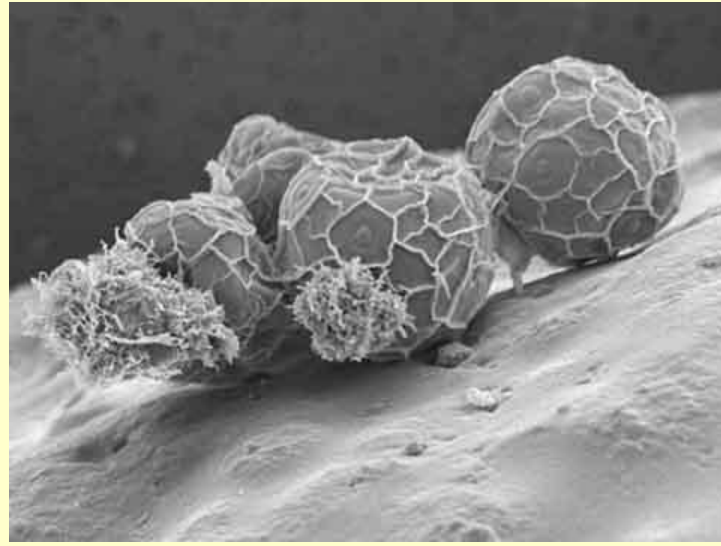
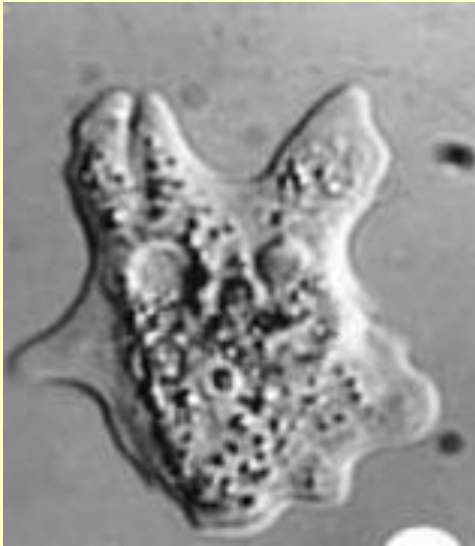
(D)

Treatment:

Successful therapy:
8 cases until now

Chemotherapeutics	Doses
Amphotericin B	0.75 mg/kg qd iv
Amphotericin B	0.1 mg 5 qd it
Rifampin	600 mg q 12 hod
Amphotericin B	1 mg/kg qd
Rifampin	450 mg qd po
Ornidazole	500 mg q 8 hod
Amphotericin B	1.5 mg/kg q 12 hod iv
	1.5 mg qd it
Miconazole	350 mg/m² q 8 hod iv
	10 mg qd it
Rifampin	10 mg/kg q 8 hod po
Sulfisoxazole	1g q 6 hod iv
Amphotericin B	60 mg qd
Rifampin	450 mg qd
Chloramphenicol	1 g qid

Acanthamoeba spp.



Epidemiology

Granulomatous amoebic encephalitis (GAE)
and **amoebic keratitis**

Cosmopolite distribution
(dust, water, soil, sediment.....)

Untill now 180 cases of GAE worldwide
Succesfull therapy: 10 cases

Incidence of *Acanthamoeba* keratitis

(M. Willcox for Cornea, 2009)

Table 1. Incidence data for *Acanthamoeba* keratitis

Area	Study type/Lenses	Rate/10,000	Reference
Scotland	Cohort/HEMA	1.49	Seal et al., 1999
Hong Kong	Epidemiology/HEMA	0.33	Lam et al., 2002
England/ Wales	Multicenter/HEMA	0.2	Radford et al., 2002
USA	CDC data/HEMA	0.02	Schaumberg et al., 1998
Australia	Epidemiology/HEMA/SiHy	0.02	Stapleton 2009, personnel communication

