Amoebiasis

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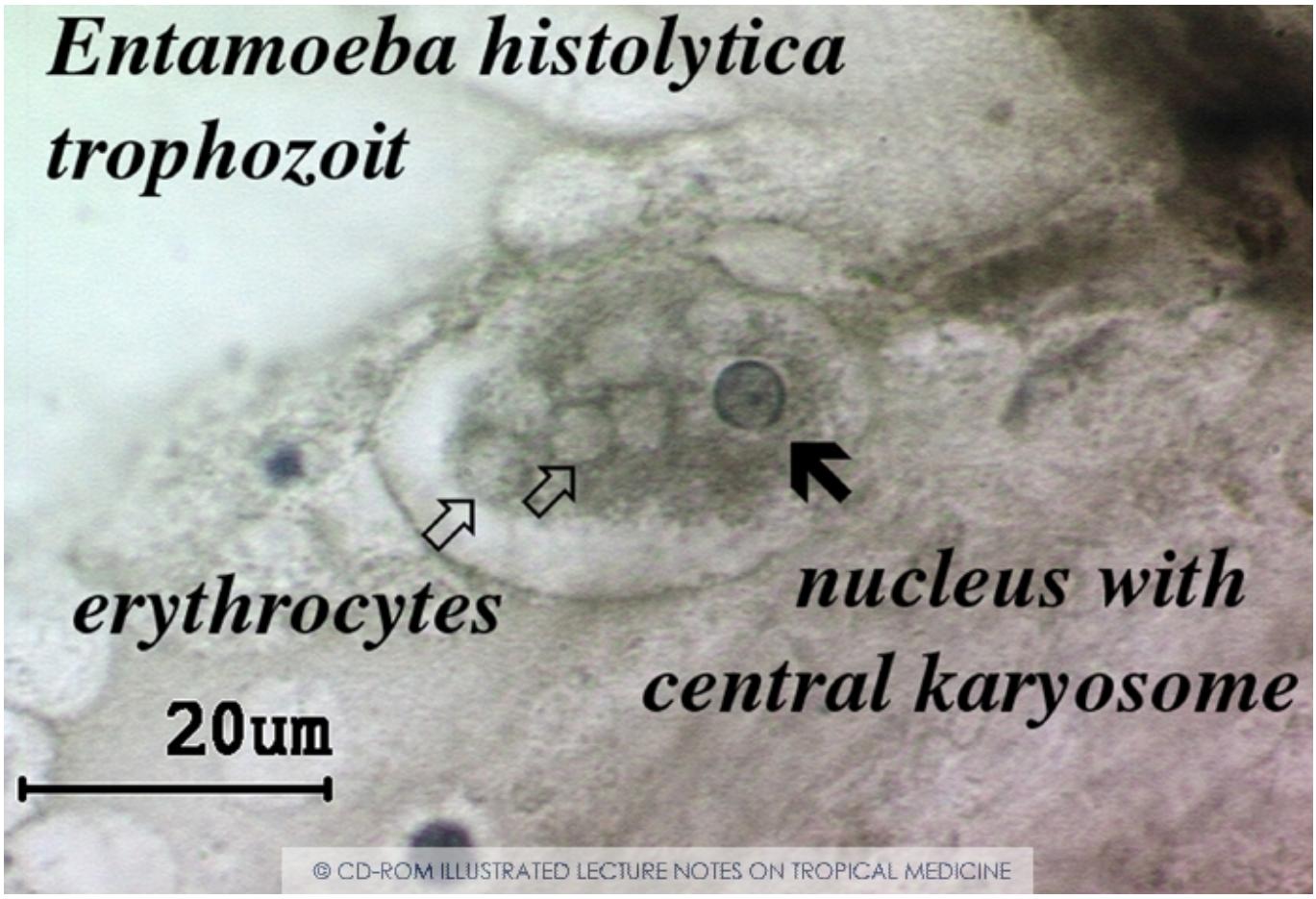
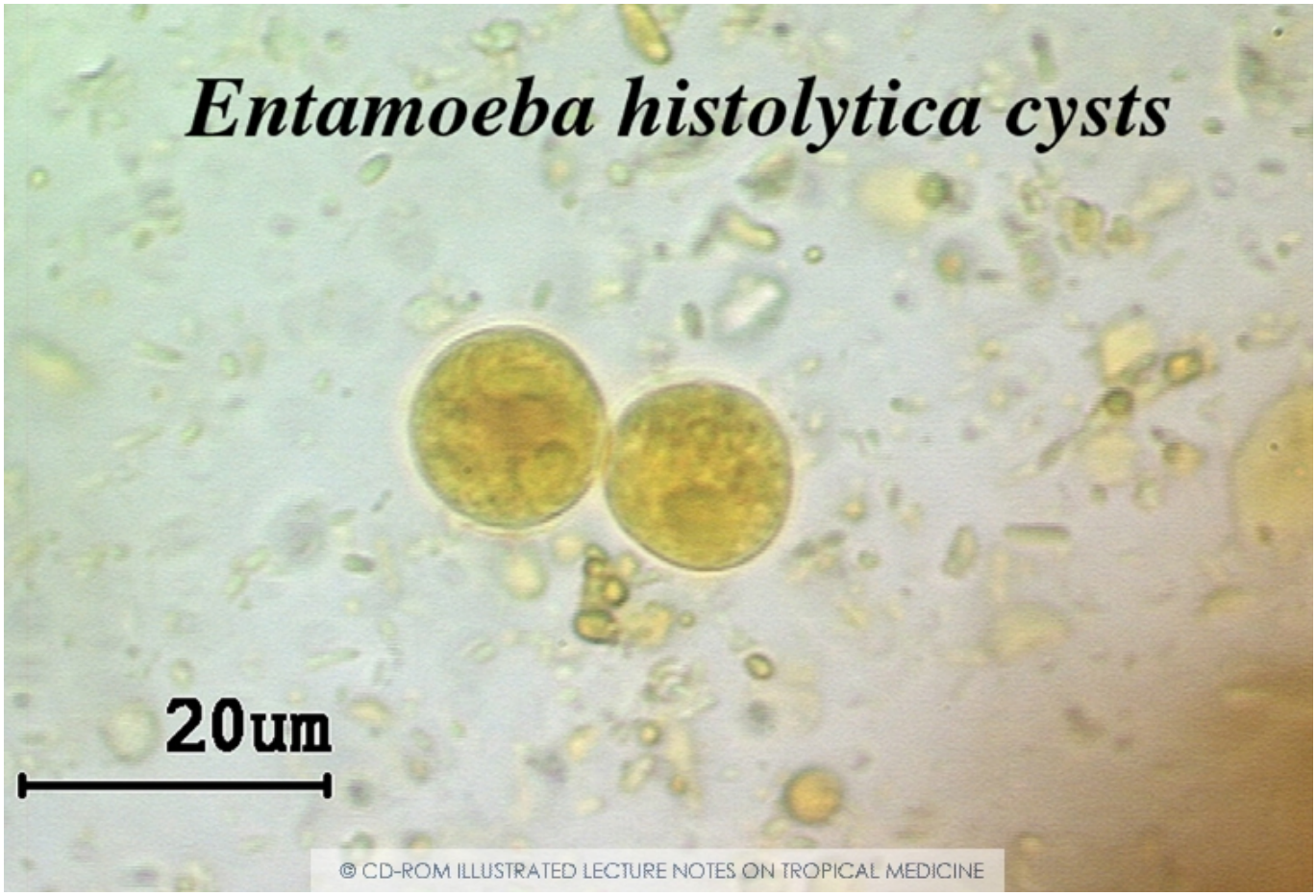
Amoebiasis – General

General

Amoebiasis in our context means infection with *Entamoeba histolytica*. This is a unicellular cosmopolitan parasite. The first description of the parasite was in 1875 by Fedor Lösch in St Petersburg. This concerned an infection in a young Russian farmer in Arkhangelsk, 150 km from the Arctic circle. This illustrates the fact that the infection is not restricted to the tropics. Transmission depends on the level of sanitation and faecal hygiene in a country or region.



