Chapter 61 Anthelmintic Drugs

Anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminths.

Helminthiasis is prevalent globally (1/3rd of world's population harbours them), but is more common in developing countries with poorer personal and environmental hygiene. Multiple infestations in the same individual are not infrequent. In the human body, g.i.t. is the abode of many helminths, but some also live in tissues, or their larvae migrate into tissues. They harm the host by depriving him of food, causing blood loss, injury to organs, intestinal or lymphatic obstruction and by secreting toxins. Helminthiasis is rarely fatal, but is a major cause of ill health.

The choice of drug for each worm infestation is based not only on efficacy, but also on lack of side effects/toxicity, ease of administration (preferably single dose) and low cost. Development of resistance has not been a problem in the clinical use of anthelmintics. The current choice of drugs for worm infestations common in the Indian subcontinent is given in Table 61.1.

Mebendazole

It is a benzimidazole introduced in 1972. This congener of thiabendazole became very popular because it retained the broad-spectrum anthelmintic activity but not the toxicity of its predecessor. It has produced nearly 100% cure rate/reduction in egg count in roundworm, hook worm (both species), *Enterobius* and *Trichuris* infestations, but is much less active on *Strongyloides*. Upto 75% cure has been reported in tapeworms, but *H. nana* is relatively insensitive. It expels *Trichinella spiralis* from intestines, but efficacy in killing larvae that have migrated to muscles is uncertain. Prolonged treatment has been shown to cause regression of hydatid cysts in the liver. Treatment after resection of the cyst may prevent its regrowth.

The immobilizing and lethal action of mebendazole on worms is rather slow: takes 2–3 days to develop. The site of action of mebendazole appears to be the microtubular protein 'β-tubulin' of the parasite. It binds to β-tubulin of susceptible worms with high affinity and inhibits its polymerization. Intracellular microtubules in the cells of the worm are gradually lost. In addition, it probably blocks glucose uptake in the parasite and depletes its glycogen stores. Hatching of nematode eggs and their larvae are also inhibited. Ascaris ova are killed.

Pharmacokinetics Absorption of mebendazole from intestines is minimal; 75–90% of an oral dose is passed in the faeces. The fraction absorbed is excreted mainly as inactive metabolites in urine/faeces.

Adverse effects Mebendazole is well tolerated even by patients in poor health. Diarrhoea, nausea and abdominal pain have attended its use in heavy infestation. Incidents of expulsion of *Ascaris* from mouth or nose have occurred, probably due to starvation of the parasite and their slow death. Allergic reactions, loss of hair and granulocytopenia have been reported with high doses.

Safety of mebendazole during pregnancy is not known, but it is contraindicated on the basis of animal data.

Uses and administration Mebendazole is available as: MEBEX, WORMIN 100 mg chewable tab and 100 mg/5 ml suspension. MEBAZOLE 100 mg tab. The dose and duration of treatment is the same for children above 2 years as for adults; ½ dose for 1–2 yr age.

TABLE 61.1 Choice of drugs for helminthiasis

	Worm	First choice drugs	Alternative drugs
1.	**ROUNDWORM** *Ascaris lumbricoides*	Mebendazole, Albendazole, Pyrantel	Piperazine, Levamisole Ivermectin
2.	**HOOKWORM**		
	Ancylostoma duodenale	Pyrantel, Mebendazole, Albendazole	Levamisole
	Necator americanus	Mebendazole, Albendazole	Pyrantel
3.	**PIN WORM** *Enterobius (Oxyuris) vermicularis*	Pyrantel, Mebendazole, Albendazole	Piperazine
4.	**THREAD WORM** *Strongyloides stercoralis*	Ivermectin	Albendazole
5.	**WHIPWORM** *Trichuris trichiura*	Mebendazole	Albendazole
6.	*Trichinella spiralis*	Albendazole	Mebendazole
7.	**FILARIA** *Wuchereria bancrofti, Brugia malayi*	Diethyl carbamazine, Ivermectin	Albendazole
8.	**GUINEAWORM** *Dracunculus medinensis*	Metronidazole	Mebendazole
9.	**TAPEWORMS**		
	Taenia saginata	Praziquantel, Niclosamide	Albendazole
	Taenia solium	Praziquantel	Niclosamide, Albendazole
	Hymenolepis nana	Praziquantel	Niclosamide, Nitazoxanide
	Neurocysticercosis	Albendazole	Praziquantel
10.	**HYDATID DISEASE**		
	Echinococcus granulosus, E. multilocularis	Albendazole Albendazole	Mebendazole