Czech republic

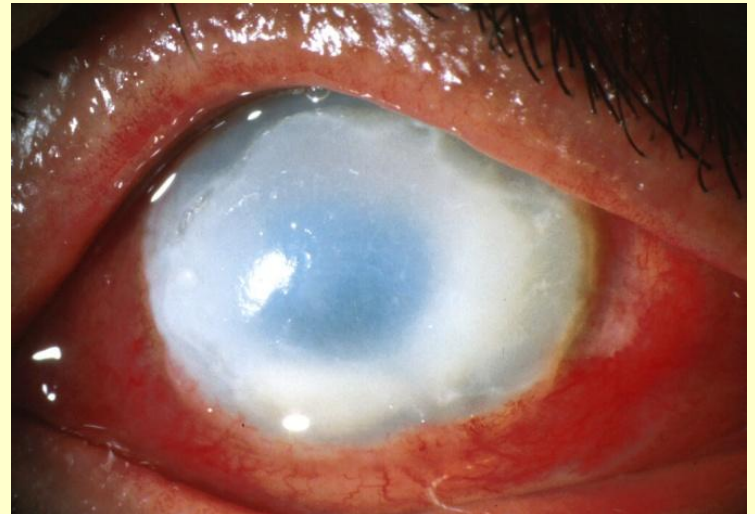
No GAE

First keratitis case 1995

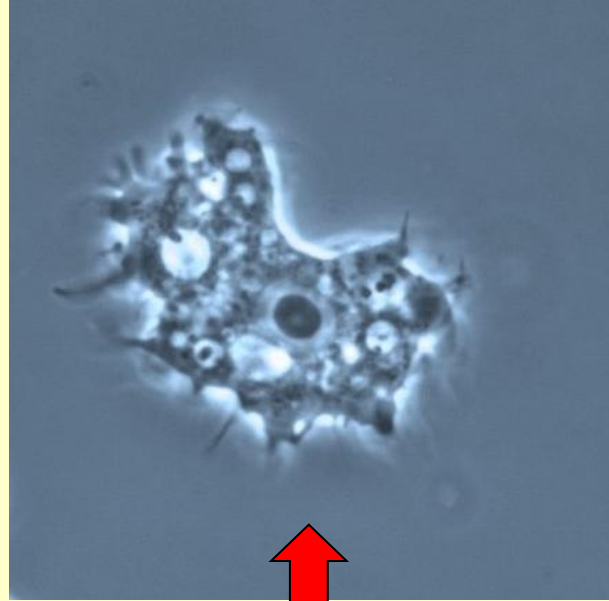
Until now 33 confirmed cases

80% contact lenses

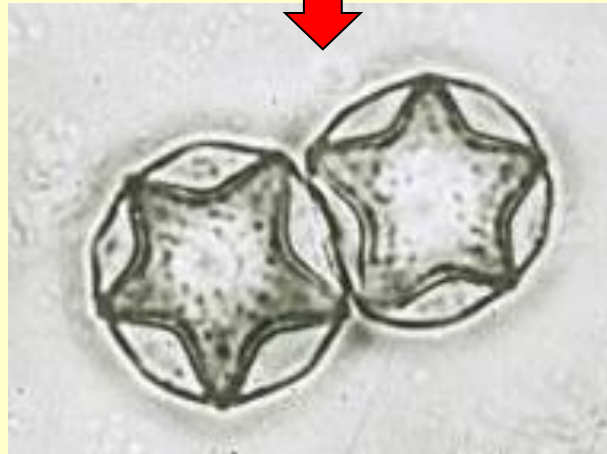
20% trauma of eye



Trophozoite



starvation
deseccation
therapy

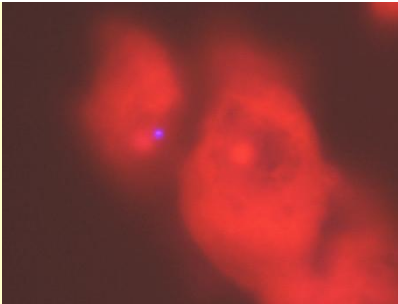


Cyst

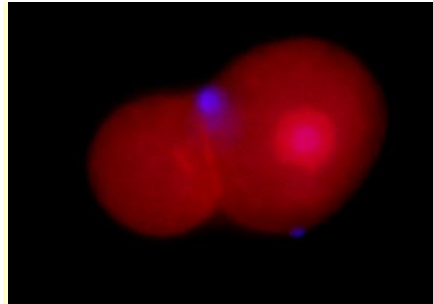
Encystation: cellulose synthesis

Exocyst formation

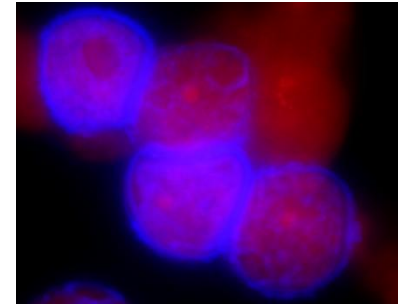
6 hrs



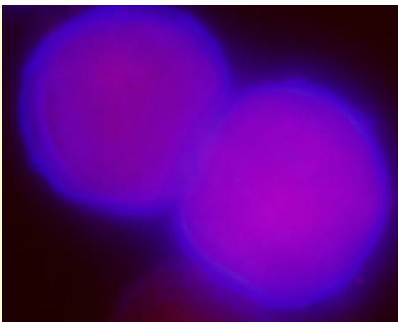
8 hrs



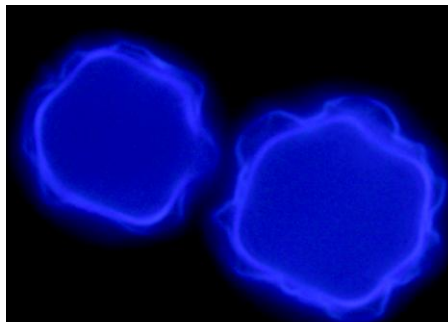
12 hrs



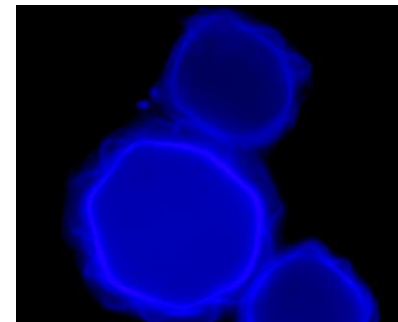
24 hrs



48 hrs

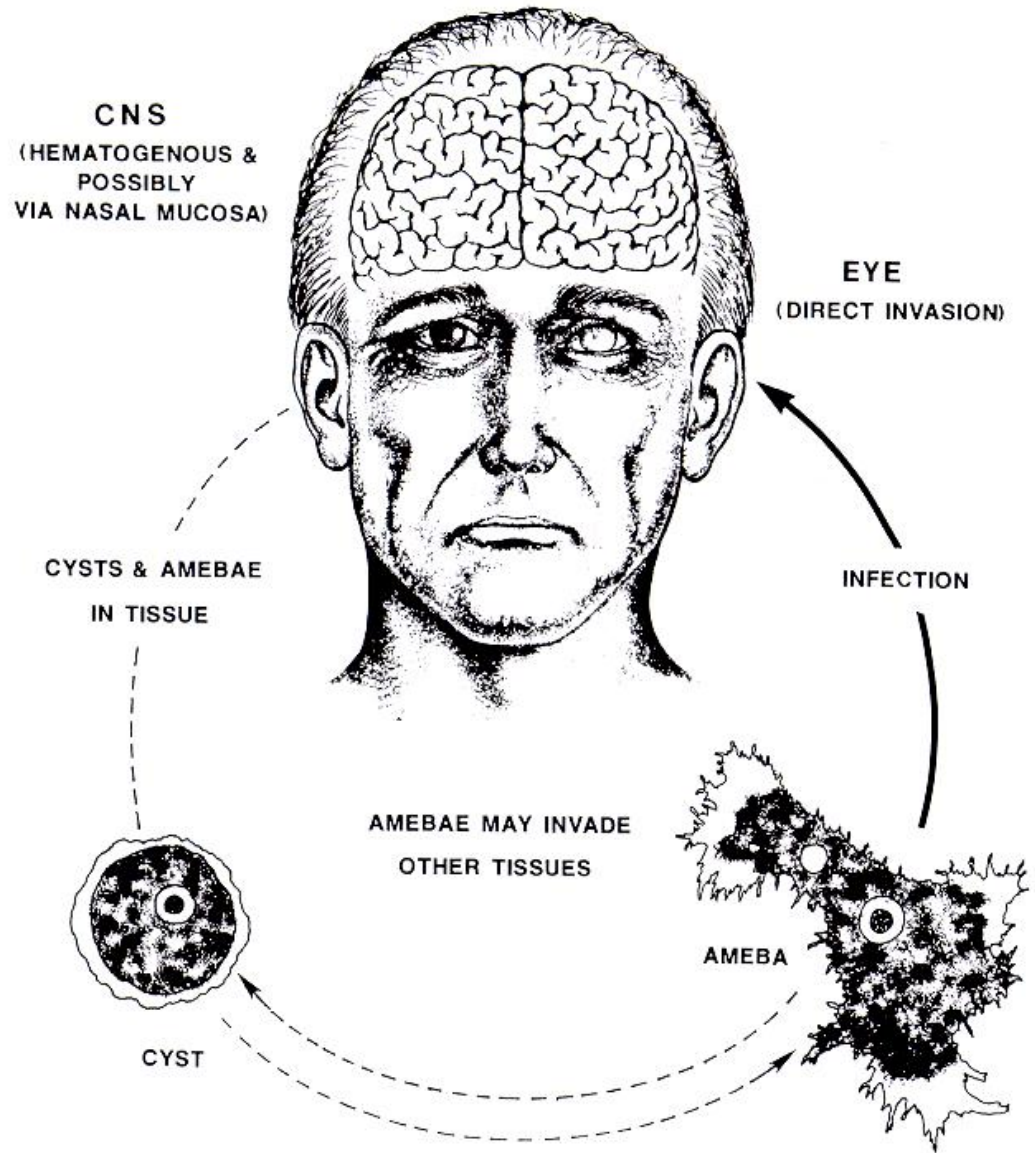


72 hrs



Edocyst formation

Hematogenous spread
from skin or lungs

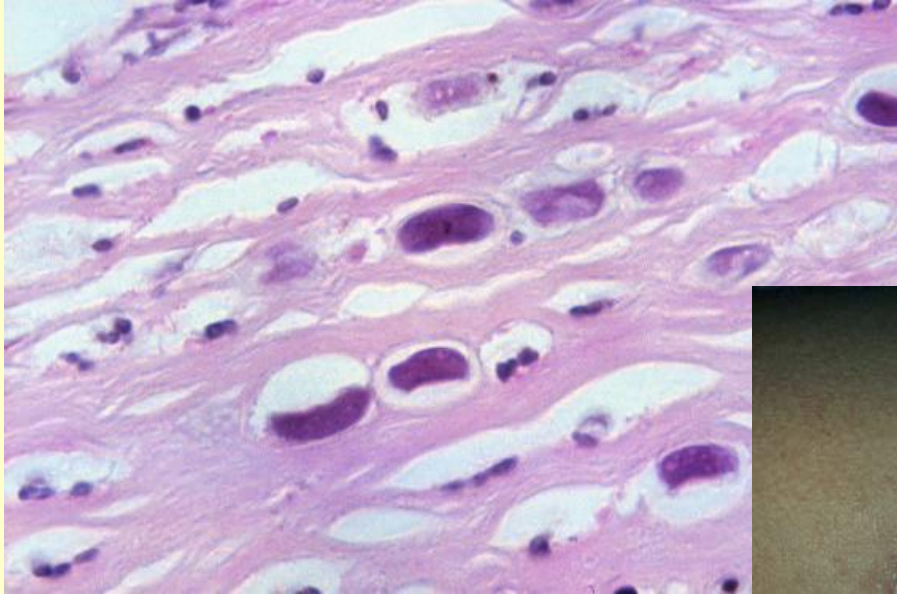


Acanthamoeba serves as a

Trojan horse for distributing bacteria in
the environment (might be responsible for outbreaks of legionellosis)

Skin lesions (non-healing skin ulcers)

are considered as a port of entry



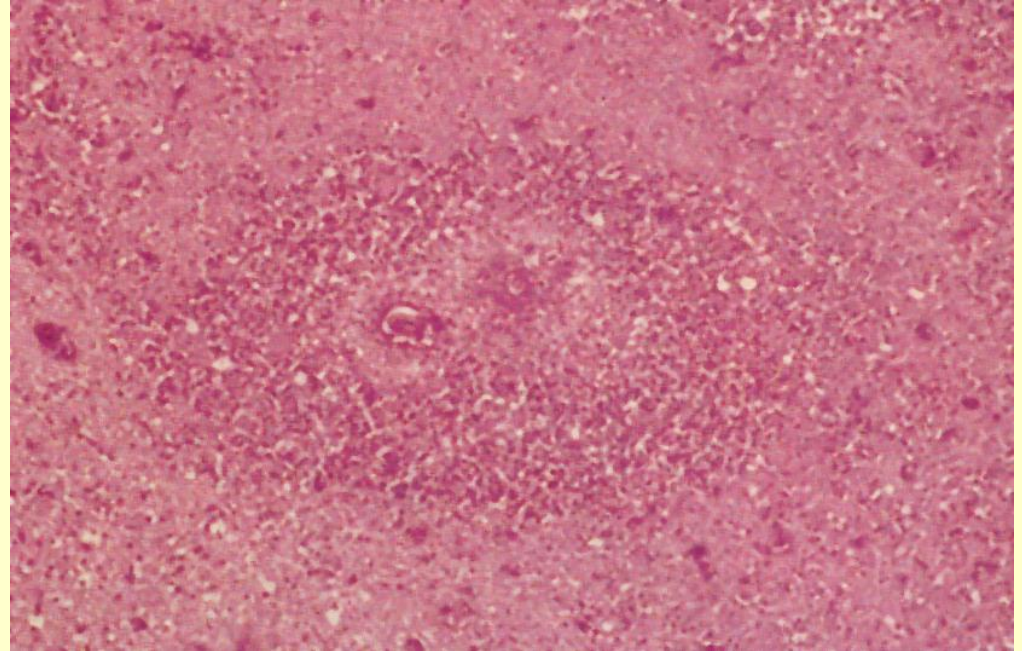
Lungs – proposed port of entry

10% individuals carrying acanthamoebae in their respiratory system



Granulomatous amoebic encephalitis – formation of granulomatous lesions in CNS

Chronic course usually leading to the death of the patient
Immunocompromised individuals (AIDS)



