CHAPTER-II - Antiamoebic drugs - A Review
2.1. **Review of anti amoebic drugs**

The modern therapy of amoebiasis includes the treatment not only of patients with acute amoebic dysentery but also of those persons who have intestinal amoebiasis without symptoms. The asymptomatic passer of cysts is a potential source of infection to himself and others and is an important public health problem. If the acute attack is not treated properly, the condition may improve temporarily and assume the chronic form. Amoebic abscesses of the liver, brain and lung may develop in carriers who have had few or no previous symptoms of intestinal amoebiasis. Though a number of drugs are available, each drug is plagued with individual limitations such as some adverse actions, toxicities and other undesirable features.

Metronidazole has become a drug of choice in the therapy of amoebiasis. It is easily administered and is rapidly acting. It has become the mainstay of treatment of all forms of amoebiasis, except asymptomatic cyst passers. In addition to metronidazole, the physician has at his disposal several classes of amoebicidal agents, including emetine, chloroquine, antibiotics, halogenated oxyquinolines, organic arsenicals and synthetic organic compounds of various types. These drugs differ in their usefulness depending upon the character of amoebic infection. Emetine, formerly known as specific cure for amoebic dysentery, is of no use in eradicating the cysts; however, still it is the most effective drug for rapidly controlling the
symptoms of severe intestinal infections. It is also of great value in treatment of amoebic liver abscesses and amoebic involvement of lung, brain, skin and other tissues. Other drugs used in amoebiasis dysentery, Dehydroemetine is preferred by some physicians because of its lesser toxicity. Chloroquine is of value only in the treatment of liver abscess. Chloroquine has the advantage of being much less toxic than emetine. The other amoebicides are useful only in intestinal amoebiasis and are useless for amoebic hepatitis and amoebic liver abscesses. The arsenicals are particularly contraindicated in cases with hepatic involvement.

2.2. Drugs used in amoebiasis

Drugs of both synthetic and natural origin are being used in the treatment of amoebiasis. They are discussed in detail in the following section.

2.2.1. Drugs of natural origin

a) Ipecac

Ipecac (ipecacuanha, "Brazil root") was long used in Brazil in the treatment of diarrhoeas. It was sold as a secret remedy to French government in 1658, and its use in dysenteries rapidly spread throughout Europe and India. Its employment was entirely empirical until 1912, when Vedder demonstrated the in vitro efficacy of emetine against Entamoeba histolytica and suggested that ipecac be used in amoebic infections (Craig, 1944).
The source of Ipecac is the dried root or rhizome of *Cephaelis ipecacuanha* or *acuminata* karsten plants native to Brazil and Central America but also cultivated in India and Malaysia.

The efficacy of Ipecac in amoebic infections depend upon its content of alkaloids, the principal one being emetine and cephaeline. Both are amoebicidal, but emetine is more active. Cephaeline is more toxic than emetine except for the heart and causes more nausea and vomiting. Emetine constitutes more than one half of the total alkaloid content of Ipecac.

Ipecac is official in the U.S. Pharmacopoea in powder form and as a syrup. It is not used in the modern therapy of amoebiasis because its administration results in severe gastrointestinal irritation, nausea and vomiting.

Ipecac probably acts both centrally and locally in the enteric tract to cause vomiting. Ipecac syrup, U.S.P. is often used to induce vomiting in cases of poisoning by orally ingested drugs and other compounds.

b) **Emetine**

*Its derivatives and preparations*

The first landmark in therapy of amoebiasis was the introduction of emetine hydrochloride by Rogers (1912). Emetine hydrochloride, U.S.P. is a hydrated hydrochloride of an alkaloid obtained from ipecac or prepared synthetically by synthetization of Cephaeline. Emetine has the following structure.
Emetine hydrochloride is a white crystalline powder; it is freely soluble in water and alcohol. The drug is very irritating and should not be allowed to come in contact with mucous membranes, especially of conjunctive. Its amoebicidal activity in vitro varies from 0.2 to 60 µg/ml depending upon the technique used; but most test methods gave the end point between 1-10 µg/ml (Woolfe, 1963).

In experimental animals, the activity was found to be variable. Jones (1947) showed that in rats it was effective from 2-20 mg/kg in a single dose therapy. It was totally ineffective in kittens (Clampit, 1948) and effective but not curative in dogs (Thompson and Lilligren, 1949). Its effectiveness in hepatic amoebiasis was shown by Thompson and Reinertson (1951) and Williams (1959).

Emetine is highly effective in acute amoebic dysentery when given intramuscularly at the dose of 60 mg/day. It is generally given daily until the acute symptoms subside. It should never be administered in dosage larger than 60 mg/day.
or for periods longer than 10 days. Although the clinical symptoms are generally improved and both trophozoites and cysts disappear from the stools during emetine medication in acute amoebic dysentery, cysts reappear in approximately 50% of cases at varying periods after the therapy has been discontinued. Emetine therapy usually does not eliminate the cysts. Such patients often become asymptomatic carriers. Treatment of asymptomatic carriers with emetine is unsuccessful. Emetine has a great value in treatment of amoebic abscesses and amoebic hepatitis.

Emetine should not be used in organic disease of the heart or kidneys. The drug must be used in with considerable caution in aged or debilitated individuals. It is also contraindicated in children unless to other measures. It is best not employed during pregnancy (Rollo, 1975).

Emetine causes degeneration of the nucleus and reticulation of the cytoplasm of amoebae; it is thought to eradicate the parasite by interfering with the multiplication of trophozoites. Later work showed that emetine prevented protein synthesis by inhibiting the translocation of peptidyl-t-RNA from the acceptor site to the donor site on the ribosome (Huang and Grollman, 1970).

Emetine causes variety of toxic effects that may occur with any dose levels depending on individual susceptibility to the drug. Large dose produce lesions in the heart,
kidney, liver, intestinal tract and skeletal muscle. It produces cardiotoxic effects like pulse irregularity, low blood pressure, myocardial degeneration etc. (Powell, 1967). The long persistence of the alkaloid in the body is the basis for cumulative toxicity.

The stereo isomers of emetine are less active than emetine itself. Dobell and Laidlaw (1926) found emetine and cephaeline to be more active than isoemetine, demethoxyemetine, normetine, psychotrine or methylpsychotrine in vitro.

c) Dehydroemetine

Since the discovery of emetine, a number of attempts have been made to synthesize emetine and its derivatives. The synthesis of emetine by Brossy et al. in 1959 lead to the ready availability of various analogues. Of these, dehydroemetine has been studied extensively. These studies suggest that it is as effective as emetine but less toxic (Johnson and Neal, 1968). In vitro dehydroemetine is as amoebicidal as emetine. In experimental infection in rats the dextrorotatory isomer is much less effective than either the naturally occurring levorotatory emetine or levorotatory dehydroemetine (Johnson and Neal, 1968).