Roundworm
Hookworm
Whipworm
} 100 mg twice a day for 3 consecutive days. No fasting, purging or any other preparation of the patients is needed.

Upto 7 day treatment may be needed in heavy trichuriasis

Pin worm *(Enterobius)* 100 mg single dose, repeated after 2–3 weeks (to kill the ova that have developed later). Strict hygienic measures and simultaneous treatment of all children in the family or class is advocated to cut down autoinfection and person to person infection. This holds true of enterobiasis, irrespective of drug used.

Trichinosis: 200 mg BD for 4 days; less effective than albendazole.

Hydatid disease: 200–400 mg BD or TDS for 3–4 weeks; less effective than albendazole.

Guinea worm: Mebendazole is an alternative drug to metronidazole for facilitating extraction of the worm, when the latter cannot be given.

Mebendazole is one of the preferred drugs for treatment of multiple infestations and is more effective than albendazole in trichuriasis. It has also been used for mass treatment, but need for multiple doses is a drawback.

Albendazole

It is a subsequently introduced congener of mebendazole: retains the broad-spectrum activity and excellent tolerability of its predecessor, and has the advantage of single dose administration in many infestations. One dose treatment has produced cure rates in ascariasis, hookworm (both species) and enterobiasis which are comparable

to 3 day treatment with mebendazole. Results in trichuriasis have been inferior to mebendazole. In strongyloidosis, it is more effective than mebendazole: a 3 day course has achieved nearly 50% cure, and a second course repeated after 3 weeks cured practically all patients. Three day treatment has been found necessary for tapeworms including *H. nana*. Results in hydatid disease and hookworm have been superior to mebendazole. Albendazole has weak microfilaricidal action, kills cysticerci, hydatid larvae, ova of ascaris/hookworm and is also effective in cutaneous larva migrans. The mechanism of action of albendazole is similar to that of mebendazole.

Pharmacokinetics Absorption of albendazole after oral administration is significant, but inconsistent. It is enhanced when the drug is taken with fatty meal (this may help in treating neurocysticercosis and hydatid disease). The fraction absorbed is converted by first pass metabolism to its sulfoxide metabolite which has potent anthelmintic action. In contrast, the metabolites of mebendazole and thiabendazole are inactive. Albendazole sulfoxide is widely distributed in the body, enters brain and is excreted in urine with a t½ of 8.5 hours. Thus, albendazole is able to exert antihelmintic activity in tissues as well.

Side effects Albendazole is well tolerated; only gastrointestinal side effects have been noted. Few patients have felt dizziness. Prolonged use, as in hydatid or in cysticercosis, has caused headache, fever, alopecia, jaundice and neutropenia.

ZENTEL, ALMINTH, ALBEZOLE, COMBANTRIN-A 400 mg tab, 200 mg/5 ml suspension.

Uses No preparation or postdrug fasting/purging is required. For intestinal worms it should be given on empty stomach, while for cysticercosis, hydatid and cutaneous larva migrans it should be given with a fatty meal.