GAE has got **non-specific symptomatology** of CNS affection

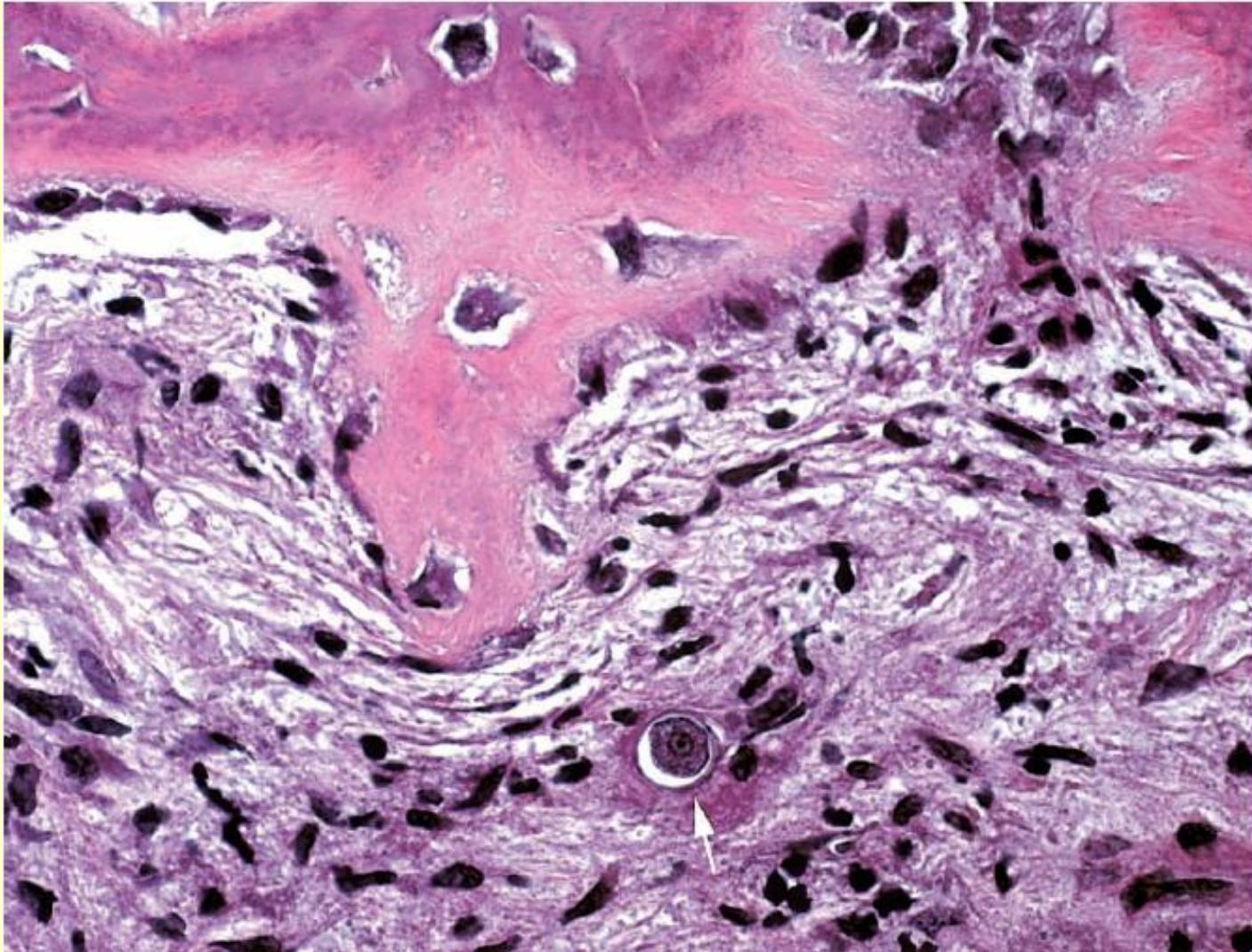
- Increased temperature
- **Focal neurological deficits**
- **Headaches**
- Nausea, vomiting
- **Seizures**
- Hemiparesis
- Mental deficit
- Personality changes
- Stiff neck
- Letargy, coma

- Possible **dissemination of the disease**
- hard erythematous nodules, skin ulcerations, affection of kidneys, lungs, osteomyelitis...