Entamoeba histolytica trophozoite in rectal mucosa. Copyright ITM



Entamoeba histolytica cysts. Cysts never contain red blood cells. Copyright ITM

Pathogenicity of Entamoeba histolytica

There was considerable confusion concerning the nomenclature and pathogenic properties of *Entamoeba histolytica*. It is now recognized that there are morphologically identical amoebae, some of which are non-pathogenic and some of which are pathogenic. This concept was introduced in 1925 by the French parasitologist Emile Brumpt. The non-pathogenic amoebae are called *Entamoeba dispar*. This should also not be confused with other completely non-pathogenic species, including *Entamoeba hartmanni* (previously sometimes called “small race” *E. histolytica).* In 1978 it was discovered in London that the two kinds of amoebae could be differentiated using isoenzymatic electrophoresis. Pathogenic amoebae always belong to one group and non-pathogenic amoebae always belong to the other group. In 1989 it was discovered that *E. dispar* always differs from *Entamoeba histolytica* by well-determined genetic (DNA) markers. Non-

pathogenic *Entamoeba dispar* never changes into pathogenic *Entamoeba histolytica*. Earlier reports of this appear to be due to laboratory errors: mixed cultures and/or contamination of cultures in the lab. In pathogenic *Entamoeba histolytica* isolates with low virulence and with high virulence can be seen (virulence is a measure of the severity of illness which certain strains can cause in certain circumstances). The degree of virulence is variable, because this is determined by several parameters, including the environment (in contrast to properties which are genetically determined). Isolates with low virulence are non-invasive, while isolates with a high degree of virulence are invasive.

Motility of Entamoeba histolytica

E. histolytica trophozoites are highly motile. The fuel for this constant motion comes from the anaerobic conversion of glucose and pyruvate to ethanol. *E. histolytica* has no mitochondria (probably through secondary loss). Many of its metabolic enzymes seem to be of prokaryotic origin, possibly acquired from the lateral transfer of genes from bacteria.

Life Cycle and transmission

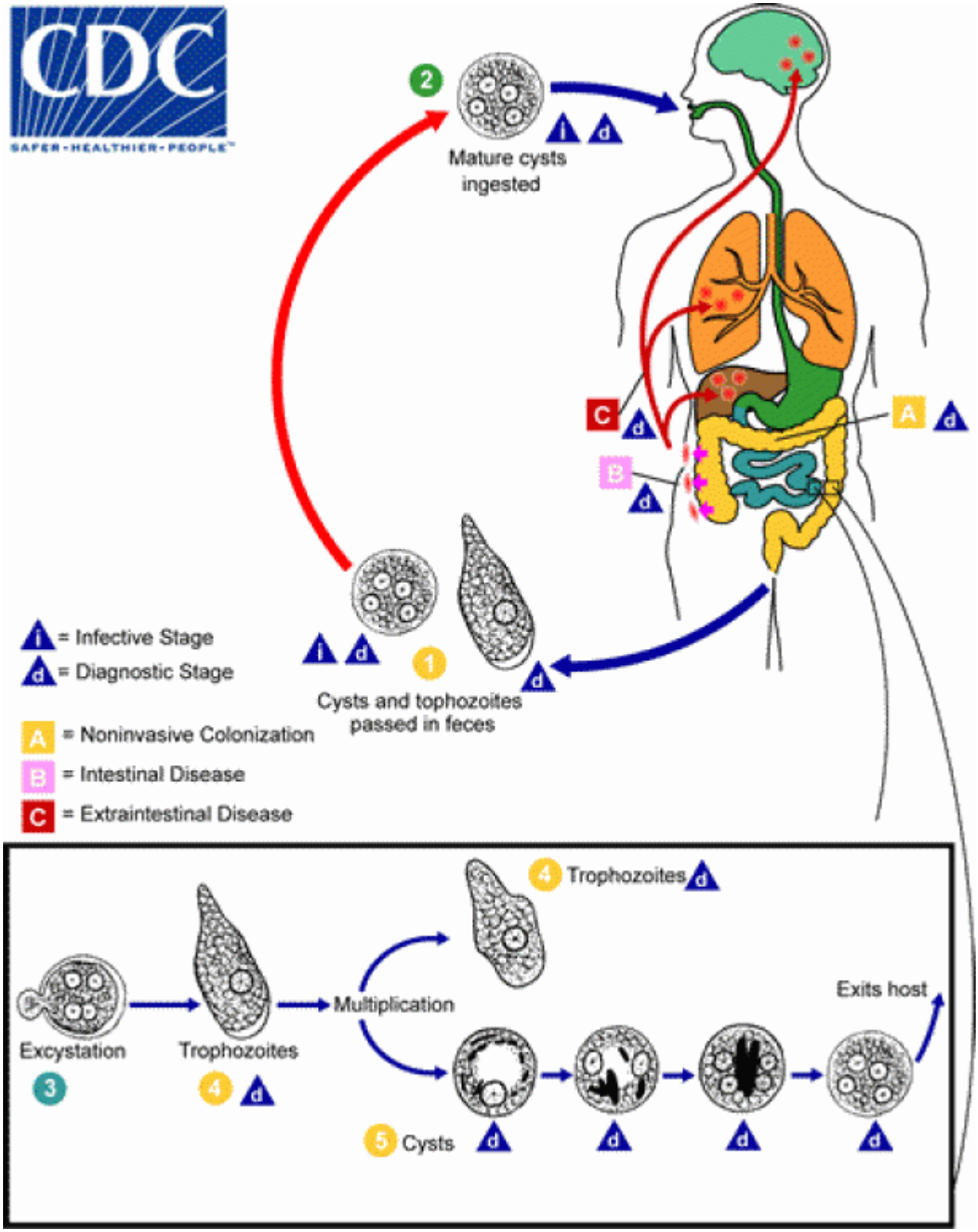
Infection is caused by ingestion of *E. histolytica* cysts. One cyst develops in the small intestine into 8 motile trophozoites (one trophozoite with 4 nuclei divides 3 times and each nucleus divides once to produce 8 trophozoites from each cyst) which then find their way into the colon. The trophozoites multiply by asexual reproduction and in turn produce cysts, which are then excreted with the faeces. The cyst is quite resistant and can survive for a long time in the outside world. Excreted trophozoites die quickly and therefore are not responsible for transmission. Cysts of *E. histolytica* are never found in tissues. The parasite is transmitted feco-orally as a cyst, usually from person to person. Transmission via water also occurs. Dogs, cats, rats, pigs and monkeys may become infected but do not form a significant animal reservoir (Note: kittens were used by E. Brumpt as a very susceptible animal model to test the pathogenicity of amoebae). Flies and cockroaches may carry cysts. Their role in transmission has not been properly investigated but is probably of minor importance. The main source of infection is humans. Amoebiasis is thus not a zoonosis. Infection via sexual intercourse is rare (via anal contact). The latter method of transmission may result in severe and mutilating lesions of the genitals.

Entamoeba histolytica is considered to be an asexual organism, but many mysteries persist. Some pieces of evidence don’t fit with this asexual idea, such as the appearance of putative heterozygous populations after mixing homozygotic populations for certain isoenzym classes. Also, *E. histolytica* has

the full complement of meoisis genes, which one would expect to have decayed over time if the organism abandoned the sexual life cycle.