- *Ascaris,* hookworm, *Enterobius* and *Trichuris:* a single dose of 400 mg (for adults and children above 2 yrs, 200 mg for 1–2 yr age). Three day treatment may be needed in heavy trichuriasis.
- Tapeworms and strongyloidosis: 400 mg daily for 3 consecutive days. Efficacy in strongyloidosis is low, and it is the 2nd choice drug to ivermectin.
- Trichinosis: Three day treatment expels the adult worm from intestine, but has limited effect on larvae that have migrated to muscles. They are not killed but symptomatic relief occurs. Corticosteroids are added if systemic manifestations are severe.
- Neurocysticercosis: Albendazole is the anthelmintic of choice for the treatment of neurocysticercosis (*see* later). Usually 8–15 days course of 400 mg BD (15 mg/kg/day) is employed. Cysticercosis of other tissues (muscles, subcutaneous area) also responds, but no drug should be given for ocular cysticercosis—blindness can occur due to the reaction.
- Cutaneous larva migrans: Albendazole 400 mg daily for 3 days is the drug of choice; kills larvae and relieves symptoms.
- Hydatid disease: 400 mg BD for 4 weeks, repeat after 2 weeks (if required), up to 3 courses. It is the preferred treatment given before and after surgery as well as to inoperable cases.
- Filariasis: Added to diethylcarbamazine (DEC) or ivermectin, albendazole has adjuvant value in treating lymphatic filariasis. A single dose of its combination with either DEC or ivermectin given yearly has been used in mass programmes to suppress microfilaraemia and disease transmission.

Because it has exhibited embryotoxicity in animals, use in pregnant women is contraindicated. It should be given with caution to patients with hepatic or renal disease.

Thiabendazole

It was the first benzimidazole polyanthelmintic introduced in 1961, which covered practically all species of nematodes infesting the g.i.t.—roundworm, hookworm, pin worm, *Trichuris, Strongyloides* and *Trichinella spiralis*. It also inhibits development of the eggs of worms and kills larvae. Thiabendazole affords symptomatic relief in cutaneous larva migrans and skeletal muscle symptoms produced by migration of *Trichinella spiralis* larvae to muscles, because it has antiinflammatory action as well. Symptomatic relief also occurs in guinea worm disease.

Since thiabendazole is well absorbed from g.i.t., systemic adverse effects like nausea, vomiting, abdominal pain, diarrhoea, giddiness, impairment of alertness, itching, etc. are common. Thiabendazole has gone out of use, due to the availability of better tolerated mebendazole and albendazole.

Pyrantel pamoate

It was introduced in 1969 for pin worm infestation in children; use soon extended to roundworm and hookworm as well. Efficacy against *Ascaris, Enterobius* and *Ancylostoma* is high and comparable to that of mebendazole. Lower cure rates (about 60%) have been obtained in case of *Necator* infestation. It is less active against *Strongyloides* and inactive against *Trichuris* and other worms.

Pyrantel causes activation of nicotinic cholinergic receptors in the worms resulting in persistent depolarization → slowly developing contracture and spastic paralysis. Worms are then expelled. An anticholinesterase action has also been demonstrated. Because piperazine causes hyperpolarization and flaccid paralysis, it antagonizes the action of pyrantel. Cholinergic receptors in mammalian skeletal muscle have very low affinity for pyrantel.

Only 10–15% of an oral dose of pyrantel pamoate is absorbed: this is partly metabolized and excreted in urine.

Adverse effects Pyrantel pamoate is remarkably free of side effects: occasional g.i. symptoms, headache and dizziness is reported. It is tasteless, nonirritant; abnormal migration of worms is not provoked. Its safety in pregnant women and in children below 2 years has not been established.

Use and administration For *Ascaris, Ancylostoma* and *Enterobius*: a single dose of 10 mg/kg is recommended. A 3 day course for *Necator* and for *Strongyloides* has been suggested.

No fasting, purging or other preparation of the patient is needed.

NEMOCID, ANTIMINTH, EXPENT 250 mg tab, 50 mg/ml suspension (10 ml bottle).

Piperazine

Introduced in 1950, it is a highly active drug against *Ascaris* and *Enterobius*; achieves 90–100% cure rates. However, because of the availability at more convenient and better tolerated albendazole/mebendazole it is now considered a second choice drug. Piperazine causes hyperpolarization of *Ascaris* muscle by a GABA agonistic action. Opening of Cl^- channels causes relaxation and depresses responsiveness to contractile action of ACh. Flaccid paralysis occurs and worms are expelled alive. They recover if placed in piperazine free medium. Therefore, often a purgative (senna) is given with it, but is not necessary. No fasting or patient preparation is required. Piperazine does not excite *Ascaris* to abnormal migration. It does not affect neuromuscular transmission in man.