In clinical trials, dehydroemetine is somewhat less effective than emetine but this is more balanced by less toxicity. In adults 80 mg daily of dehydroemetine is as
effective as 60 mg daily of emetine. The recommended dosage is a single intramuscular or subcutaneous injection of up to 1.5 mg/kg given for 10 days. The total dose should not exceed 1.0 gm. The course of treatment should not be repeated in less than 14 days. The toxicity of dehydroemetine is less than emetine possibly because it is excreted more rapidly (Schwartz and Herrero, 1965).

Side effects of dehydroemetine are the same but its cardiotoxic effect is less frequent and less severe than emetine. In general, it is now accepted that dehydroemetine does not offer any real advantage over emetine.

d) Emetine Bismuth Iodide

Dumez (1915) used emetine bismuth iodide first time in amoebiasis in Phillipines. It contains about 25% anhydrous emetine and 20% bismuth. It is an orange powder insoluble in water. This is the only oral preparation of emetine which is useful against amoebae moving loose in the bowel. It can be used for the treatment of cyst passers (Woodruff, 1959). The dose is 0.2 gm daily for 12 consecutive days. The toxicity is same as emetine. Its status is controversial. In some countries, it is widely used in conjunction with other amoebiacides.

e) Conessine and Kurchi

Extracts of Holarrhena tissues have been used for many years for the treatment of dysentery and the use of 'Kurchi' has been traditional in India. Holarrhena antidysenterica
is a small deciduous tree with white flowers. It is mainly found in Himalaya. It is also found throughout the dry forests of India even as far as South Travancore.

The bark of both stem and roots, similarly the seeds are the important medicines of the 'Hindu Material Medica'. The bark is considered to be a powerful antidiysenteric agent.

Conessine is the principal alkaloid of *H. antidysenterica*. Conessine is a steroidal alkaloid with following structure -

The crystalline alkaloid is sparingly soluble in water, but the more commonly used dihydrochloride or dihydrobromide are soluble in water.

Relatively few laboratory studies of conessine have been reported. Siguier *et al*. (1949a) reported conessine to be about a fourth as active as emetine. Piette (1950) and Bonnin *et al*. (1950) reported similar results. Woolfe (1957) found conessine to be inactive at 100 μg/ml while emetine was active at 2 μg/ml. Clinically 'Kurchi' itself or its preparation Kurchi-Bismuth iodide has given conflicting results.
Leishman and Kelsall (1944) reported Kurchi Bismuth Iodide to be quite ineffective in the treatment of dysentery. According to Rail (1947), even with concurrent administration of carbarsone, the effect was short lived and most patients relapsed quickly. Crosnier et al. (1948) and Durieux et al. (1948 and 1948a) found it to be as effective as emetine in acute or chronic amoebiasis. Siguier et al. (1949b) supported this view but mentioned that larger doses of drug were required as compared to emetine.

Value of the conessine or kurchi extracts lost due to availability of better drugs with less toxic effects. Conessine has toxic effects mainly, neurological. Burn (1915) stated the conessine as the cardiac toxic.

A few derivatives of conessine had been tried in an attempt to overcome the drawbacks of parent alkaloid. Crosnier et al. (1952) reported amino-oxy conessine to be as effective as conessine clinically. According to them, it did not give rise to neuropsychological complications. They suggested that it can be used safely instead of conessine. Muhlpfordt and Martinez-Silva (1956) tested isoconessine and neoconessine in vitro and found them far less active than conessine itself.

f) Glaucarubin (Glaumeba)

Extracts of Simarouba amara have long been used in South and Central America for the treatment of dysentery.
The use of the purified glycoside, glaucarubin is, however, more recent.

Glaucarubin is a crystalline glycoside with a bitter taste. It is slightly soluble in water and stability is greater in acid than in alkaline solutions.

Glaucarubin has only a low order of activity in vitro (Cuckler et al. 1958) and emetine was found to be 2-8 times more potent.

Glaucarubin is more active in experimental animals than might be expected from in vitro results. Cuckler et al. (1958) gave the $\text{CD}_{50}$ in rats as 9 mg/kg but even 50 mg/kg given daily for 3 days did not eliminate the infection from all animals. Two out of three dogs were cured of amoebic colitis by 0.25 mg/kg per day; the failure responded to 0.5 mg/kg per day. Toxicity was relatively low. Rats given 100, 200 or 400 mg/kg per day for 10 days survived; but growth was slightly reduced; dogs did not tolerate doses greater than 6 mg/kg per day continuously but monkeys tolerated more than 100 times the effective therapeutic dose in man.

Van Assendelft et al. (1956) and Woodruff et al. (1956) reported cure rates of 70-80% following adequate dosage of glaucarubin, and side effects were only slight. Del Pozo and Alcaraz (1956) found the drug to be even more effective, and there were no toxic signs nor changes in the blood picture. The normal dose is about 3 mg/kg per day, but this is reduced if there are signs of intolerance.
It has been recommended that glaucarubin should not be used in patients with anaemia or low white cell counts and all patients treated with the drug should have periodic blood cell counts.

g) **Yanatoside, Kosam, Ya-Tan, Tzu**

Ya-tan-tzu, an extract of *Brucea juvanica* or *B. sumatrana* sometimes known as Kosam has been used by Chinese herbalists for dysentery. Ground kosam seed was shown to be effective *in vitro* against *Entamoeba histolytica*, but although treatment with kosam of patients with amoebiasis brought about symptomatic relief, there were many relapses (Kuzell et al. 1941). Liu Shao-Kwang et al. (1941) reported that Yatanine, a white base prepared from seeds of *B. juvanica*, was specific in the treatment of amoebic dysentery and did not cause vomiting or other symptoms that follows emetine.

In dogs, Ya-tan-tzu was effective but toxic (Chou and Jang, 1949). Smyly (1948) showed that cold aqueous extracts of *B. juvanica* wseeds were highly amoebicidal *in vitro*, but found the powdered seeds to be ineffective both in acute dysentery and cyst passers. Toxic symptoms were common. Chang (1951) reported results of tests on Yanatoside, a colourless crystalline glucoside isolated from the seed kernels.

Huang (1953) isolated a phenolic compound and a glucoside in crystalline form from ethanol and aqueous extracts
of the seeds of *Brucea amarissima*. He found that the phenolic compound had a bitter taste, was soluble in ethanol and insoluble in water, melting point 265-6°C and formula $C_{24}H_{29}O_{10}$.

The glucoside had a bitter taste and was soluble in ethanol and water. Its formula $C_{22}H_{34}O_{11}$.

Chen-yu-sung (1949) found that the active principle of ya-tan-tsu was brucellin, glycoside with molecular weight 332.