Disseminated infection in the AIDS



Acanthamoeba in a decalcified bone



Amoebic keratitis

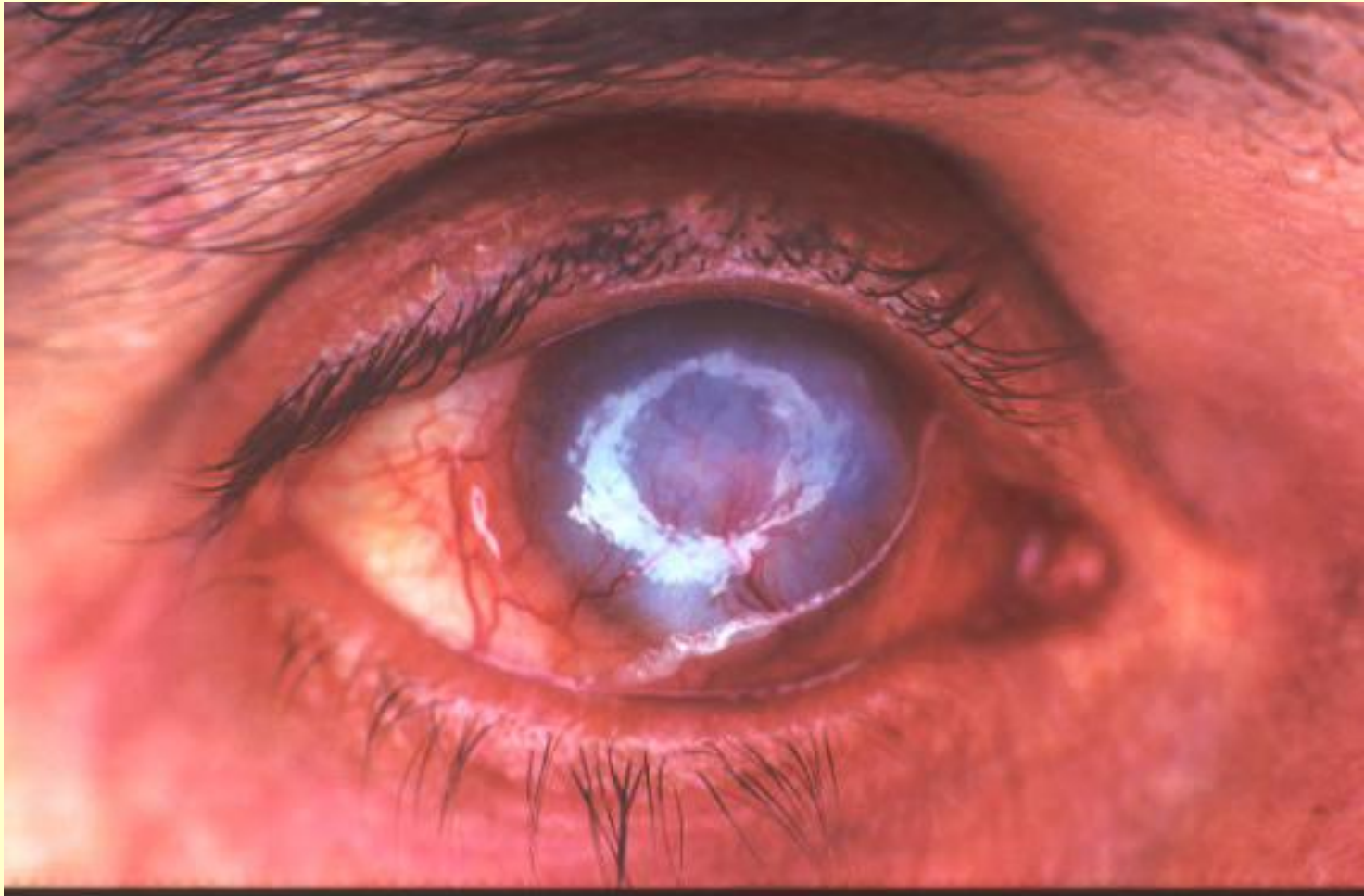
Excruciating **pain**

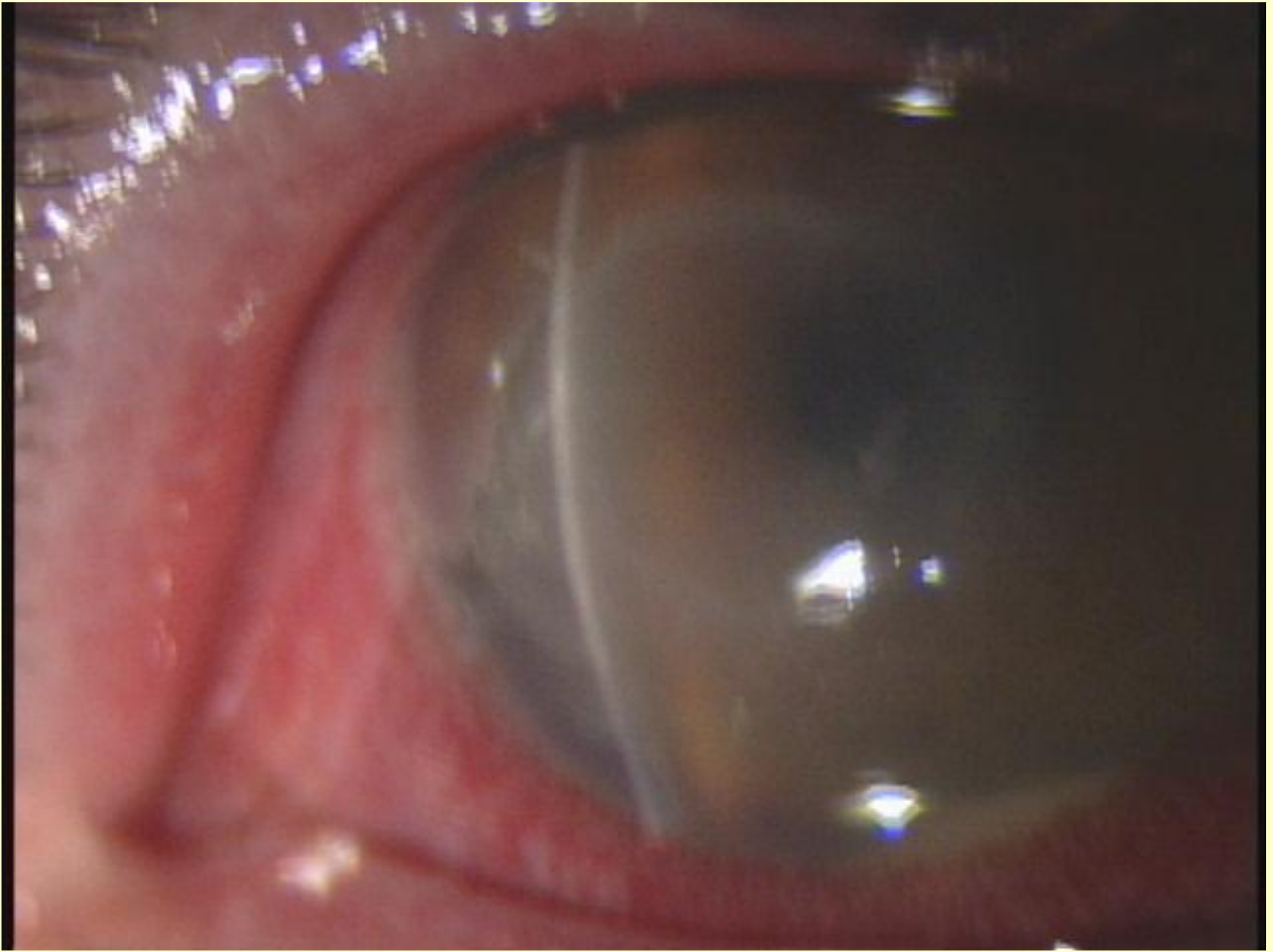
Loss of the vision

Infiltrate formation

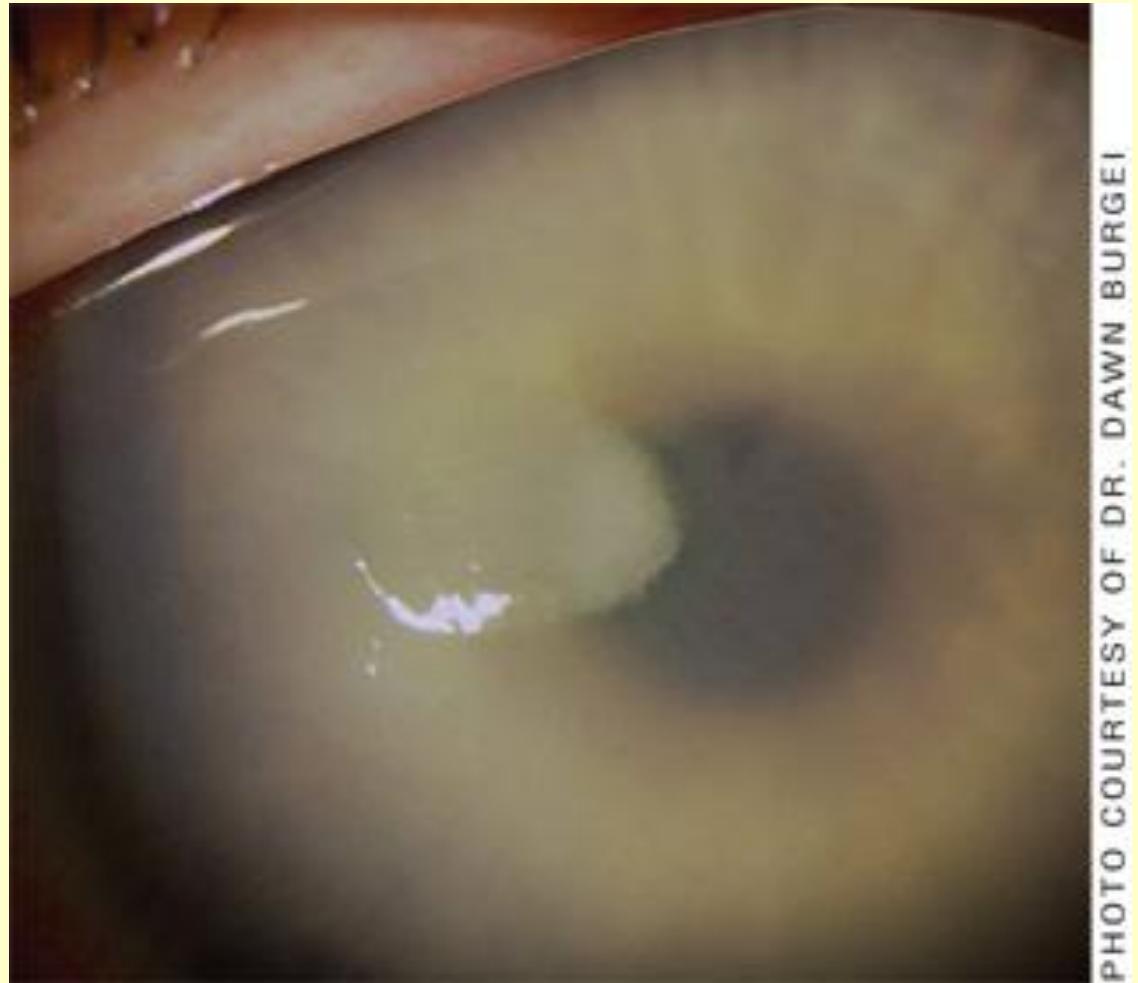
Unresponsibility to the ATB treatment

Keratitis is characterized by **ring infiltrate** of the cornea





Delayed diagnosis: central ulcer and corneal oedema



Therapy of the keratitis

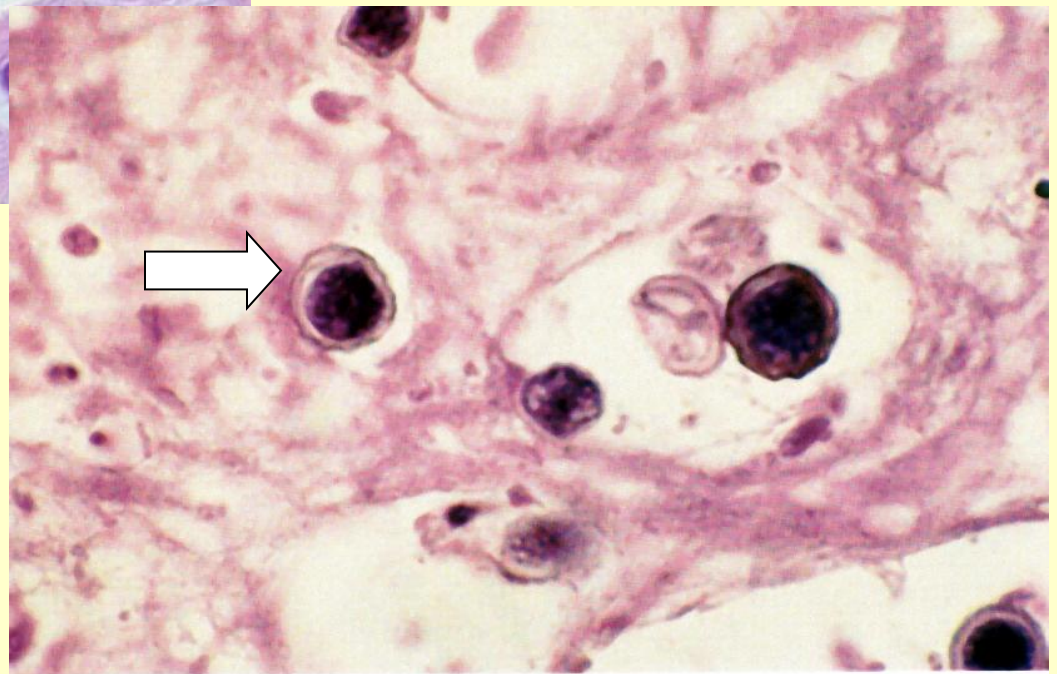
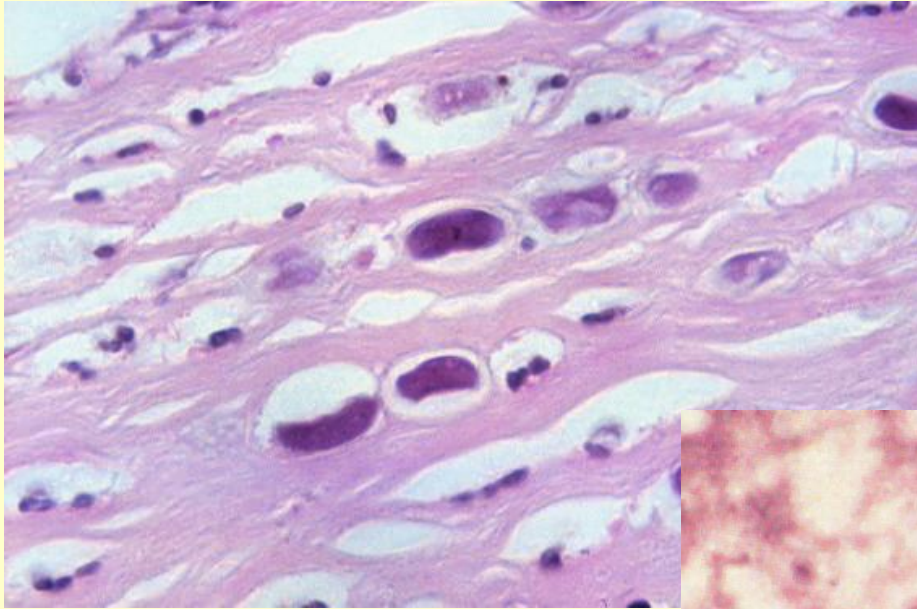
Prolonged therapy (one month)

Propamidine isothionate

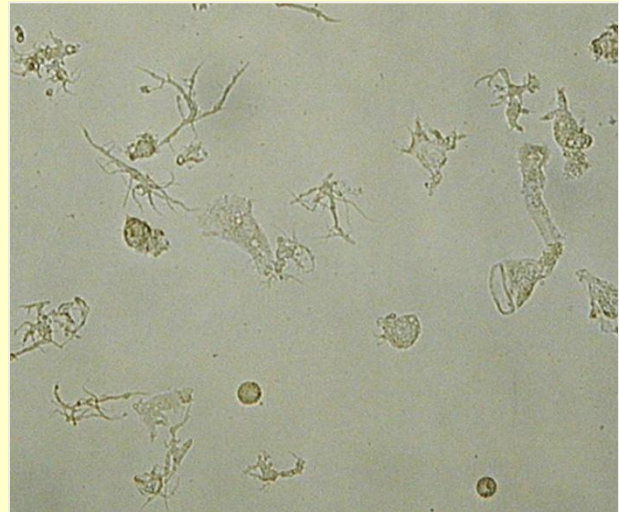
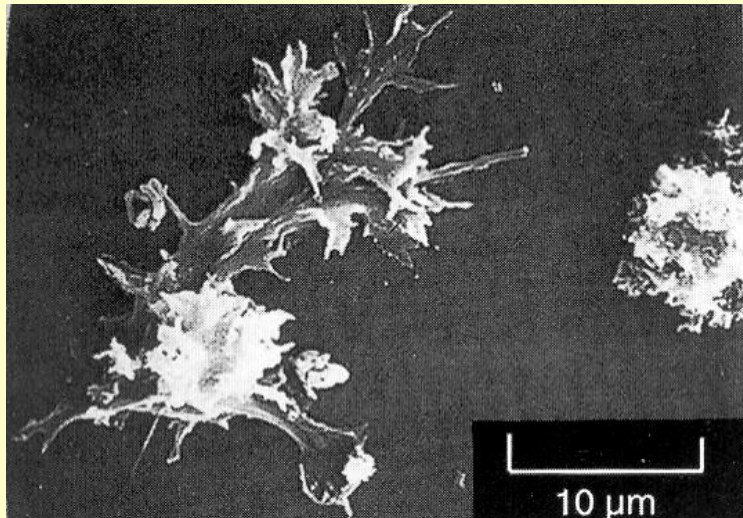
Polyhexamethylene biguanide

Penetrating keratoplasty

Reason for unsuccessful therapy is the cyst formation in the affected tissues



Balamuthia mandrillaris



Balamuthia is causative agent of **granulomatous amoebic encephalitis**

Cosmopolite distribution