A considerable fraction of the oral dose of piperazine is absorbed. It is partly metabolized in liver and excreted in urine. Piperazine is safe, but nausea, vomiting, abdominal discomfort and urticaria may be felt. Dizziness and excitement occur at high doses; toxic doses produce convulsions; death is due to respiratory failure. It is contraindicated in renal insufficiency and in epileptics, but is safe in the pregnant.

Dose: For roundworm infestation 4 g once a day for 2 consecutive days; children 0.75 g/year of age (max. 4 g) is considered curative. Because of its capacity to relax ascarids, it is of particular value in intestinal obstruction due to roundworms. It can be used during pregnancy while other drugs cannot be used.

Pin worm: 50 mg/kg (max. 2 g) once a day for 7 days or 75 mg/kg (max. 4 g) single dose, repeated after 3 weeks.

PIPERAZINE CITRATE 0.75 g/5 ml elixir in 30 ml, 115 ml bottle; 0.5 g (as phosphate) tablets;

Combination of any other anthelmintic (except piperazine) with a purgative in the same formulation is banned in India.

Levamisole, Tetramisole

Tetramisole was developed in the late 1960s. It is racemic; its levo isomer (levamisole) was found to be more active and is preferred now. Both are active against many nematodes, but use is restricted to ascariasis and ancylostomiasis as a second line drug. The ganglia in worms are stimulated causing tonic paralysis and expulsion of live worms. Interference with carbohydrate metabolism (inhibition of fumarate reductase) may also be contributing.

Dose: Ascariasis—Single dose 150 for adults, 100 mg for children 20–39 kg body weight, 50 mg for 10–19 kg.

Ancylostomiasis—Two doses at 12 hour intervals. It is less effective against *Neccator*: not indicated.

Tetramisole: DECARIS 50, 150 mg tab.
Levamisole: DEWORMIS, VERMISOL 50, 150 mg tab, 50 mg/5 ml syr.

Levamisole is an immunomodulator as well: restores depressed T cell function. It was used as a disease modifying drug in rheumatoid arthritis and as an adjunct in malignancies, aphthous ulcers and recurrent herpes, but repeated doses produce severe reactions; not used now.

Adverse effects One or two doses used in helminthiasis are well tolerated. Incidence of side effects—nausea, abdominal pain, giddiness, fatigue, drowsiness or insomnia is low.

Diethylcarbamazine citrate (DEC)

Developed in 1948, it is the first drug for filariasis caused by the nematodes *Wuchereria bancrofti* (90% cases) and *Brugia malayi*. DEC is absorbed after oral ingestion, distributed all over the body (V = 3–5 L/kg), metabolized in liver and excreted in urine. Excretion is faster in acidic urine. Plasma t½ of usual clinical doses is 4–12 hours, depending on urinary pH.

Diethylcarbamazine is microfilaricidal. It has a highly selective effect on microfilariae (Mf). A dose of 2 mg/kg TDS clears Mf of *W. bancrofti* and *B. malayi* from peripheral blood in 7 days. However, Mf present in nodules and transudates (hydrocoele) are not killed. The most important action of DEC appears to be alteration of organelle membranes of the Mf promoting cell death. It is also suggested that muscular activity of Mf and adult worms is affected so that they are dislodged. Prolonged treatment may kill adult *B. malayi* and probably *W. bancrofti* worms also. Thus, DEC is slow acting macrofilaricidal.

DEC is active against Mf of *Loa loa* and *Onchocerca volvulus* as well. The adult worm of *L. loa* but not *O. volvulus* is killed. DEC reduces worm burden in ascariasis, but efficacy is low.