Stoecklin and Geissman (1968) isolated from non-lipophilic material from the seeds of *Brucea sumatrana*, a new bitter principle, a lactone m.p. 258-258.5°C but it is not clear whether the amoebicidal activity of kosam is due to such compounds.

In *vitro* Yanatoside was about half as active as emetine but in infected monkeys doses of 12 to 30 mg/kg merely caused temporary improvement. Anderson and Chang (1953) reported Yanatoside to be half to a tenth as active as emetine according to the medium used, a total dose of 16 mg/kg over 5 days was effective in one monkey, but in others there was a temporary effect only. Various toxic symptoms were reported in both mice and monkeys. $LD_{50}$ in mice was $\pm 1.74$ mg/kg.
given intraperitoneally.

Lee et al. (1953) found that a fraction isolated from the alcohol extract of the seeds of *Brucea* spp. was directly toxic to amoebae *in vitro*. They reported that effective results were obtained in 10 human cases of amoebiasis treated orally with 20-80 mg/day for 4-9 days. They reported LD$_{50}$ in mice to be 50 mg/kg.

**h) Quassin**

Amin et al. (1945) reported quassin to be more effective than emetine against *E. histolytica in vitro*. Quassin is one of the bitter constituents of the wood of *Quassia amara* L., Simaroubaceae known in commerce as Surinam quassia. It is obtained by the resolution of the mixture of bitter constituents of quassia wood (London et al. 1950).

The drug was tried clinically in acute amoebic dysentery and results were said to be encouraging.

**i) Henna**

Hanke and Talaat (1961) reported that administration of total leaf powder of henna (*Lawsonia alba*) was effective in clearing the stools of patients of amoebae. Patients who relapsed (on stool examination) remained symptom-free, and a further course treatment was effective in removing all amoebae from the stools. The henna had no effect on the stool flora except for the disappearance of all anaerobic organisms, the
aerobic organisms remaining unaffected. Although the active principle in the plant has not been identified and its mode of action has not been sufficiently clarified, it seems probable that its therapeutic effect is an indirect one acting through the inhibition of the anaerobic intestinal bacteria which are necessary for the well being of the amoebae.

j) **Extracts of Euphorbia Hirta**

Ridet and Chartol (1964) reported antiamoebic activity of alcohol extract of *Euphorbia hirta*. In vitro studies of preparations of *E. hirta* against cultures of *Entamoeba dysenteriae* showed that extracts or decoctions had amoebistatic or amoebicidal activity comparable to emetine. There were no toxic effects in rats and guinea pigs or humans. Alcohol extracts were administered orally to 53 patients with intestinal amoebiasis. The results were excellent and the drug was well tolerated. Two failures were attributed to resistance of strains or to inadequate dosage; a third case had persistent diarrhoea and was refractory to other forms of treatment as well. Chemical analysis of an alcohol extract of *Euphorbia hirta* did not indicate any specific compound responsible for its antidysenteric effect.

Martin et al. (1964) further studied the clinical value of *Euphorbia hirta* extracts. 150 patients with intestinal amoebiasis were treated and cure (rapid clinical relief and the total disappearance of parasites from stools) was obtained in 125, i.e. 83.34%. Best results were claimed in acute cases of short duration.
k) **Decoction of Anemone and Anemohin**

Ming-Shin Kiang et al. (1958) reported the antiamoebic activity of the decoction made by boiling roots of *Anemone chinensis*, and the anemonin which was obtained by neutralisation of the anemone decoction with 1 N NaOH, *in vitro* and *in vivo*.

A 1:40 dilution of anemone decoction completely suppressed the growth of *E. histolytica* in a diphasic medium, *in vitro*, the same effect was obtained with 1:200 dilution of anemonin.

In infant rat caecal model, the drug in the dose of 1.0 gm/kg given orally for 7 days suppressed amoebic growth effectively. The drug produced no toxic effect in mice at the dose of 0.4 ml of 1:2 diluted Anemone root decoction given orally.

1) **Berberine**

It is an alkaloid derived from the Indian medicinal plant *Berberis aristata* Linn (Daru Haridra - in Sanskrit). It has been shown to be useful in the treatment of experimental cholera in the infant rabbit model (Dutta and Panse, 1962). It compares well with chloramphenicol in the chemotherapy of cholera and severe diarrhoea in humans (Lahiri and Duttagi 1967). In 1967, Subbaiah and Amin reported the compound to be amoebicidal. They reported the activity *in vitro* to be 0.5 - 1.0 µg/ml. They found the drug to be effective both in rat caecal and
hamster liver model at 2 mg/kg dose intramuscular or 3 mg/kg if given orally. The drug was direct amoebicidal.

Dutta and Iyer (1967) reported the antiamoebic activity of berberine hydrochloride to be 10 μg/ml which was equal to that of emetine. At 100 mg/kg per day dose of berberine hydrochloride given orally for 5 days was found to reduce 83% of infection in infant rat caecal model whereas emetine was found to reduce infection by 75% at the dose 2 mg/kg given subcutaneously. In hamsters, berberine hydrochloride was found to reduce 80% infection at the dose of 150 mg/kg per day for 4 days given orally whereas emetine reduced 75% infection at the dose of 2 mg/kg given intramuscularly.

But there are no further trials to prove the effectiveness.

m) Miscellaneous plants

A team of scientists of Central Drug Research Institute, Lucknow, has screened a large number of Indian medicinal plants (about 800) under medicinal plants project (Dhar et al., 1968 and Bhakuni et al., 1969). They screened the plants for a number of biological activities. Each plant was extracted with 50% alcohol and the extract was tested. Antiamoebic activity testing was initially done in vitro in modified Boeck and Drbohlav medium (inactivated horse serum
diluted to 1:8 with M/40 phosphate buffer in 0.85% sodium chloride, pH 7.0). Extracts having amoebicidal activity at a concentration of 125 μg/ml or less were then tested in vivo in infant rat model using Jones (1946) method. \( \text{LD}_{50} \) or Maximum Tolerated Dose (MTD) was also determined. Table shows the plants with antiamoebic activity with the part of the plant extracted and \( \text{LD}_{50} \) or MTD.