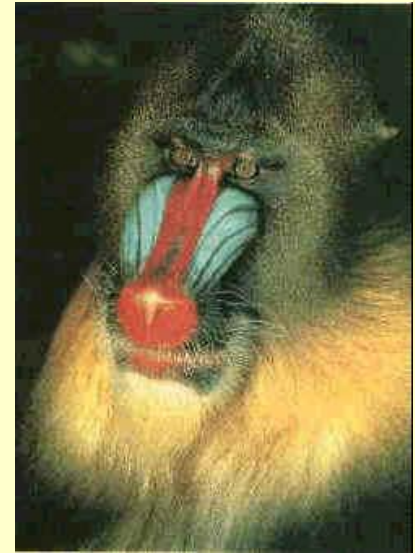
Soil?

Higher prevalence in the countries
with **warm clima** – Australia,
California

High prevalence among
hispanic population

Until now: 100 cases worldwide

Succesfull therapy: 3 cases



Czech republic

1995 – 3.5 year old boy died on encephalitis
of unknown origin

Post portem confirmed *B. mandrillaris*
presence in the brain lesions (CDC)

First case of GAE in Europe

Unknown source of infection for long time

First isolation from the environment: 2003

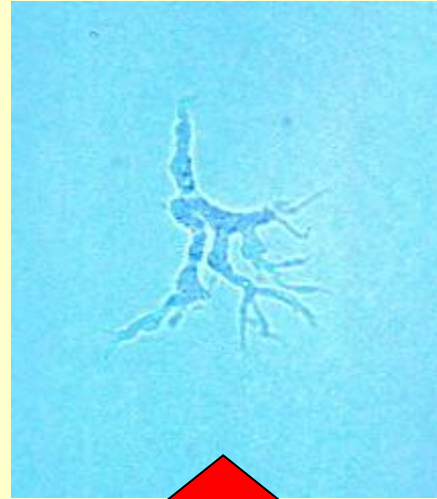
Isolate **from the soil** from the **flower pot** and isolate from the patient confirmed to be identical

2004 – isolate from the soil (flower pot) in California,

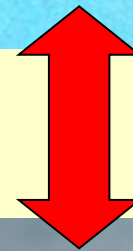
2009 – isolate from the dust in Teheran



Trophozoite

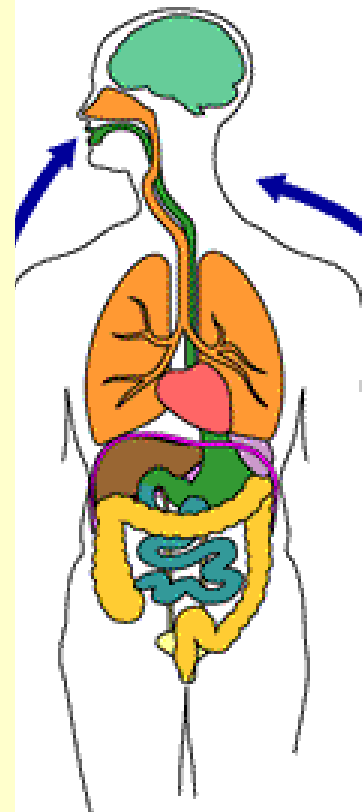


Cyst: three layers of wall







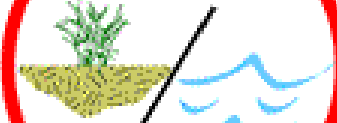
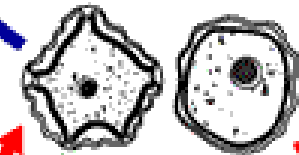