Prevention

Amoebic cysts are resistant to normal chlorination of drinking water. Boiling and filtering drinking water eliminates the parasite. Large scale prevention depends mainly on improved sanitation and hygiene. No vaccine is available. Amoebiasis is not an opportunistic infection in HIV patients.



Entamoeba histolytica Life Cycle (courtesy of CDC)

LAST UPDATED BY ADMIN ON JULY 13TH, 2022

Intestinal amoebiasis

Clinical aspects

We can differentiate 4 different situations in intestinal amoebiasis:

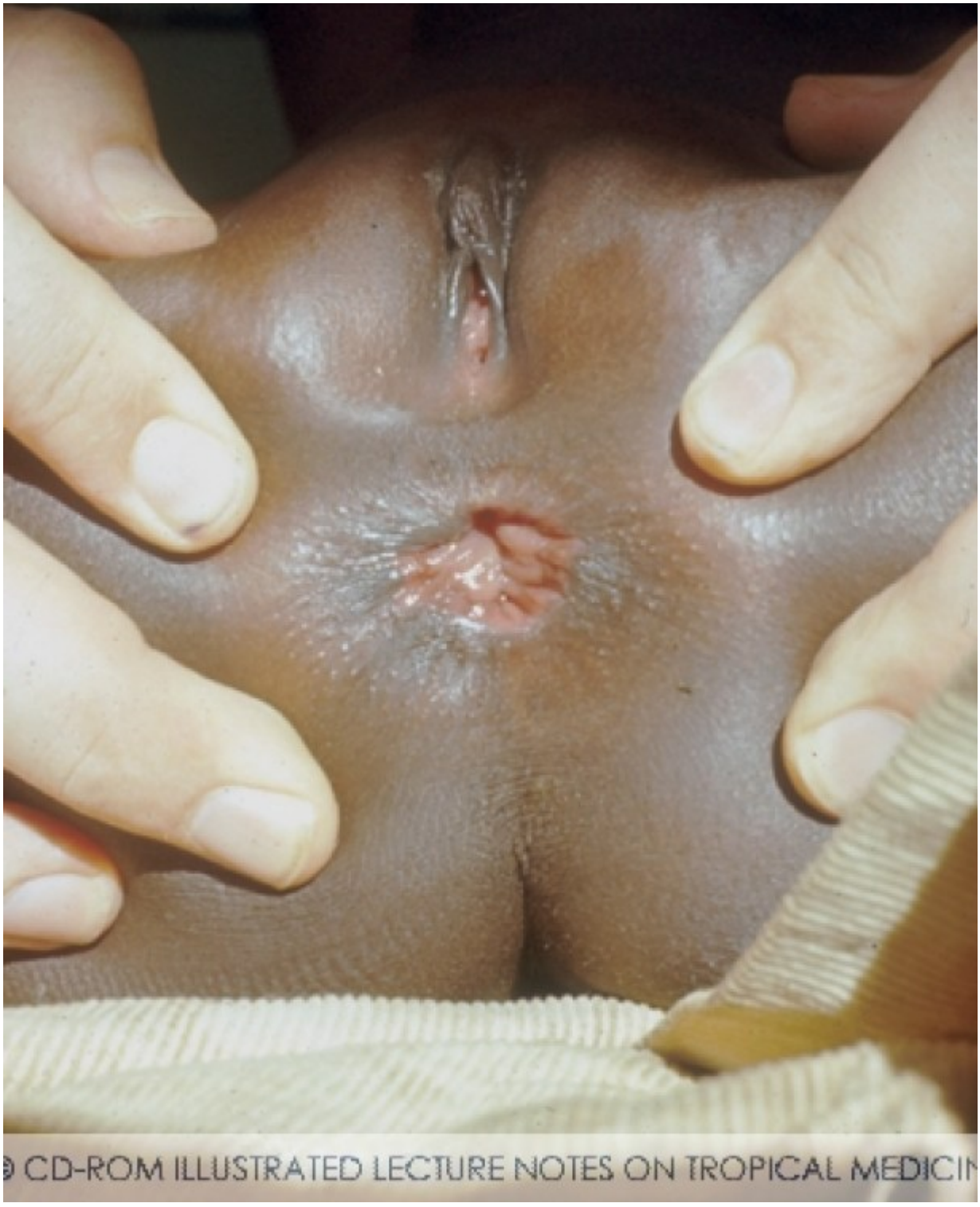
- asymptomatic carriers
- amoebic colitis
- fulminant colitis
- amoeboma

Asymptomatic carriers

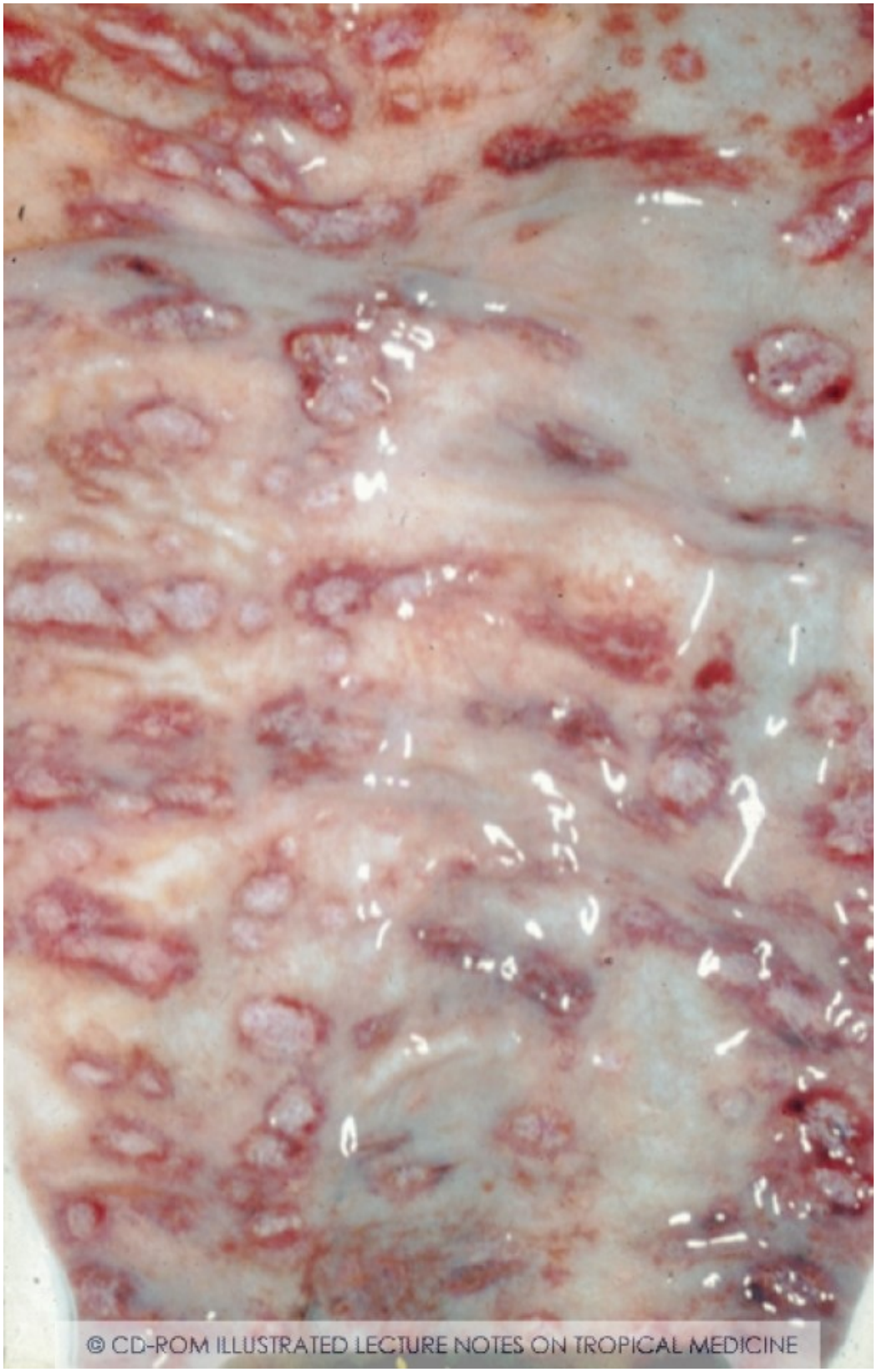
Cysts can sometimes remain in the intestinal lumen for years without causing any damage: the patient is then an asymptomatic carrier. The majority (90%) of patients fall into this group. Asymptomatic carriers have by definition no symptoms of amoebiasis. These persons can be detected by faeces analyses. This may show cysts of non-pathogenic *E. dispar* or of potentially pathogenic *E. histolytica*, which for unknown reasons is not invasive. Differentiation with cysts of *Entamoeba coli* (which are larger and have 8 nuclei) is important. *Entamoeba coli* is not pathogenic.