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<th>Plant</th>
<th>Part used</th>
<th>MTD</th>
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<td>2. <em>Ainsliaea pteropoda</em> DC</td>
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<td>3. <em>Alangium salvifolium</em> (L.f) Wang</td>
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<td>4. <em>Alibizia lebbeck</em> (L) Benth</td>
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<td>5. <em>Alhagi pseudalhaqi</em> DESV</td>
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<td>6. <em>Asparagus filicinus</em> Buch-Ham</td>
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<td>9. <em>Berberis lycium</em> Royle</td>
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<td>13. <em>Cedrela toona</em> Roxb</td>
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<td>14. <em>Celosia argentea</em> Linn</td>
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<td>15. <em>Centella asiatica</em> (L) Urban</td>
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<td>17. Cissus setosa Roxb</td>
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<tr>
<td>45. Sarcococca trinervis wight</td>
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<tr>
<td>46. Scindapsus officinalis (Roxb)</td>
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<td>47. Scutia myrintina Kurz</td>
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<td>49. Solanum seaforthianum Ander</td>
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<td>52. Urginia indica Kunth</td>
<td>BU</td>
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<td>53. Withania somnifora Dunal</td>
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<td>54. Ziziphus rotundifolia Lam</td>
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2.2.2. **Drugs of synthetic origin**

a) **Metronidazole**

The discovery of azomycin (2-nitroimidazole) by Nakamura in 1955 and the demonstration of its trichomonacidal activity by Horie (1956) opened the way for the chemical synthesis and biological testing of nitroimidazoles. Soon after this,
metronidazole (1-/ -hydroxyethyl-2-methyl-5-nitroimidazole) was also shown to possess useful activity against giardiasis and acute ulcerative gingivitis (Fowler, 1960; Shinn, 1962). However, its value in amoebiasis was not recognised until several years later, when in 1966 Powell et al. reported it. The drug metronidazole is now proved to be very useful in the treatment of intestinal and extraintestinal amoebiasis. Metronidazole has the following structural formula -

```
H—C—N
||
O2N — C — N
CH2CH2OH
```

Metronidazole

It occurs as pale yellow crystals and are slightly soluble in water and alcohol.

The drug is very active against *E. histolytica*. Gordeeva (1965) reported that the morphology of the microorganisms is altered markedly within 6-20 hours by concentrations of 1-2 μg/ml of metronidazole, in culture. Within 24 hours, all the amoebae are killed. At a concentration of 0.2 μg/ml the same effect is seen within 72 hours.

In experimental amoebiasis, it protected rats at the dose of 100 mg/kg per day given orally, whereas 35 mg/kg per day orally suppressed the hepatic infection in hamsters (Cosar et al., 1961).
In all geographical areas, regardless of the virulence of the strains, it is recommended that the patients with invasive intestinal infection be treated with 750 mg of metronidazole, three times a day for 5-10 days. The daily dose for children is 35-50 mg/kg, given in three equal doses. Amoebic hepatic abscess also respond to smaller dosage. There is less unanimity of opinion regarding the treatment of the asymptomatic cysts passer. Despite considerable clinical use over the last several years, resistance of E. histolytica to metronidazole has not occurred. Attempts to produce resistance to the drug in vitro have been unsuccessful.

In relatively large doses used in treating amoebiasis, nausia, headache, dry mouth and metallic taste are frequently encountered but rarely necessitate interruption of treatment. Occasionally, stomatitis, vomiting, diarrhoea, dizziness, transient ataxia, confusion, insomnia, paresthesia and rash are encountered. The most severe toxic effect is that it induces malignancy (Shubic and Rustia, 1972; Leagator, et al., 1975; Wilson and Searle, 1975) in experimental animals.

Mode of action of Metronidazole

Several nitroimidazole derivatives including metronidazole are good chemotherapeutic agents against anaerobic and facultative anaerobic microorganisms. These compounds are taken up selectively by these microorganisms and kill them
selectively. A major step in the uptake and killing is the reduction of the nitro group of metronidazole and other nitroimidazoles by ferredoxin or flavodoxin compounds characteristic of the metabolism of anaerobes and facultative anaerobes. The reduction generates a gradient driving the uptake of the drug. One or more products formed by reduction are cytotoxic, possibly because they bind to cell compounds.

The membrane of any cell is permeable to these nitroimidazole derivatives. Entering unchanged compound do not significantly bind to or inhibit any intracellular component and thus for all practical purposes are not toxic to the cell. In cells of anaerobes and photosynthetic organisms that contain enzyme systems using ferredoxin and flavodoxin as electron acceptor or donor, a non-enzymatic redox interaction occurs in which the ferredoxin is oxidised and the nitrogroup of nitroimidazole is reduced. The reduction decreases, the intracellular concentration of the unchanged compound leading to further uptake of the drug. Products of the reduction have the ability to bind to certain intracellular components or to inhibit certain cellular processes and thus to kill the cell. The toxic compound probably are intermediates and not the biologically inactive final products of the reduction (Muller et al., 1976).

b) Chloroquine

The unique therapeutic value of chloroquine in extra-intestinal amoebiasis in man was first reported by Conan (1948, 1949). It is one of the derivatives of 4-aminquinolines
investigated for its antimaterial activity in the United States during II World war. It is usually supplied as the diphosphate which is a white crystalline powder, freely soluble in water, the solution having a pH about 4.5. The solution is stable to heat, but both solid and solution are unstable if exposed to light. The structural formula of chloroquine is as follows –

![Chloroquine](image)

Chloroquine has only low activity against *E. histolytica* in vitro. Conan (1948) reported it to be more active than the holoegenated 8-hydroxyquinolines and carbarsone, but less active than the emetine. In most tests, it is active in concentrations between 200-1000 ug/ml. The discovery that chloroquine localises in the liver in a concentration several hundred times greater than that in plasma, suggested its use in hepatic amoebiasis (Rollo, 1975). Clinical trials have showed that the signs and symptoms of amoebic hepatitis disappear within a few days after the start of chloroquine therapy and the disease adequately controlled and often cured. Numerous clinical reports showed the high efficacy of chloroquine in extra intestinal amoebiasis especially amoebic hepatitis and liver abscess (Lane, 1951; Sodeman, et al, 1951). Wilmot and collaborators (1958) suggested that chloroquine was somewhat less effective than
emetine. It was also determined that the drug is relatively ineffective in intestinal amoebiasis and that an amoebicidal agent effective in intestinal amoebiasis should be used concurrently. The drug has proved effective in some individuals who fail to respond to emetine. Chloroquine, like emetine, is not always curative and therefore adjuvant medical and surgical measures may be necessary. There is no evidence that amoebae develop resistance to chloroquine.

The conventional course of chloroquine phosphate for extraintestinal amoebiasis in adults is 1 gram daily for 2 days followed by 500 mg, daily for 2 to 3 weeks. Because of the low toxicity of the drug, the schedule can be revised upward if necessary. The course of chloroquine may be repeated. Some authorities suggest that chloroquine therapy should immediately follow a course of emetine while others suggest the two drugs concurrently.

Chloroquine may produce side effects such as headache and gastrointestinal disturbances, visual and psychic disturbances. It should not be given during pregnancy. Official in U.S.P. 1980.

c) 8-Hydroxyquinolines

There are a number of halogenated 8-hydroxyquinolines synthesized and utilized clinically for their amoebicidal activity. There were the first amongst the earliest synthetic
products introduced in the chemotherapy of amoebiasis. Earlier reports on the use of these compounds is reviewed by Anderson and Hansen (1950). Out of many derivatives of 8-hydroxyquinolines, 3 drugs namely, iodochlorohydroxyquin, di-iodohydroxyquin and lodohydroxyquin sulphonic acid (chiniofon) are useful in intestinal amoebiasis, but are of no use in the hepatic amoebiasis. None of these drugs are official in U.S.P. in 1980.