***Acanthamoeba* spp. and
*Balamuthia mandrillaris***

- 4 Enter through lower respiratory tract or through ulcerated or broken skin causing granulomatous amebic encephalitis (GAE) in individuals with compromised immune system

d Cysts and trophozoites in tissue

1 Cysts



2 Trophozoites **i**

3 Mitosis

i = Infective Stage
d = Diagnostic Stage



<http://www.dpd.cdc.gov/dpdx>

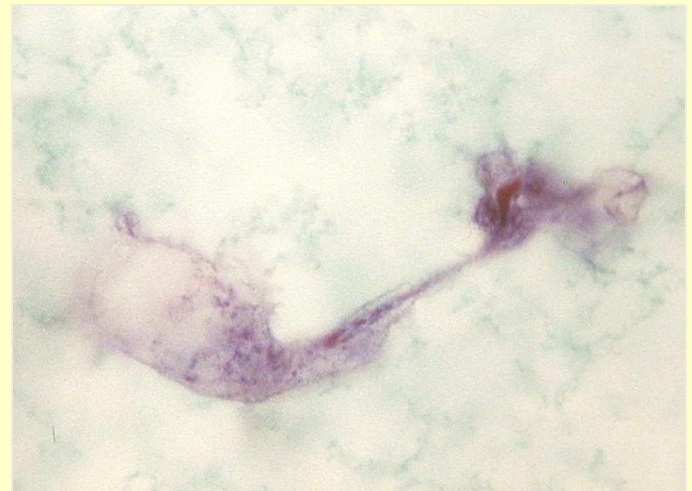
The **role of the immune status** for establishment of the infection remains **unclear**

Immunocompromised

Immunocompetent individuals?

(often young children and elderly, DM, homeless....)

Incubation period: unknown (months?)



Many cases: wounds contaminated by soil

**Erythematous skin
nodule**

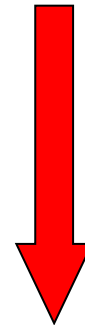


Ulceration

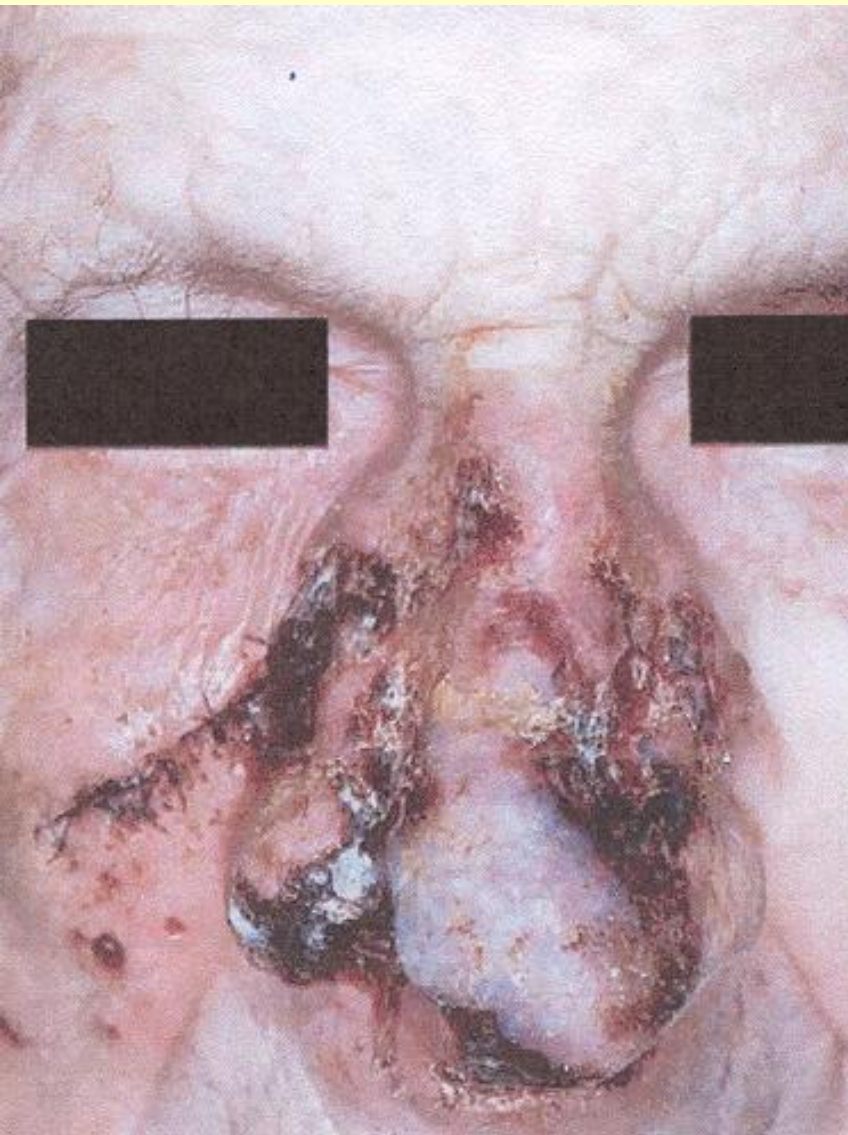


CNS

Otitis media???