Uses

1. *Filariasis*: DEC 2 mg/kg TDS is a first line drug: produces rapid symptomatic relief; Mf disappear from blood and patient becomes noninfective to mosquitoes in 7 days. However, the adult worm survives in the lymphatics and gives rise to intermittent microfilaraemia and symptoms. Prolonged treatment with different schedules has been found to achieve radical cure in most patients. A total dose of 72–126 mg/kg spread over 12 days to 3 weeks has been found satisfactory; more than one course may be needed with a gap of 3–4 weeks. Elephantiasis due to chronic lymphatic obstruction is not affected by DEC, because fibrosis of lymphatics is irreversible. Yearly treatment with a combination of DEC (6 mg/kg) and albendazole (400 mg) single dose on mass scale has brought down transmission of filariasis by reducing microfilaraemia.

2. *Tropical pulmonary eosinophilia*: DEC (2–4 mg/kg TDS) for 2–3 weeks produces dramatic improvement in the signs and symptoms of eosinophilic lung or tropical eosinophilia. The benefit probably reflects anti-microfilarial action: the symptoms of the disease being presumably due to reaction to the Mf.

The associated cough may respond to inhaled corticosteroids.

HETRAZAN, BANOCIDE 50, 100 mg tab, 120 mg/5 ml syr; 50 mg/ 5 ml pediatric syr; to be taken after meals.

Loa loa and *O. volvulus* infections can also be treated with DEC, but the risk of life-threatening reaction to dying Mf is high. It is imperative to give small (25–50 mg) test dose initially which avoids severe reaction. Ivermectin does not produce such severe reactions and is preferred for initial treatment.

Adverse effects Side effects are common but generally not serious. Nausea, loss of appetite, headache, weakness and dizziness are the usual complaints.

A febrile reaction with rash, pruritus, enlargement of lymph nodes, bronchospasm and fall in BP may occur due to mass destruction of Mf and adult worms. This is usually mild, but may be severe. The reaction can be minimized by starting with a low dose (0.5 mg/kg). When it occurs, DEC should be temporarily withheld and antihistaminics and/or corticosteroids given. Subsequent administration of DEC does not cause such reaction. Leukocytosis and mild albuminuria are also noted.

Ivermectin It is an extremely potent semisynthetic derivative of the antinematodal principle obtained from *Streptomyces avermitilis*. Ivermectin is the drug of choice for single dose treatment of onchocerciasis and strongyloidosis,

and is comparable to DEC for bancroftian and brugian filaria. It is microfilaricidal but not macrofilaricidal. Ivermectin is also highly effective in cutaneous larva migrans and ascariasis, while efficacy against *Enterobius* and *Trichuris* is moderate; has been used as addon drug to albendazole/mebendazole in heavy trichuriasis. Certain insects, notably scabies and head lice are killed by ivermectin.

Nematodes develop tonic paralysis when exposed to ivermectin. It acts through a special type of glutamate gated Cl^- channel found only in invertebrates. Such channels are not involved in the motor control of flukes and tapeworms which are unaffected by ivermectin. Potentiation of GABAergic transmission in the worm has also been observed. The lack of GABA-related actions in man could be due to its low affinity for mammalian GABA receptors and its exclusion from the brain, by P-glycoprotein mediated efflux at the blood-brain barrier.

A single 10–15 mg (0.2 mg/kg) oral dose of ivermectin, preferably with 400 mg albendazole, given annually for 5–6 years has been used for filariasis. Single 0.15–0.2 mg/kg dose has yielded highest cure rate in strongyloidosis and reduces burden of other intestinal nematodes as well.

Ivermectin has replaced DEC for onchocerciasis and has been used in the 'river blindness' control programme of WHO in Africa and Latin America. One dose of ivermectin is given at 6–12 month intervals—produces long lasting reduction of Mf counts in eye and skin, without affecting the adult worm. Though it does not cure *O. volvulus* infection, ocular inflammation/damage as well as lymphadenopathy are suppressed with only mild ocular or systemic reactions.

Ivermectin is the only drug effective orally in scabies and pediculosis. Single 0.2 mg/kg dose cures most patients.

IVERMECTOL, IVERMEC, VERMIN 3, 6 mg tabs; to be taken on empty stomach.