The 8-hydroxyquinolines are directly amoebicidal, but the mechanism of action is not known. These drugs are ineffective against amoebic abscess and hepatitis and act only on microorganisms in intestinal tract. These drugs are active against motile trophozoites as well as cysts.

i) Iodochlorohydroxyquin (Vioform)

It was originally introduced as a substitute for iodoform for use as a dusting powder for skin, wound and burns. Anderson and Koch (1931) first tested its value in experimental amoebiasis in monkeys.

**Structural formula**

![Iodochlorohydroxyquin (Vioform)](image)

It is a tasteless, brownish, yellow powder nearly insoluble in water. Testing of 8-hydroxyquinolines becomes complicated by the low solubility of the drug.
Its *in vitro* activity is low. It is active at the concentration 20-100 µg/ml (Bradin and Hansen, 1950) while Bradner and Rawson (1951) reported its activity at 126 µg/ml in *E.histolytica* Treponosoma cruzi cultures. Woolfe (1957) reported the active dose in rats to be 150 mg/kg.

It is given for amoebiasis in the form of oral tablets; a course consists of 500 to 750 mg, three times a day for 10 days. This is repeated after an 8 day rest period. The most important toxic reaction of vioform is a "subacute-myelo optic neuropathy". The disease is a myelitis like illness that was first described in Japan. At first there were few cases, but as the number of cases increased a special investigation was carried out in Japan. In its findings, iodochlorohydroxyquin was an important etiological factor (Kono, 1971 and Oakley, 1973). This resulted in cessation of sale of the drug in Japan in 1970 and restrictions were imposed on its sale and use in some other countries including the United States and India.

Other side effects with 8-hydroxyquinolines are severe generalised furunculosis (iodine toxicoderma), chills, fever, mild to severe dermatitis, irritation and itching, transitory, abdominal discomfort, diarrhoea and headache. Thyroid enlargement is occasionally noted. These drugs are contraindicated in patients with hepatic damage or iodine intolerance.
ii) **Di-iodohydroxyquin** (Diodoquin, Yodixin)

It is a yellowish-brown powder insoluble in water and contains about 60% iodine.

**Structural formula**

It was found to be active *in vitro* at the concentration of 100 µg/ml (Goodwin *et al.*, 1948), whereas *in vitro* it was found to be active in repeated doses of 600 mg/kg in rats (Goodwin *et al.*, 1948). The therapeutically dose for adult patients of intestinal amoebiasis is 650 mg, 3 times daily for 20 days. Children should be given a fraction of the adult dosage up to 10 years of age depending upon the age. The initial course should not be repeated without an interval of 2 to 3 weeks. A daily dose of 650 mg may be adequate in asymptomatic carriers. In the treatment of intestinal amoebiasis, it is common practise to administer diodoquin either concurrently with another effective intestinal amoebicide or to give the two drugs in alternating course. While the exact relationship is uncertain, administration of di-iodohydroxyquin to children for chronic diarrhoea has been associated with optic atrophy and permanent loss of vision (Medical Letter, 1974).
iii) **Iodohydroxyquinoline sulphonic acid** (Chiniofon, Quinoxyl).

It was first introduced for amoebiasis in 1921 by Muhlens and Menck. It contains 36% iodine and has the following structural formula -

![Chemical structure of Iodohydroxyquinoline sulphonic acid](image)

Chinioton

It is supplied with 20% sodium bicarbonate or as sodium salt. The solid is unstable if exposed to light. **In vitro** it is active at the concentration of 100 μg/ml (Goodwin *et al.*, 1948). **In vivo**, it was effective if given in large doses. It was found to be active against intestinal amoebiasis in rats in repeated doses of 300-1000 mg/kg (Jones, 1946). Goodwin *et al.* (1948) found it effective in repeated doses of 300 mg/kg. Woolfe (1957) reported the 'just active' dose of chiniofon to be 200 mg/kg.

It is used in acute amoebiasis with emetine in the doses of 0.25 to 1.0 gram, three times a day or by enema 1-5 grams doses dissolved in 100 ml of warm water. In cases of cyst passers, it is given in dose of 1 gram, three times daily for 7-14 days.

d) **Arsenicals**

Various compounds of arsenic have been used for the treatment of amoebiasis, e.g. carbarsone, acetarsone, diphetarsone,
glycobiarsol etc. Out of these carbarsone was found to be less toxic and more active. Trivalent arsenicals are more toxic than corresponding pentavalent compounds but generally are more active against parasites (Ross, W.J. 1979).

i) Carbarsone

It is a trivalent arsenical. In the chemotherapy of amoebiasis, it was first introduced in 1931 by Anderson and Reed. It is phenylarsenic acid derivative. It is a white crystalline powder, insoluble in water and contains 28.8% arsenic.

\[
\begin{align*}
\text{Carbarsone} \\
\text{AsO(OH)}_2 \\
\text{NHCONH}_2
\end{align*}
\]

It has a very low in vitro activity against \textit{E. histolytica}. Goodwin et al. (1948) reported it to 100 \text{pg/ml} whereas Bradin and Hansen (1950) found the activity between 500–2000 \text{ug/ml}.

In experimental animals, it is active in larger doses. Jones (1946) and Goodwin et al. (1948) reported it active in rats at 1000 and 600 \text{mg/kg} respectively. Thompson and Lilligren (1949) found it to be inactive in infected dogs.

Clinically it is recommended to be given orally in dosage of 0.25 gram twice daily for 10 days. It is used in the
treatment of acute and chronic amoebiasis but it has no value in the treatment of extraintestinal amoebiasis. The action of this drug on motile amoebae is not as rapid as that of emetine. It eradicates cysts by destroying the trophozoites that are the source of the cysts (Rollo, 1970).

Despite the wide use of the drug, few cases of serious poisoning have been reported (Radke and Baroody, 1957). Rashes of varying severity may occur, but they are usually mild. Localized edema is occasionally observed. Exacerbation of diarrhoea, mild nausea and vomiting and vague abdominal pains are sometimes noted. Arsenical encephalitis with confusion, disorientation, coma, convulsions and fever has been recorded in two patients who ingested overdose of carbarsone (Schwartz and Donnenfeld, 1965). Carbarsone is contraindicated if renal or hepatic disease is present and therefore, should not be used concurrently with either emetine or chloroquine in the treatment of amoebic hepatitis. Skin eruptions, pruritus, neuritis, gastrointestinal irritation, renal damage and visual disturbance may be indications of arsenic intolerance and so the arsenic therapy should be discontinued. Official in U.S.P. 1980.

ii) Glycobiarson (Milibis)

It is a pentavalent arsenical first studied in Germany and promoted in U.S. by Berberian and associates (1950).
It is an odourless, yellowish to pink powder, slightly soluble in water. It contains 15% pentavalent arsenic and 42% Bismuth.