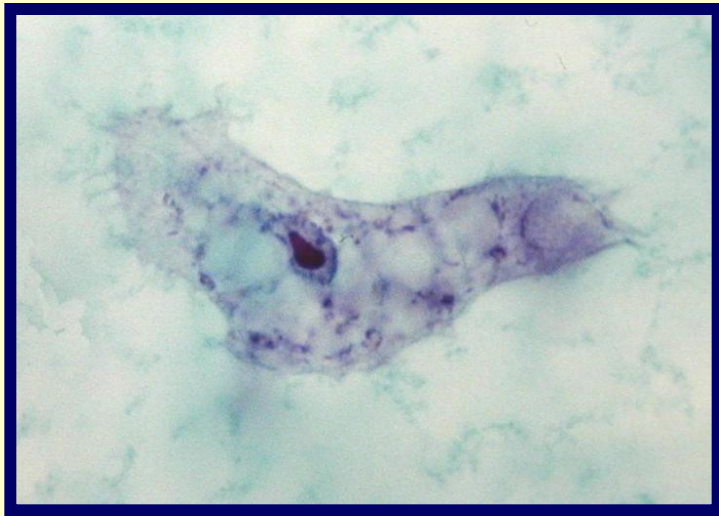


CNS





Chronical course of
disease, mostly fatal



Headache,

Slightly elevated
temperature

Nausea, vomiting

**Focal neurological
deficiency**

(motoric deficiency; I.-XII.),

Personality changes

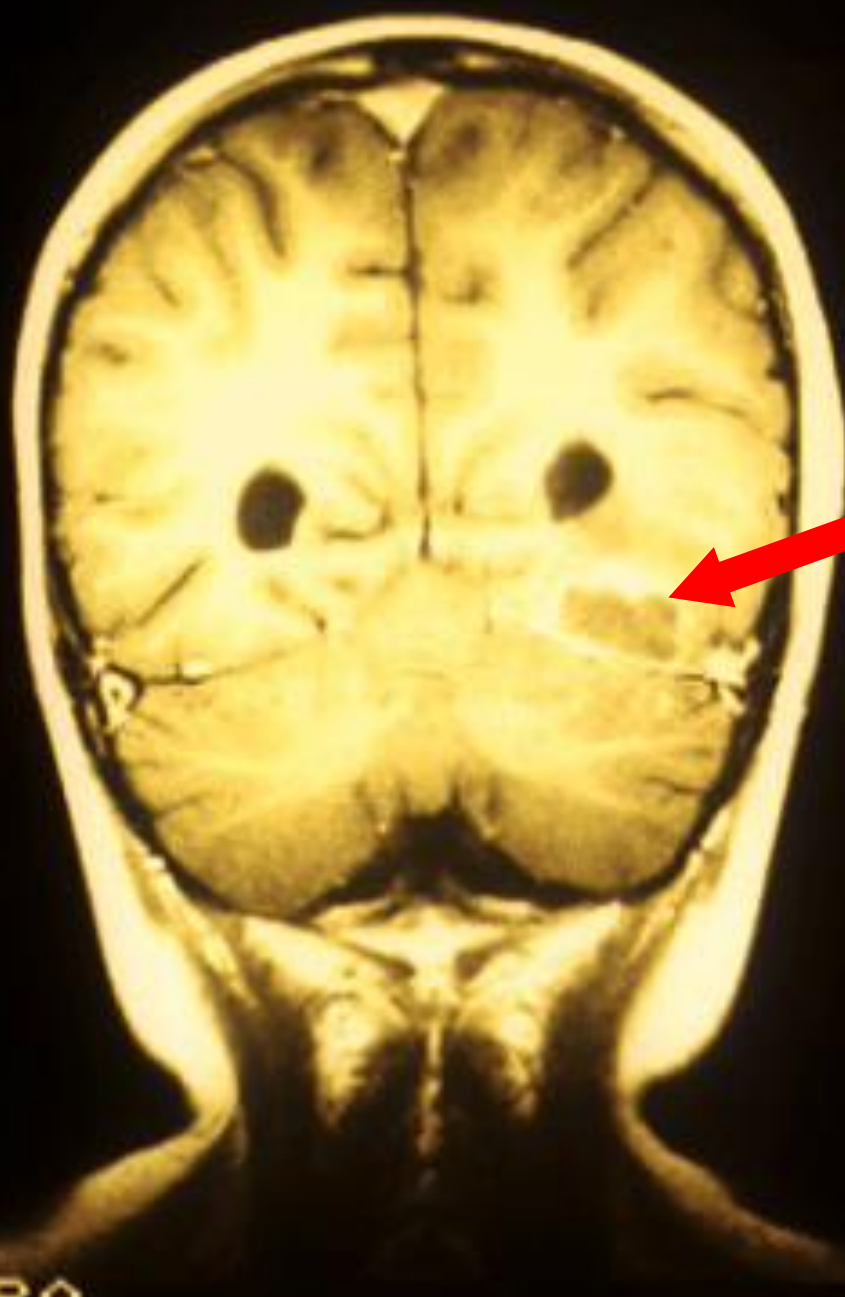
Stiff neck

Ataxy

Seizures

Lethargy, coma

7-OCT-95
1:41:09
STORE>97



LEFT

5 C

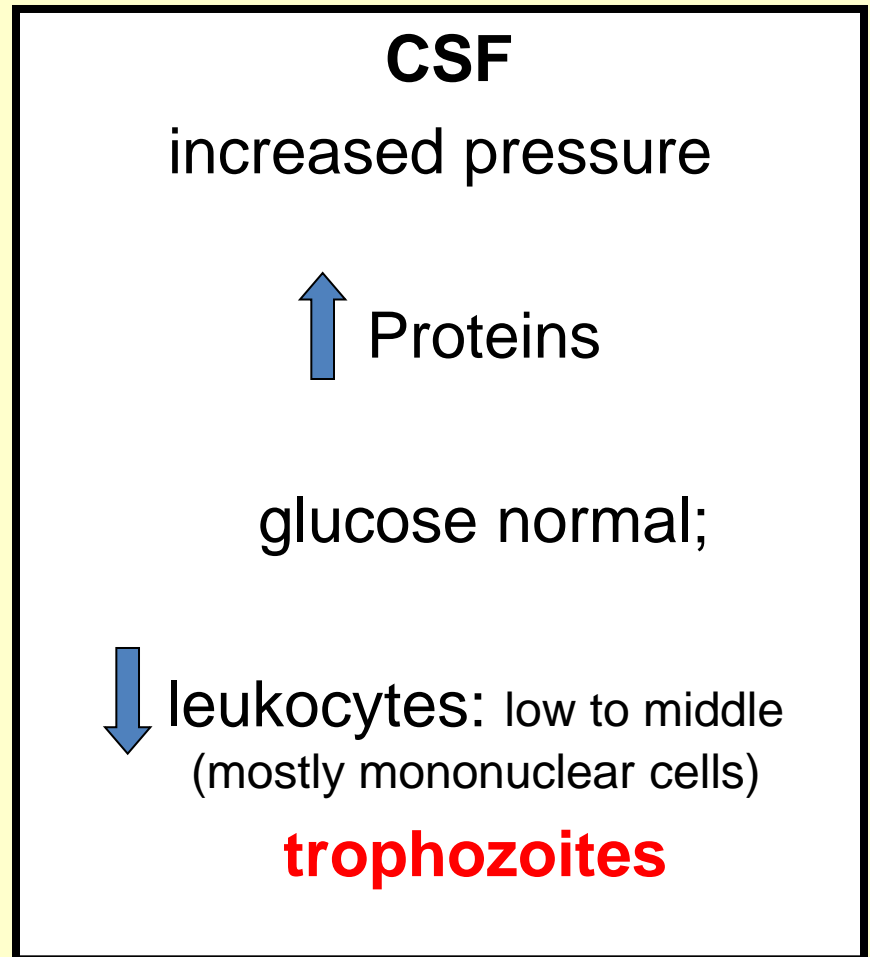
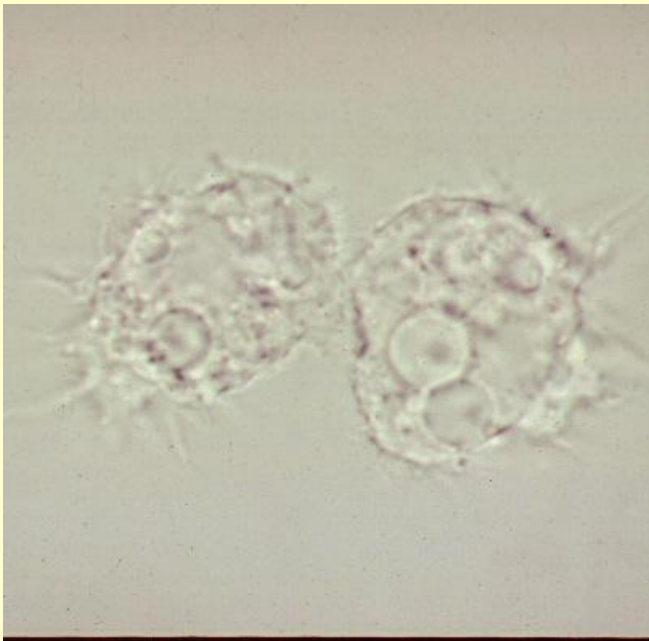
R .60
E 15
L 5.0
P -48.0
0
F 1.40