Amoebic colitis

The incubation period of amoebic colitis varies greatly. When *Entamoeba histolytica* penetrates the intestinal mucosa (becomes invasive) it produces ulcerations of the colonic mucosa [Gr. histo-lytica, i.e. referring to breaking down tissues]. The ulcerations are sharply defined and have eroded undermined edges. This is expressed clinically as abdominal pain, diarrhoea with blood in the faeces, and only moderate or no fever, with good general condition. When the rectum is affected there is tenesmus (painful cramps in the anus). Peri-anal ulcers may occur via direct spread from rectal amoebiasis. The ulcers develop rapidly and are painful. After suffering from amoebic colitis there may be persistent intestinal problems, the aetiology of which is unclear.



Entamoeba histolytica rectitis, with spread to the perianal skin. Copyright prof Gigase, ITM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Entamoeba histolytica colitis. Notice the typical skipping lesions. Copyright ITM

Fulminant colitis

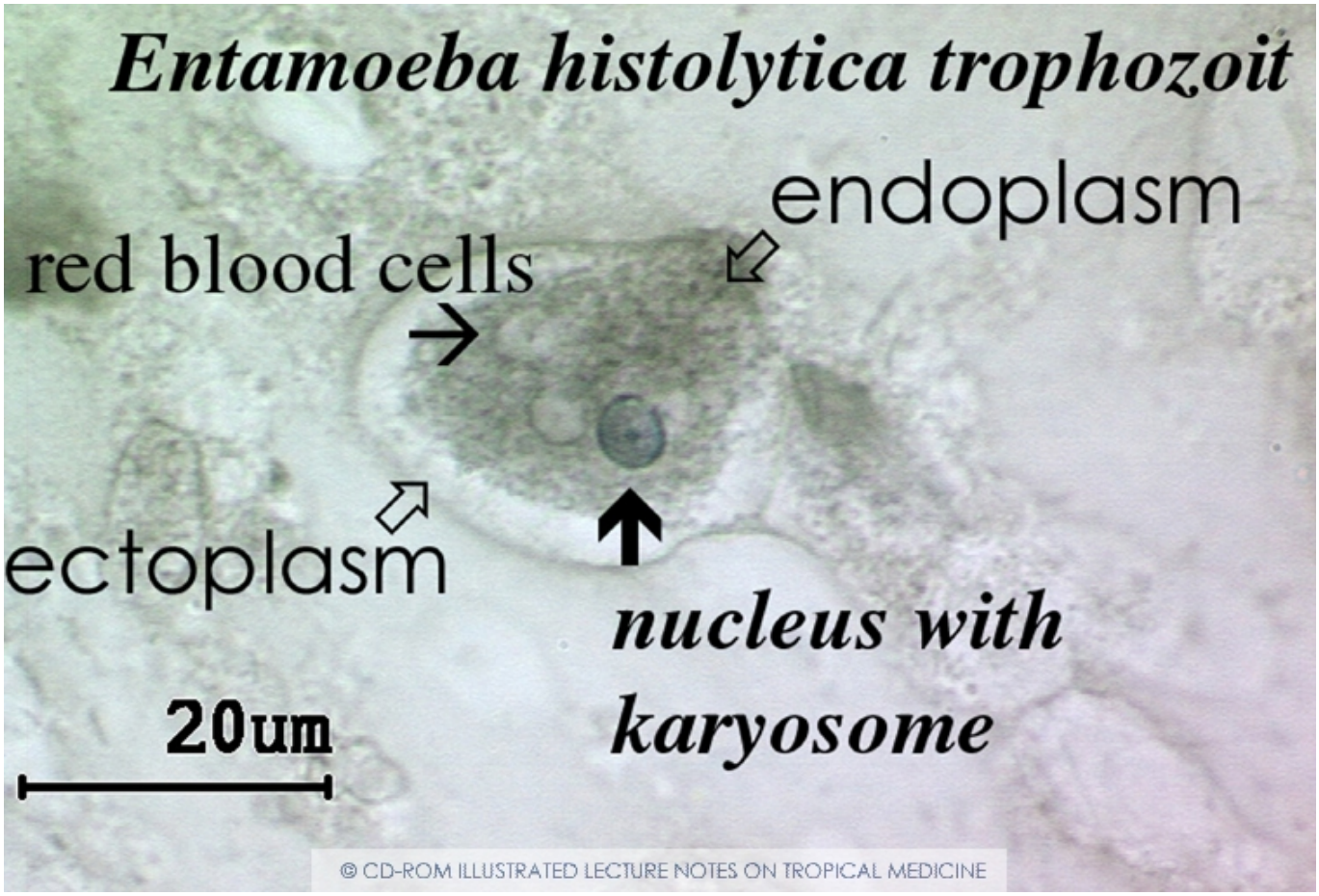
There is sometimes a fulminant course with high fever, a severely ill patient, intestinal bleeding or perforation of the colon. A slow seepage of intestinal content into the peritoneum is very likely in a severely ill patient whose condition deteriorates progressively, together with the formation of ileus (intestinal paralysis) and a distended abdomen. A fulminant course may occur if patients are treated with steroids or other immunosuppressive drugs (e.g. if amoebic colitis is wrongly thought to be Crohn's disease or haemorrhagic ulcerative colitis) and sometimes in very young children and elderly.