The drug is effective only in subacute intestinal amoebiasis. It is ineffective in extraintestinal amoebiasis. In subacute or chronic amoebiasis, it is given along with chloroquine. Precautions and contraindications for glycobiarsol are same as for carbarsone. Official in U.S.F. 1980.

e) Antibiotics

A number of antibiotics have been found to be useful in the treatment of intestinal amoebiasis, especially paromomycin and some of the tetracyclines. Paromomycin is the only one that is acting directly on amoebae; other antibiotics are not direct amoebicidal but act by interfering with enteric flora essential for pathogenic amoebae. If a tetracycline is used, it should be administered together with the appropriate drugs for either intestinal or extraintestinal amoebiasis.

i) Tetracyclines

These are obtained by the fermentation of Streptomyces spp. These are amphoteric substances insoluble in water as the
bases but soluble as salts. Solutions are stable under slightly acid conditions, but unstable if alkaline.

The in vitro amoebicidal concentration of chlorotetracycline varied from 2-250 pg/ml (Bradin and Hansen, 1950; Watt and Van de Grift, 1950). Bradner and Rawson (1951) reported oxytetracycline and chlorotetracycline active at 250 pg/ml and 62 pg/ml respectively. In vivo in rats chlorotetracycline was active at 5-10 mg/kg (Jones, 1950). Thompson et al. (1956) reported tetracycline, oxytetracycline and chlorotetracycline all to be effective. In hamsters, all these forms of tetracyclines had a suppressive effect in the lesion formation in livers. All the survivors did show lesion (Thompson et al. 1956).

Mc Vay et al. (1949) first reported the successful treatment of amoebiasis with tetracyclines. In acute amoebiasis, tetracyclines are outstandingly effective but in amoebic liver abscess they are not effective. They should be used along with other amoebicidal drugs. The dose recommended is 1-2 gram daily along with amoebicidal drug.

ii) Paromomycin (Humatin)

Coffey and co-workers (1959) as well as Thompson et al. (1959) showed that paromomycin, an antibiotic isolated from Streptomyces rimosus, is amoebicidal both in vitro and in vivo. It acts directly on amoebae but is also antibacterial to normal and pathogenic organisms in the gastrointestinal tract.
In vitro, the activity varies between 3.9 to 10 µg/ml in a liquid medium, depending on the strain and bacterial associates. In rats, it is highly effective at the dose of 22 mg/kg when given orally (Thompson et al., 1959). When given orally, large doses are required to reduce the lesion size in hamsters with hepatic amoebiasis, but when given subcutaneously, found significant active at the dose of 75 mg/kg per day (Woolfe, 1963).

It is effective in the treatment of acute and chronic intestinal amoebiasis when given orally in the dose of 25 to 35 mg/kg in three divided doses for 5-10 days but ineffective in extra intestinal forms of the disease (Chaudhuri et al., 1961; Wagner and Burness, 1961). The side effects reported so far have been limited to gastrointestinal upset and diarrhoea.

Present status

Paromomycin is effective only in intestinal amoebiasis but is completely ineffective against extraintestinal forms of the disease. It has also been shown to be effective in the treatment of bacterial diarrhoeas and in suppressing nitrogen forming bacteria in the gastrointestinal tract of patients with hepatic coma. It has been used to suppress intestinal flora prior to bowel surgery. It is also effective against infections with various tapewarms.
iii) **Antibiotic G-418**

It is an aminoglycoside antibiotic of undisclosed structure and elaborated by *Micromonospora rhodorangea*. The fermentation, isolation and primary characterization of G-418 has been reported by Wagman et al. (1974). The antibiotic is produced by submerged fermentation in a soybean-dextrin medium. G-418 is an amorphous white powder with m.p. 138-144°C. It is soluble in water or methanol. It is stable for at least 30 minutes at 100°C in 0.1 M buffers, pH 2-10. It has broad-spectrum antibacterial activity and is highly active against protozoa, amoebae, tapeworm and pinworm infections in mice.

Loebenberg et al. (1975) studied its antiparasitic activity. They reported that, all but 1 of 53 rats with caecal *Entamoeba histolytica* infections were cured by this antibiotic in an oral dose of 3.5 mg/kg or higher given for 6 days. All but 1 of 12 rats treated orally with 6.5 mg/kg or more for 3 days were also cured. Thus, in this model, the drug was shown to be considerably more effective, in relation to dosage and length of treatment than either paromomycin or metronidazole. Against *Trichomonas vaginalis* the drug was effective *in vitro*, but it was not so effective in mice.

f) **Diloxanide (Entamide) and Diloxanide Furate (Furamide)**

Diloxanide was introduced by Bristow and his co-workers in 1956 as a result of examination of a series of substituted
acetanilides for amoebicidal activity. Clinical trials showed diloxanide to be effective in cyst passers but to be relatively ineffective in the treatment of acute intestinal amoebiasis. This was due to the inadequate concentration of the drug at the site of infection. Many attempts were made to overcome this disadvantage by preparing different derivatives. Only the furoate ester of diloxanide was more active than the parent compound in experimentally infected rats (Main et al., 1960). In clinical trials, it was found to be effective in acute intestinal amoebiasis (Shaldon, 1960 and Woodruff and Bell, 1960). Neither of these compounds showed significant activity against hepatic amoebiasis in hamsters (Williams, 1959).

Furamide is a white, crystalline powder insoluble in water. Its structural formula is as follows -

![Structural formula of Diloxanide furoate (Furamide)](image)

Diloxanide furoate (Furamide)

Diloxanide was found to be active in vitro at the concentration of 0.1 ug/ml and diloxanide furoate at 0.01 pg/ml by using capillary method (Woolfe, 1957). In experimental amoebiasis in rats, given by Woolfe (1957), 'just active dose' of diloxanide was 10 mg/kg per day and that of diloxanide furoate was 2.5-5.0.
When given in the dose of 20 mg/kg per day of diloxanide a cure rate of 80% cyst passers was reported by Woolfe (1957). Diloxanide furoate was found to be very active in chronic amoebiasis in the dose of 20 mg/kg per day and was also found to be effective in acute amoebiasis (Woodruff and Bell, 1960). The therapeutic dose of diloxanide furoate given in acute and chronic intestinal amoebiasis is varied from 0.5 gram three times a day for 5 days. The most generally used dose has been 0.5 gram three times daily for 10 days. If necessary, a second course may be given immediately following the first. So far, no serious side effects have been reported except mild gastrointestinal symptoms.