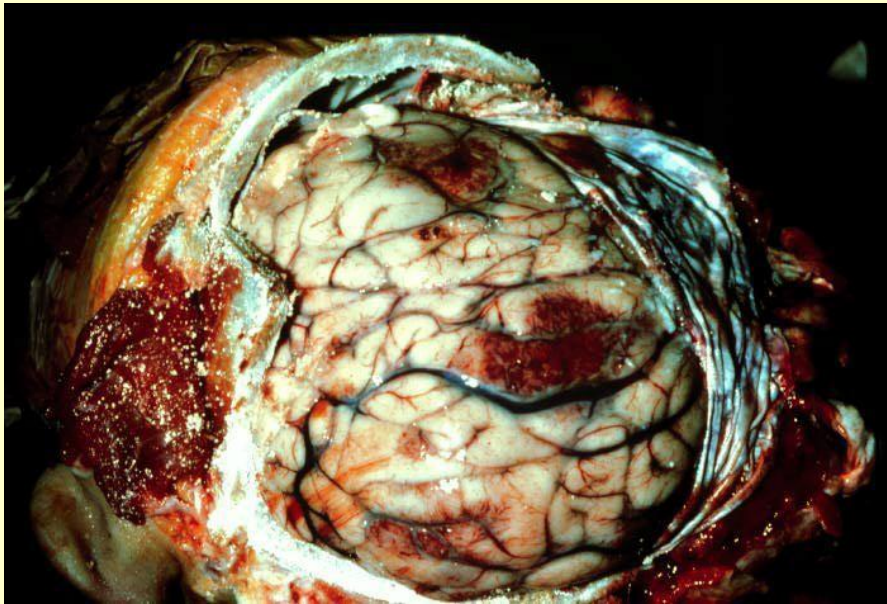
W 118
C 59

GdDTPA

Acanthamoeba spp, *Balamuthia mandrillaris*

Blood and biochemistry:
normal

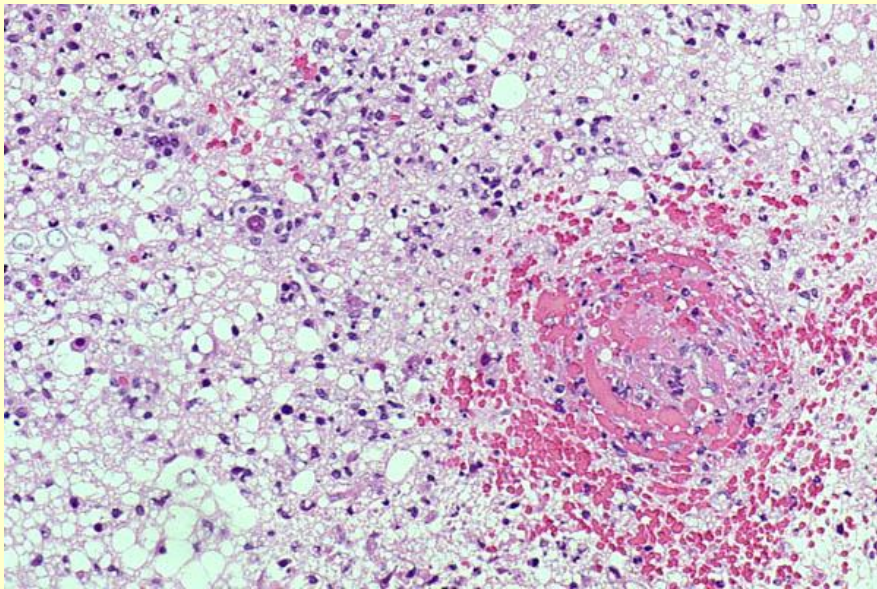




Perivascular infiltration
with trophozoites

Granuloma formation
in **immunocompetent**
individuals

WBC - neutrophils
perivascularly



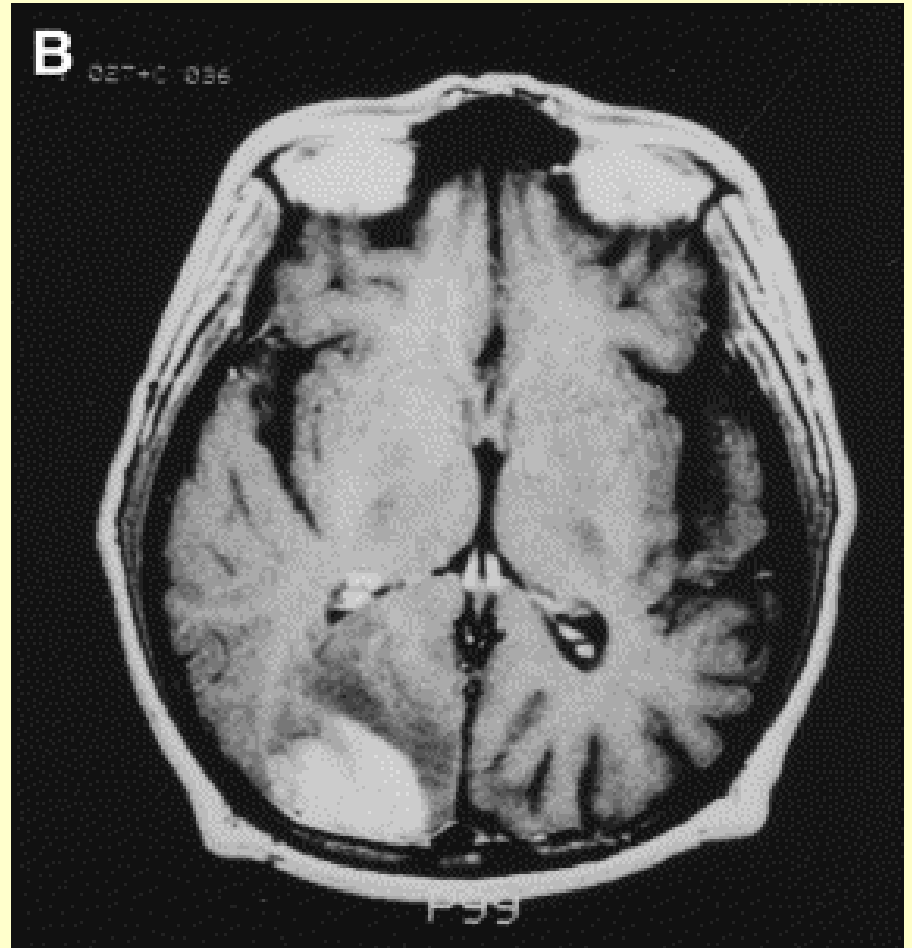
CT:

multiple abnormalities,
usually

Hypodense lesions

Ring enhancing lesions

NMR: abnormal signal



Signs and Symptoms in Primary Amebic Meningoencephalitis (PAM) and Granulomatous Amebic Encephalitis (GAE)

Symptoms and Signs	PAM	GAE
Symptoms		
Mental status abnormalities*	+	+
Headache	+	+
Fever > 38.2°C	+	0
Nausea and vomiting	+	+
Stiff neck	+	+
Seizures	+	+
Anorexia	+	+
Diplopia and blurred vision	+	+
Photophobia	+	+
Hallucinations	+	+
Sleep disturbances	0	+
Sore throat	+	0
Rhinitis	+	0
Ageusia	+	0
Parosmia	+	0
Hearing difficulties	+	0
Signs		
	Early	Late
Coma	0	+
Papilledema	+	+
Cranial nerve palsies (nerves III & VI)	+	0
Nystagmus	+	+
Gait ataxia	+	+
Babinski's sign	+	+
Kernig's sign	+	+
Hemiparesis	0	+
Aphasia	0	+
Anisocoria	+	0
Disconjugate gaze	+	0
Cause of death	Cardiorespiratory arrest Pulmonary edema Brain edema	Bronchopneumonia Liver/kidney failure

* Lethargy, drowsiness, stupor, disorientation, confusion, delirium, obtundation, restless, irritability, combativeness.

Characteristic	Nonviral		Viral	
	Balamuthia patients referred (n = 10)	MTB cases (n = 26)	HSV-1 cases (n = 52)	EV cases (n = 82)
Demographic characteristic				
Age, median years (range)	18 (1–72)	46 (0–77)	41 (0–89)	13.5 (0–75)
Male sex	9 (90)	15 (58)	26 (50)	50 (59)
Race/ethnicity				
American Indian	1 (1)
Asian	...	8 (31)	3 (6)	9 (11)
Black	...	1 (4)	2 (4)	6 (7)
Hispanic	8 (80)	12 (46)	9 (17)	25 (30)
Pacific Islander	1 (10)	2 (8)	...	1 (1)
White	1 (10)	3 (12)	27 (52)	30 (37)
Other	2 (4)	5 (6)
Unknown	9 (17)	5 (6)
Clinical characteristic				
Interval from onset to presentation, median days (range)	8.5 (1–30)	5.5 (0–61)	2 (0–19)	2 (0–154)
Duration of hospitalization, median days (range)	16.5 (3–120)	32 (7–753)	15 (0–1295)	7 (0–1124)
Fever	7 (70)	20 (77)	46 (88)	61 (74)
Severe headache	6 (60)	7 (27)	9 (17)	17 (21)
Lethargy	7 (70)	26 (100)	45 (87)	54 (66)
Altered consciousness	5 (50)	15 (58)	32 (62)	30 (37)
Ataxia	1 (10)	8 (31)	8 (15)	22 (27)
Focal neurologic findings	4 (40)	15 (58)	17 (33)	23 (28)
Seizures	4 (40)	10 (38)	30 (58)	22 (27)
Coma	3 (30)	9 (35)	8 (15)	5 (6)
Intensive care unit care	5 (50)	18 (69)	31 (60)	28 (34)
Death	9 (90)	5 (19)	10 (19)	5 (6)
Laboratory value,^a median (range)				
CSF WBC count, cells/mm ³	188 (11–540)	171.5 (20–2845)	90 (0–975)	58 (0–1332)
CSF protein, mg/dL	131 (64–674)	182 (47–500)	64.9 (6–297)	56 (16–881)
CSF glucose, mg/dL	40 (15–74)	35.5 (8–132)	68 (39–112)	67 (27–159)
Abnormal neuroimaging finding				
First MRI	7 (70)	17 (65)	41 (79)	21 (26)
Second MRI	3 (30)	3 (12)	4 (8)	3 (4)
CT	8 (80)	14 (54)	24 (46)	13 (16)
Electroencephalography	1 (10)	11 (42)	22 (42)	14 (17)

Acanthamoeba spp. Therapy

6 successfully treated cases

Antimicrobials	Dosage	Literature
Sulfamethazine	1 g qid	Cleland et al., 1982
Cotrimoxazole 5-Fluorocytosine Sulfadiazine	75 mg/kg a 12 hod iv 150 mg/kg a 6 hod 150 mg/kg a 6 hod	Karande et al., 1991
Penicillin G Chloramphenicol	2x10 U a 3hod iv 500 mg a 6 hod po	Lalitha et al, 1985
Sulfadiazine Pyrimethamine Fluconazole	500 mg qid 50 mg qd 200 mg bid	Martinez et al., 2000
Ketoconazole Rifampin TMP-SMX	5 mg/kg qd 10 mg/kg qd 20 mg/kg qd	Singhal et al., 1993
Amphotericine B Ketoconazole	50 mg qd	Ofori-Kwaye et al., 1986

Balamuthia mandrillaris therapy

3 successfully treated cases

Antimicrobials	dosage	Patient	Literature
Flucytosine Fluconazole Pentamidine isethionate Sulfadiazine Azithromycin, clarithromycin Trifluoperazine	2 g q 6 hod po 400 mg qd 4 mg/kg qd iv 1.5 g q 6 hod po 500 mg qd 10 mg q 12 hod	64 year old male	Deetz et al., 2003
Flucytosine Fluconazole Pentamidine isethionate Azithromycin, clarithromycin Thioridazine	110 mg/kg qd 14 mg/kg qd 1 mg/kg qd 14 mg/kg qd 1 mg/kg qd	5 years old girl	Deetz et al., 2003
Pentamidine isethionate Sulfadiazine Fluconazole Clarithromycin	300 mg qd 1.5 g q 6 hod 400 mg qd 500 mg q 8 hod	72 years old female	Jung et al., 2003