Amoeboma

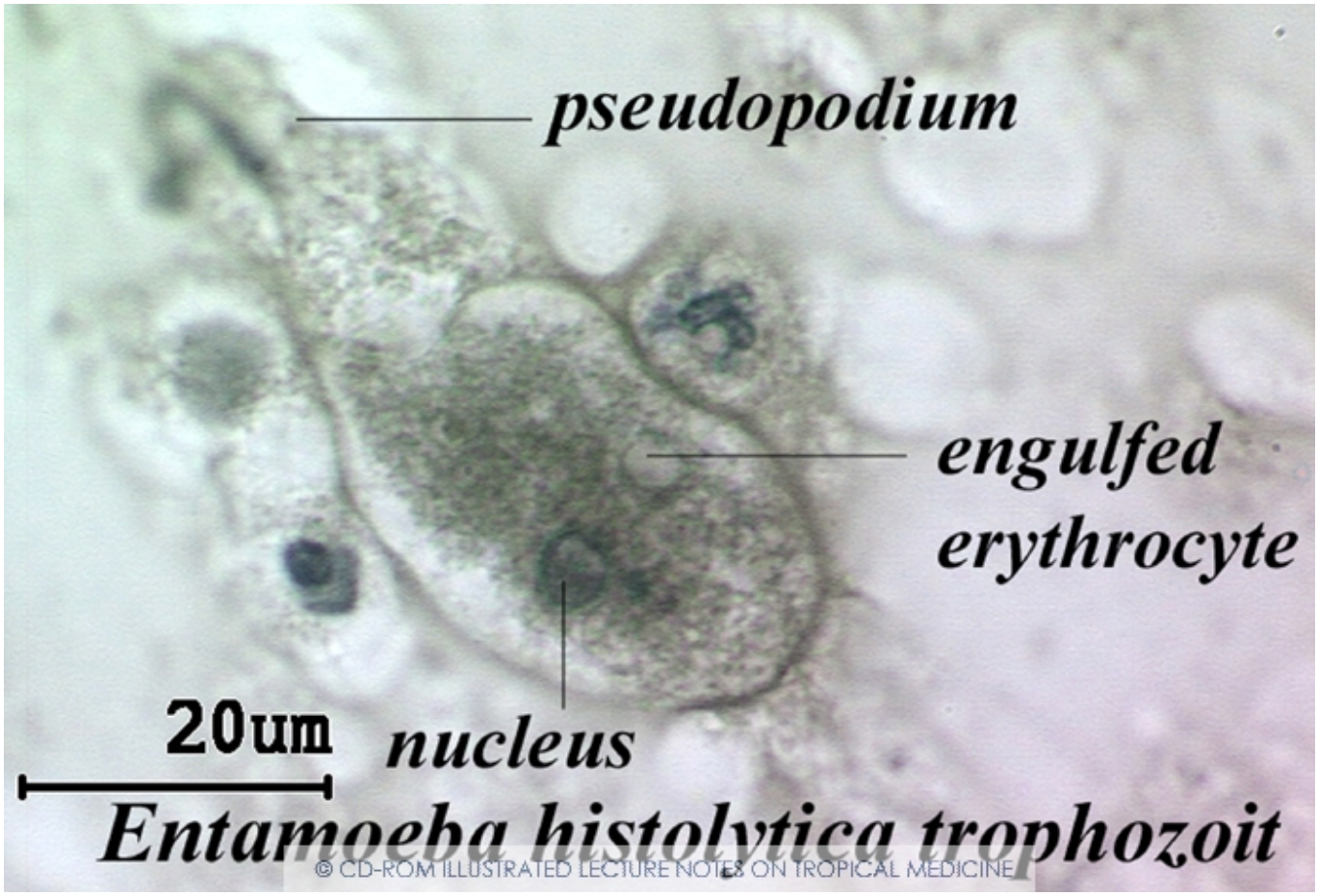
In 1% of patients an inflammatory thickening of the intestinal wall occurs. A mass may then be palpated (amoeboma). The diagnosis may be made via biopsy. The inflammatory mass may mimic colon carcinoma. Countless trophozoites are found in the tissues (never cysts). Correct therapy produces a pronounced reduction in the volume in approximately 3 days.

Diagnosis

When amoebic dysentery is suspected, a fresh faecal sample or a swab from a rectal ulcer should be examined under a microscope. If examined quickly (a fresh stool, still warm) the colourless motile trophozoites can be seen. Motility disappears when cooled, and the parasites are then difficult to recognize. They should be differentiated from actively motile macrophages. The trophozoite (motile form) has one nucleus. When colourless this nucleus is scarcely if at all visible. Once stained the nucleus is moderately visible. Lugol staining kills the parasite almost immediately (motility disappears). Stained *Entamoeba histolytica* trophozoites have a transparent outer border (ectoplasm) and an opaque inner border (endoplasm). The trophozoite measures 20 to 40 µm and may contain red blood cells (unlike other amoebae). The last detail is probably pathognomonic for pathogenic *Entamoeba histolytica,* but is not always present and this statement is contested by some.



Entamoeba histolytica trophozoite. Morphologically, it is only possible to differentiate Entamoeba dispar from E. histolytica if the trophozoite contains engulfed red blood cells. Only E. histolytica is haematophagous, although this statement is contested. Copyright ITM



Entamoeba histolytica trophozoite. Copyright ITM

The cysts have 1, 2 or 4 nuclei and measure 8 to 15-20 µm. The nuclei are best revealed by means of an iodine stain. They have a dark circumference and a dark central point (karyosome), these features are helpful in distinguishing with non-pathogenic species such as *Entamoeba coli*. Iodine staining can also detect glycogen (brown) in young cysts. Fresh cysts of *Entamoeba histolytica* also contain what are called chromatoid bodies. These are squat, oval inclusions which can easily be detected (black) with an iron-haematoxylin stain (not with iodine stain). They are not present in *Entamoeba coli* or *Endolimax nana* cysts. In active dysentery, often no cysts are found in the faeces, but if there is little diarrhoea, the parasites have time to encyst. Since excretion of the parasites is intermittent, it is best to carry out 3 different stool analyses before deciding upon a negative result.

Antigen detection is sensitive, specific, rapid, easy to perform and can distinguish between E. histolytica and E. dispar. Stool and serum antigen detection assays that use monoclonal antibodies to bind to epitopes present on pathogenic E. histolytica strains (but not on non-pathogenic E. dispar

strains) are commercially available for diagnosis of E. histolytica infection. Detection of parasitic DNA or RNA in faeces via probes can also be used to diagnose amoebic infection and to differentiate between the different strains. PCR is about 100 times more sensitive than faecal antigen tests.

Intestinal amoebiasis: Differential diagnosis

The intestines may contain several species of harmless commensal amoeba. Differentiation with these other non-pathogenic amoebae is important; they include:

Iodamoeba butschlii : mononuclear cysts, big glycogen supply

Entamoeba hartmanni : small cysts with four nuclei

Endolimax nana : smaller round or oval cysts with 2-4 nuclei (measuring 6-12 µm) and slow-moving trophozoites (L.: limax =slug)

Entamoeba coli : larger cysts containing 1, 2, 4 or 8 nuclei

Entamoeba dispar is a special case (see above)

In dysentery it is important to distinguish between bacillary and amoebic dysentery since their treatment is completely different. A diagnosis may be made clinically but it is best to confirm this by microscopy as there is partial clinical overlap of the two diseases.

Balantidium coli is a pathogenic ciliate which can cause severe colitis. This illness is very similar to intestinal amoebiasis and the diagnosis can only be made by faeces examination. Treatment is with tetracyclines or metronidazole.

Pseudomembranous colitis is caused by infection with toxicogenic *Clostridioides difficile*. These bacteria can be selected out and can proliferate after administration of certain antibiotics. Metronidazole is a good treatment in this case. Vancomycin is equally effective but will not be given in third world countries in view of its high cost. A related bacterium, *Clostridium perfringens*, can cause necrotizing colitis (necrotic enteritis, Pigbel syndrome). This disorder has an acute course and is very severe.

Sometimes gonococcal proctitis or lymphogranulomatosis venereum (due to *C. trachomatis*) can be confused with amoebiasis. There are then no proximal intestinal lesions and culture of the mucus or

PCR methods provide a diagnosis. Crohn's disease and ulcerative colitis are rare in the tropics. Radiology and biopsies are essential for their diagnosis.

Bacillary dysentery	**Amoebic dysentery**
Acute onset	Gradual onset
Poor general condition	General condition normal
High fever	Little fever (adult)
Severe tenesmus	Moderate tenesmus
Dehydration frequent	Little dehydration (adult)
Faeces: no trophozoites	Trophozoites present
Faecal culture positive	Faecal culture negative

Treatment

Asymptomatic carriers

Since high percentages of the population may be cyst carriers (e.g. 10%) there is little point in treating cyst carriers found by chance in an endemic region. In any case, 90-95% of these people are infected with the non-pathogenic *Entamoeba dispar*. If this is nevertheless desired (e.g. in people who prepare food) paromomycin (Gabbroral®, Humatin®) is indicated. Diloxanide furoate (Furamide®) and iodoquinol (Intetrix®) can be used. In regions of low endemicity it may make sense to treat asymptomatic carriers to prevent transmission and to prevent possible development of later invasive amoebiasis (even if this risk is low). 5-Nitro-imidazoles are not effective against cysts.