Its status as a luminal amoebicide for use against asymptomatic cyst passers is well established. It is also used in invasive amoebiasis.

**Present status**

Diloxanide furoate is regarded by some authorities as an agent of first choice in the treatment of asymptomatic cyst passers (administered alone) (Krogstad et al., 1978) or in the treatment of invasive and extraintestinal amoebiasis (administered with other appropriate drugs) (Powell, 1969). It is ineffective when administered alone in the treatment of extraintestinal amoebiasis. There is no unanimity of opinion on its efficacy when used alone in the treatment of acute amoebiasis with dysentery. While good results have been reported
by some, other trials have been less successful (Suchak et al., 1962; Wilmot et al., 1962). In trials carried out primarily on asymptomatic subjects passing trophozoites or cysts or on patients with non-dysenteric, symptomatic intestinal amoebiasis, treatment with diloxanide furoate resulted in a high percentage of cures (Woodruff and Bell, 1960; Woolfe, 1973). Forsyth (1962) compared the value of several forms of treatment and pointed out that the low cost of the drug might be a major factor in underdeveloped countries.

g) Teclozan

The compound teclozan has been known by a number of names like, teclosan, teclosine, teclozine, Win-13, 146, Win AM 13, 146, Falmonox etc. Chemically N,N'-bis (ethoxyethyl)-N,N'-bis (dichloroacetyl)-1,4-xylylenediamine or N,N'-bis (dichloroacetyl)-N,N'-bis (2 ethoxyethyl)1,4-bis (aminomethyl)benzene; C_{20}H_{28}Cl_{4}N_{2}O_{4} with molecular weight 502.29.

It was prepared by reductive alkylation of 2-ethoxyethylamine with terephthalaldehyde followed by acylation of the diamine with dichloro acetyl chloride. Surrey and Mayer (1961) first reported the synthesis and antiamoebic activity of the compound in vitro and in vivo.

The compound is white, crystalline with melting point 142°C. It is slightly soluble in water. The structural formula of the compound is as follows -
The compound was then studied in detail by Bernerian et al. (1961) for its antiamoebic activity in vitro, in vivo and in human patients. They also studied the toxicity of the compound. They found that the compound to be amoebicidal at 1:10 million dilution in vitro as compared to that of emetine which was amoebicidal at 1:5000 dilution in vitro. They also tested the activity of teclozan in vivo in hamsters with natural infection of Entamoeba criceti in caecum. They found the ED$_{50}$ (Effective dose to clear 50% of hamsters of E. criceti) to be 1.14. The LD$_{50}$ was found to be more than 8000 mg/kg orally in mice.

They have given the successful use of teclozan in some patients with E. histolytica infection. The drug was directly amoebicidal.

After this report, a number of successful clinical trial reports have been published by a number of clinicians from different parts of the world (Huggins, 1970, 1971).

Effectiveness of teclozan as a prophylactic has been reported (Botero and Zuluaga, 1968).
The clinical toxic effects of the drug include headache, nausea, vomiting, diarrhoea and constipation, but the drug is generally tolerated (Martindale, Extra pharmacopea, 1979). The usual dose of teclozan is 100 mg thrice a day for 5 days, in acute attacks 200 mg may be given along with emetine.

h) **Furazolidone**

(Syn: NF 180; Furovag, Furoxane, Furoxone, Giarlam, Giardil, Medarun, Neftin, Nicolen, Nifulidone, Ortazol, Roptazol, Tikofuran, Topazon).

It is official in Brish Pharmacopoeia 1968. It is 3-(5-Nitrofurfurylideneamino) oxazolidin-2-one. C₈H₇N₃O₅. It is a colourless to pale yellow crystalline powder with 225.2 molecular weight. It is tasteless at first followed by bitter after taste. Its melting point is 259°C at which temperature it decomposes. It is practically insoluble in water and ether, and very slightly soluble in alcohol and chloroform. A 1% suspension in water has pH 4.5 to 7.0. It is sensitive to light. The structural formula of furazolidone is as follows -

![Furazolidone](image)

Khan (1971) claimed the successful clinical use of the drug. He reported that cysts and trophozoites of *E. histolytica*
were eliminated from the stools of 11 out of 13 patients with diarrhoea or dysentery after 3 days treatment with furazolidone 100 mg and clioquinol 200 mg 4 times daily for 7-10 days. The author considers this combination of amoebicidal and a bactericidal drug to be the therapy of choice for the treatment of dysentery and diarrhoea where facilities for accurate diagnosis are not available.

Mild toxic symptoms including headache, nausia, vomiting sometimes occur, vesicular or morbilliform rashes occur with high dosage but usually subsides on reduction of the dose. Agranulocytosis has been reported. Acute haemolytic anaemia may occur in patients with a genetic deficiency of glucose-6-phosphate dehydrogenase. Intolerance to alcohol has been reported in patients while on furazolidone therapy. When used intravaginally, it may occasionally give rise to vulval oedema and pruritus.

The recommended dose is 100 mg 4 times daily for 2-5 days and for children 5 mg/kg daily in divided doses.

1) Chlorphenoxamide (Mebinol)

It is N-(2-hydroxyethyl)-N-(2-hydroxyethyl)- dichloroacetamide.

It was found to be active in vitro at the concentration of 0.25 to 0.6 mg/ml (De-Carneri, 1958a, 1958b). In intestinal amoebiasis in rats, it was effective at 20 mg/kg per day.
Clinically, it is more effective in cyst passers than in acute amoebiasis. It is well tolerated. It is ineffective in hepatic amoebiasis.

j) Phanguone (Entobex)

It is 4,7-phenanthroline-5,6-quinone. It is a yellow substance, slightly soluble in water, but more soluble in dilute mineral acids. It was found to be highly active in repeated doses of 21.5 mg/kg, and 100% active at the dose of 75 mg/kg (Ka (Kradolfer and Neipp, 1958). Kradolfer and Neipp (1958) gave the effective concentration of Enthobex as about 70 ug/ml in 24 hours.

Clinically it has proved effective in treatment of both acute and chronic amoebiasis. A dose of 10 mg/kg per day appears to be most effective. It is effective in both dysenteric and nondysenteric types of infection. Side effects include nausia and vomiting.

2.3. Present day treatment

As suggested by Zoheir Farid et al. (1979).

A) Asymptomatic cyst passers (Luminal infections)

1. Metronidazole, 750 mg three times daily for 10 days.

   In resistant cases this treatment is repeated or

2. Diloxanide, 500 mg three times daily for 10 days or

3. Di-iodohydroxyquin, 650 mg three times daily for 3 weeks.
B) **Intestinal amoebiasis**

(Amoebic dysentery, Trophozoite passers)

1. **Metronidazole, 750 mg 3 times daily for 10 days**
   is quite effective. In cases with severe diarrhoea
   tetracycline 250 mg 4 times daily for 10 days is
to be added.