Amoebic colitis

Parasites in the tissues (intestinal wall) can be treated with nitro-imidazoles, such as metronidazole, secnidazole, ornidazole or tinidazole. Secnidazole has the longest serum half-life (17h) compared with 12-13h for tinidazole, 11h for ornidazole and 8h for metronidazole. The dose of metronidazole (Flagyl®) is 500 mg q.i.d. for 5 or more consecutive days (adults). Tinidazole (Fasigyn®) is more expensive but has fewer side effects. Two grams per day x 3 days is sufficient for amoebic colitis.

Ornidazole 500 mg b.i.d is given for 5 days. Alcohol is forbidden during treatment due to disulfuram effect with severe nausea. These drugs are rapidly absorbed in the proximal intestine. For this reason, they are insufficiently active upon the parasites in the distal intestinal lumen.

The latter are treated with paromomycine (Gabbroral®, Humatin®) 10 mg/kg or 500 to 750 mg t.i.d. for 7 days. These drugs are not active against parasites in the tissues. The two drugs thus complement each other. An alternative contact amoebicide is diloxanide furoate (Furamide® =a contact amoebicide). Dose: Furamide® 500 mg t.i.d. for 10 days (adults). Children: 30 mg/kg/day. Nitazoxanide (Alinia® 500 mg tablets and 100mg/5 ml oral suspension) proved very effective as a tissue amoebicide and as a luminal amoebicide. However it is not readily available and is extremely costly.

LAST UPDATED BY ADMIN ON JULY 13TH, 2022

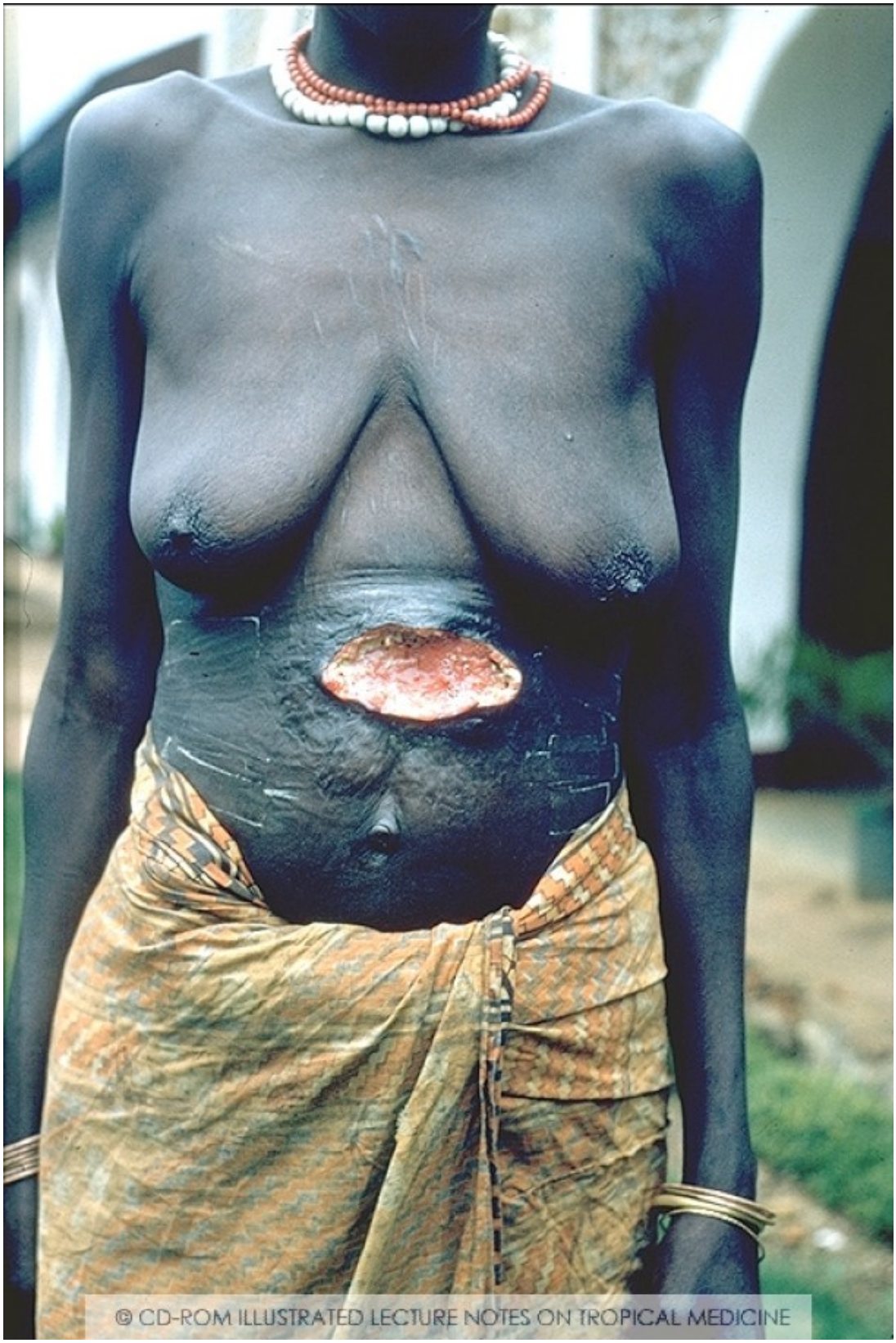
Hepatic amoebiasis

Open a section to read more.

General

If amoebae are transported with the venous blood from the intestinal wall to the liver, an abscess in the liver may be formed: hepatic amoebiasis. If the abscess is adjacent to the fibrous capsule of the liver, adhesions are formed. A subphrenic abscess is less frequent than direct perforation of the diaphragm with empyema or fistula formation to the bronchi. Perforation to the peritoneum is rare. Perforations of the intestine, biliary ducts or navel with secondary phagedenic ulceration of the skin are more frequent than generalized peritonitis. Abscesses of the left hepatic lobe may perforate the pericardium in a life-threatening manner.
[The term “abscess” is not correct here in the strictest sense as this is not a collection of pus cells (white blood cells). It is local cytolysis of liver tissue.]

Clinical aspects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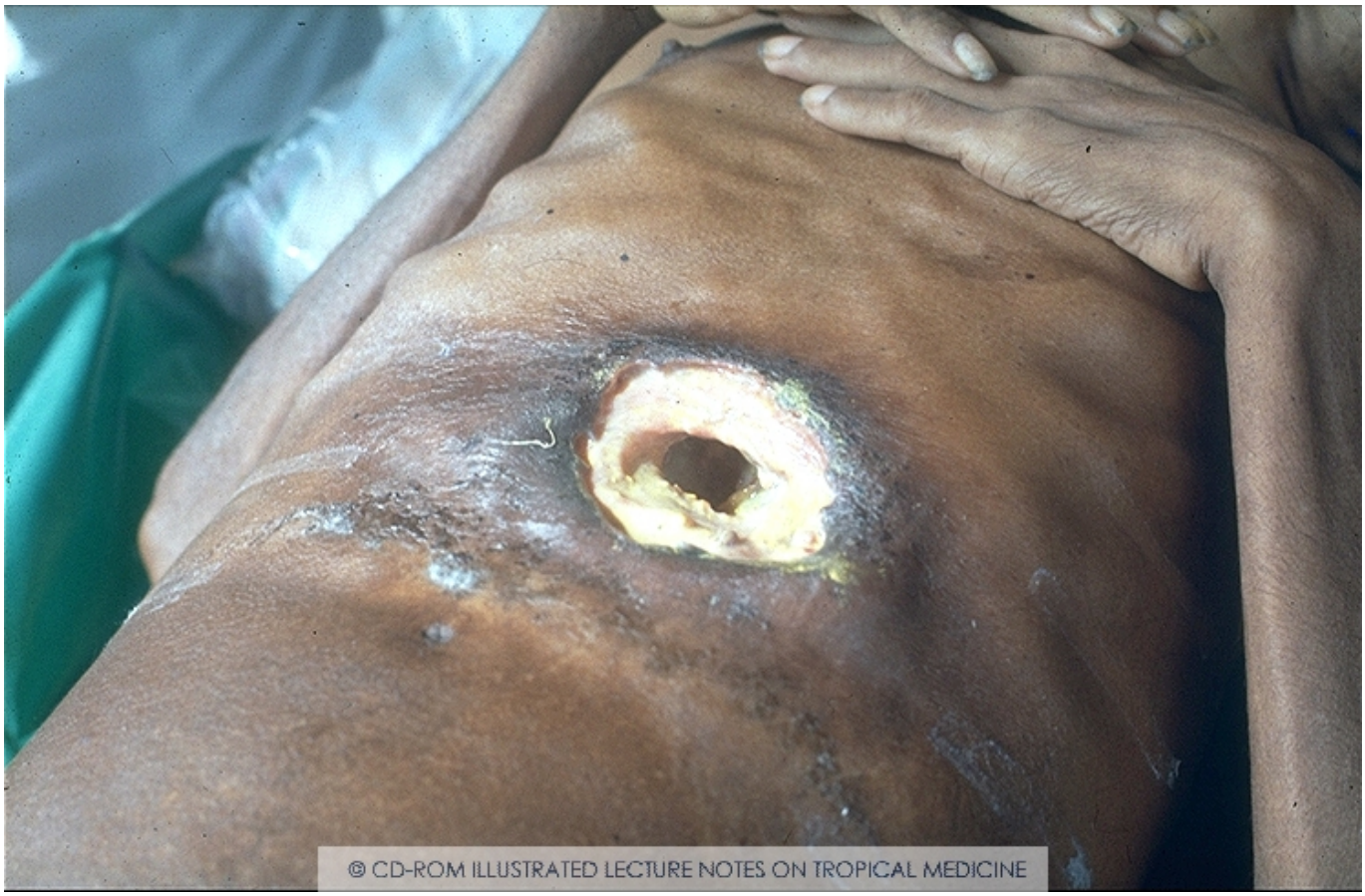
Liver amoebiasis with perforation of the abscess through the abdominal skin. Photo Prof. Gigase. Copyright ITM



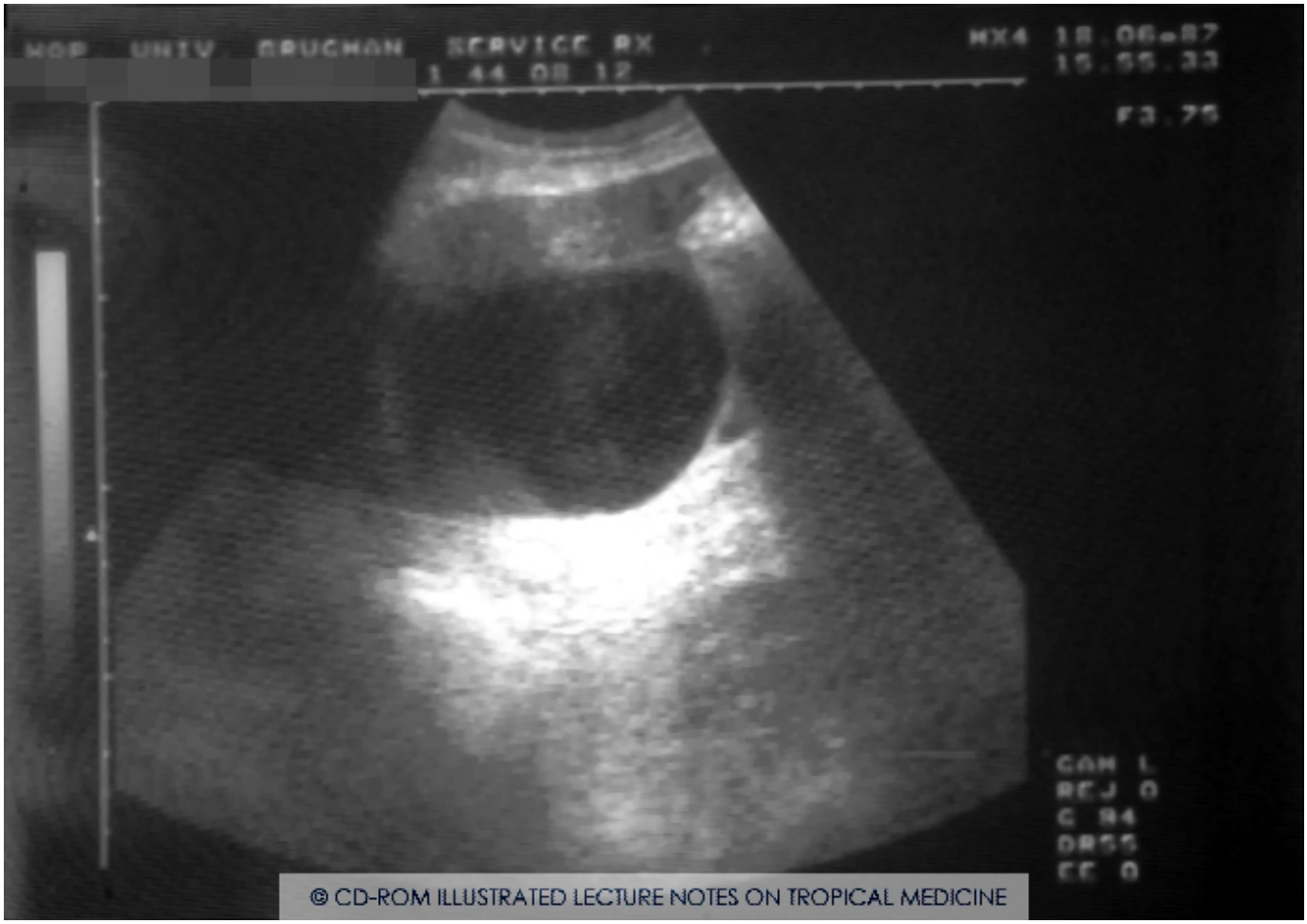
Liver amoebiasis with perforation of the abscess through the abdominal skin. Photo Prof. Gigase. Copyright ITM

Upon physical examination, there is fever and pain in the liver region (pain upon palpation or percussion). The pain increases during deep inspiration or coughing. If the abscess volume is significant, the liver will be enlarged, and the diaphragm will be elevated (percussion, auscultation, chest X-ray). The patient may develop pain in the right shoulder (referred pain). Dullness upon percussion of the base of the right lung may be due to the elevation of the diaphragm, reactive pleural fluid or breakthrough to the pleura, or atelectasis of the lung. Jaundice occurs in a minority (6-29%) of patients and tends to be a very late symptom. Jaundice can result from biliovascular fistula (with backflow of the bile into the hepatic veins) or compression of bile ducts. The abscess spreads until it breaks through to the surroundings: the pleura (empyema), the lung, the pericardium or the