   In resistant cases or where patients do not
tolerate metronidazole, a combination of drugs has
to be used. Either of the following regimens is
effective.

2. **Emetine or dehydroemetine 1-1.5 mg/kg daily,**
   subcutaneously or intramuscularly plus tetracycline
   250 mg 4 times daily for 10 days; plus either
   di-iodohydroxyquin 650 mg 3 times daily for 3
   weeks, or diloxanide 500 mg three times daily for
   10 days.

3. **Chloroquine 150 mg base twice daily for 2 weeks**
   is substituted for emetine or dehydroemetine;
   tetracycline plus di-iodohydroxyquin or diloxanide
   is given as above along with chloroquine.

   In severe amoebic dysentery, when oral administration
   may be impossible, the regimen no. 2 should be used. Dehydration
   and electrolyte balance must be corrected by intravenous fluids.
Codeine sulphate, 30 mg 3 times daily, may help to control severe diarrhoea.

Amoeboma usually responds rapidly to emetine or dehydroemetine plus tetracycline and di-iodohydroxyquin or diloxanide.

C) Hepatic amoebiasis

1. Metronidazole, 750 mg 3 times daily for 10 days is usually very effective in hepatic amoebiasis and in small abscesses may be the only drug necessary. If there is severe dysentery or a markedly elevated white blood cell count (indicating secondary bacterial infection), tetracycline 250 mg four times daily for 10 days is added. If abscess is large, then aspiration of the abscess should be done. A combination of metronidazole, tetracycline and aspiration of the pus is usually effective in curing the majority of amoebic liver abscesses.

2. Patients who cannot take drugs orally, emetine or dehydroemetine 1-1.5 mg/kg per day for 10 days subcutaneously or intramuscularly must be started immediately and once oral therapy is possible, chloroquine is added. Chloroquine is given in a 600 mg base first dose, followed 6 hours later by 300 mg then 150 mg twice daily for 4 weeks. Tetracycline is to be given to control severe dysentery and di-iodohydroxyquin or diloxanide added to eliminate luminal infection.
Occasionally, an abscess may rupture in the lungs, pericardium or peritoneum. Amoebic lung abscesses usually drain through a bronchus, specific therapy with metronidazole and tetracycline or with emetine or dehydroemetine plus chloroquine should be given. In resistant cases, surgical drainage through an intercostal tube may be necessary.

Amoebic pericarditis with effusion should be treated with emetine or dehydroemetine plus chloroquine and aspiration if necessary.

Amoebic peritonitis is usually treated by surgical drainage of the pus and with emetine or dehydroemetine and chloroquine.

2.4. Evaluation of chemotherapy of amoebiasis

The foundations of our modern knowledge of clinical amoebiasis date from the latter part of the last century and are based on a clearly described invasive disease, manifest as amoebic dysentery and liver abscess.

Although ipecacunha had long been used in treatment (Docker, 1858) the first landmark in therapy was the introduction of emetine hydrochloride by Rogers (1912). Its value rapidly became apparent and it has remained universally successful wherever severe invasive amoebiasis is encountered. However, despite its efficacy as a tissue amoebicide the drug frequently fails to eradicate amoebae from the lumen of the intestine and
hence, recurrence of symptoms is common. Because of its cardio-toxic effects and narrow margin of safety, its value is seriously affected (Powell, 1967). On an attempt to achieve greater activity within the bowel lumen, oral emetine preparations were introduced (Du Mez, 1915) but none of them have offered any real advantage over emetine.

After World War-I, it was thought that there were vast numbers of individuals with occult amoebiasis in need of treatment and hence, great impetus was given to the development of numerous luminal amoebicides, chiefly arsenicala and quinoline derivatives. In more recent years diloxanide preparations have also become popular. Since all these drugs are capable to some degree of eradicating lumen dwelling amoebae, they have enjoyed a vogue for the treatment of symptomless and mildly symptomatic bowel infections but wherever amoebiasis is associated with a significant amount of invasion they were inadequate. The value of arsenicals became limited because of arsenic poisoning. The value of quinolines was affected because of iodine tolerance in many patients as well as the disease caused by them named as Subacute Myelo-optic Neuropathy (SMON). This resulted in the cessation of its sale in Japan in 1970 and restrictions were imposed on its sale and use in some other countries including India and United States.

Chloroquine was found to be effective in amoebic liver abscess (Conan, 1948) although it has little activity in the
bowel. It has achieved wide usage as a less toxic alternative to emetine but it is less active (Harinasuta, 1951; Wilmot et al., 1958). Nevertheless, it is still used as a supplementary medication.

Soon after the advent of antibiotics, Hargreaves (1945) demonstrated the value of penicillin and sulphonamides in amoebic dysentery. It was not long become this combination was replaced by the tetracyclines which have remained the antibiotics of choice, acting on *E. histolytica* apparently indirectly by modifying the bacterial flora of the bowel (Mo Vay et al., 1949; Armstrong et al., 1950; Most and Van Assendelft, 1950). However, relapse may occur after apparent cure and tetracyclines are not effective in treating hepatic amoebiasis (Powell et al., 1965).

Cosar and Julou (1959) found metronidazole to be systematically active against *Trichomonas vaginalis*. Soon after this, it was also shown to possess activity against giardiasis and acute ulcerative gingivitis (Fowler, 1960; Shinn, 1962). Its value in amoebiasis was realized by Powell et al. in 1966. Metronidazole approximates most closely the ideal amoebicide. It is easily administered, rapidly activating, well-tolerated, without significant toxicity and effective in course of short duration. Although the cure rate achieved are no better than those obtainable by combinations of other drugs, metronidazole is the nearest approach to an all purpose amoebicide.
Nevertheless, its balance of activity at all sites is not perfect because it is more effective against *E. histolytica* in the tissues than in the intestine. Larger doses are needed to cure amoebic dysentery than liver abscess. Its status as a predominantly luminal amoebicide for use against cyst-passers is less certain. However, many cheap alternative luminal amoebicides are available (Powell, 1972).

Although the place of metronidazole in the therapy of invasive amoebiasis is established, many workers have reported the cases where metronidazole has failed to cure the infection (Griffin, 1973; Canby and Ariz, 1974; Dutta et al., 1974; Fisher et al., 1976; Koutsaimanis et al., 1979).

The most unwanted toxic effect of metronidazole which cannot be underestimated is that it produces malignant lymphomas in experimental animals (Rustia and Shubik, 1972; Voogd et al., 1974; Leagator et al., 1975; Wilson and Searle, 1975; Rustia and Shubik, 1979; Olive, F.L., 1979; Olive, P.L., 1979a).