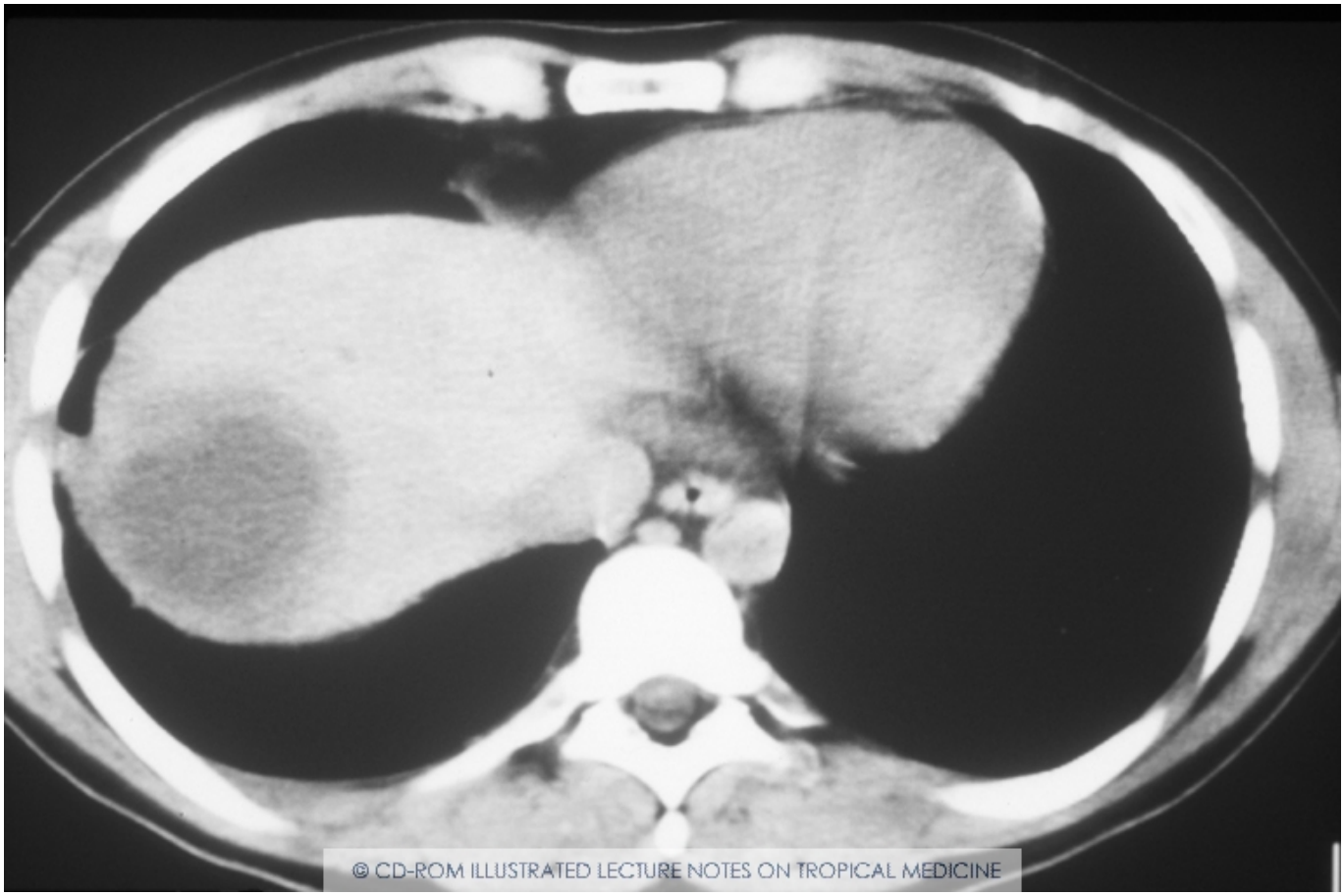
skin. If fistulisation to the skin occurs, there may be a swift progression of a painful skin ulcer. Untreated amoebic liver abscess is often fatal.

Diagnosis

The diagnosis of a hepatic abscess may be suspected from clinical findings. Leukocytosis will be high (and there is no eosinophilia). Ultrasound and serology (ELISA, Latex agglutination) can confirm the diagnosis but are often unavailable. Antibodies will remain present for a long time -often years- after infection. An amoebic abscess of the liver will contain necrotic liver tissue at its center. Upon aspiration, this often has a dark brownish-red color called “anchovy” or “chocolate” pus, but the pus may also be yellow, grey or greenish. The pus has no offensive odor, unlike most bacterial (anaerobic) abscesses, which is an important difference. The abscess wall contains trophozoites, but the necrotic liver tissue does not. Local edema or bulging of the skin with or without fluctuation indicates the proximity of the abscess and the site where a puncture can be carried out. In case of doubt, a trial therapy quickly produces a spectacular improvement. Fewer than 20 % of people with a hepatic abscess have Entamoeba histolytica in the feces. Therefore, the absence of amoebae in the stools does not rule out the diagnosis.



Entamoeba histolytica. Ultrasound of the liver showing an amoebic liver abscess. Copyright ITM



Liver abscess due to infection with Entamoeba histolytica. CT scan of the liver shows a circular necrotic area. Copyright ITM

Hepatic amoebiasis: Differential diagnosis

1. Pyogenic/anaerobic hepatic abscess: stinking pus, poor general condition, often icterus, negative serology, sometimes portal-of-entry in the intestine (e.g. colon tumor, appendicitis).
2. Hydatid cyst: slow development, no fever, no toxemia, serology positive for *Echinococcus*, sometimes calcifications on abdominal X-ray, no leukocytosis. Ultrasound may show daughter cysts.
3. Biliary cysts: ultrasound shows a thin wall with anechoic content, otherwise asymptomatic.
4. Haemangioma: hyperreflective on ultrasound, otherwise asymptomatic. On CT scans with dynamic sequences, there is a centripetal staining with a delayed isodense appearance to the surrounding liver tissue. On MRI, a haemangioma is extremely hyperreflective on T2-weighted images (T2 = “water images”).

5. Metastases: ultrasound shows generally (but not necessarily) irregular and hyperreflective structure; central necrosis may occur. Frequently peripheral edema.
6. Hepatoma: no fever or toxemia, no response to trial therapy, elevated alpha-feto protein, negative serology, often related to HBV or HCV; biopsy is diagnostic.

Treatment

An amoebic liver abscess is treated with **metronidazole** for 10 days (often initially IV) or **tinidazole** 2 gr daily for 5 days, followed by **paromomycin** or **diloxanide furoate** for 10 days. The latter is to destroy any amoebae in the lumen of the intestines. If the diagnosis is known, aspiration is only carried out for very large abscesses or if there is a risk of breakthrough. Surgery is indicated if the abscess ruptures (e.g. into the peritoneum). If a relapse of the abscess occurs, this usually happens within two months.

Amoebiasis of other organs

Amoebiasis of the lungs is generally the result of the spread of an amoebic abscess of the liver, which perforates through to the base of the lung. Breakthrough to a bronchus may occur. The prognosis is usually favorable. Amoebic pleuritis (empyema) is an unpleasant complication because of the need to drain the empyema. Other locations are rare and include:

Primary amoebiasis of the lung without prior hepatic amoebic abscess.

Abscesses in muscles, e.g. the thigh.

Ulceration of the skin of the lower limbs by amoebae could result from superinfections of skin wounds due to scratching with dirty nails.

Urogenital forms, either due to fistula formation of intestinal lesions to the bladder or of peri-anal ulcers to the vagina and cervix of the uterus. Location on the penis if the partner has ulcers of the vagina/cervix or anal ulcers.

Parasites may appear elsewhere and lead to abscesses in other organs, e.g. the brain.

LAST UPDATED BY ADMIN ON OCTOBER 6TH, 2023