Ivermectin is well absorbed orally, widely distributed in the body, but does not enter CNS, sequestrated in liver and fat, and has a long terminal t½ of 48–60 hours. It is metabolized by CYP3A4, but no drug interactions related to this isoenzyme are known. Side effects have been mild—pruritus, giddiness, nausea, abdominal pain, constipation, lethargy and transient ECG changes, but more important are the reactions due to degeneration products of the Mf, which are similar to those occurring after DEC. Safety of ivermectin in pregnant women and young children is not established.

Niclosamide

Niclosamide is a highly effective drug against cestodes infesting man—*Taenia saginata*, *T. solium, Diphyllobothrium latum* and *Hymenolepis nana*, as well as pin worm. The drug appears to act by inhibiting oxidative phosphorylation in mitochondria and interfering with anaerobic generation of ATP by the tapeworm. Injured by niclosamide, the tapeworms are partly digested in the intestine. In cases of *T. solium*, digestion of the dead segments can be hazardous, because the ova released from them may develop into larvae in the intestine, penetrate its wall and cause visceral cysticercosis. Though, the magnitude of such risk is uncertain, many experts do not use niclosamide now for *T. solium* infestation.

Regimen for tapeworm Niclosamide is available as 0.5 g tab (NICLOSAN). After a light breakfast, 2 tablets are to be chewed and swallowed with water, followed by another 2 tablets after 1 hr (total 2 g); total dose for children 2–6 years is 1 g. A saline purge is given 2 hours after the later dose to wash off the worm. The scolex should be searched in the stools to be sure that the worm will not grow again. Cure rate of 85–95% has been obtained by one day treatment. A thorough purge is essential in the cases of *T. solium* so that all segments are passed out and cysticercosis does not occur. Because praziquantel does not lead to digestion of the worm and kills encysted larvae as well, it is the drug of choice for *T. solium.*

For *H. nana,* the 2 g dose is repeated daily for 5 days. This is needed because cysticerci of *H. nana* (which are not affected by niclosamide) develop in the jejunal villi of the same host and worms appear in the intestinal lumen after 4 days. However, no purgative is required. In some cases treatment may have to be repeated after 10 days. Praziquantel is now preferred due to single dose treatment.

Adverse effects Niclosamide is tasteless and nonirritating. It is minimally absorbed from g.i.t.—no systemic toxicity occurs. It is well tolerated; minor abdominal symptoms are produced occasionally. Malaise, pruritus and light headedness are rare. Niclosamide is safe during pregnancy and in patients with poor health.

Praziquantel

This anthelmintic has wide ranging activity against *Schistosomes*, other trematodes, cestodes and their larval forms but not nematodes. It is rapidly taken up by susceptible worms and appears to act by causing leakage of intracellular calcium from the membranes → contracture and paralysis. Selectivity of action of praziquantel on tapeworms and flukes may be dependent on the presence of a specific variant of Ca^{2+} channel sensitive to praziquantel in these worms. The tapeworms lose grip of the intestinal mucosa and are expelled. Flukes and schistosomes are also dislodged in tissues and veins. Praziquantel is active against adult as well as juvenile and larval stages of tapeworms.

At relatively higher concentrations, it causes vacuolization of the tegument and release of the contents of tapeworms and flukes followed by their destruction by immune mechanisms of the host. This action appears to be more important in cases of schistosomes and flukes.

Pharmacokinetics Praziquantel is rapidly absorbed from intestines; absorption is enhanced if it is ingested with food. High first pass metabolism in liver limits its systemic bioavailability. Phenytoin, carbamazepine and dexamethasone induce praziquantel metabolism and further decrease its bioavailability. Patients of neurocysticercosis are mostly receiving these drugs which may contribute to therapeutic failure of praziquantel. It crosses blood-brain barrier and attains therapeutic concentrations in the brain and CSF. The plasma t½ is short (1.5 hours). Metabolites are excreted chiefly in urine.

Adverse effects Despite systemic absorption, praziquantel has exhibited no systemic toxicity. It tastes bitter: can produce nausea and abdominal pain. Other side effects are headache, dizziness and sedation. When used for schistosomes and visceral flukes, symptoms like itching, urticaria, rashes, fever and bodyache occur as a reaction to the destroyed parasites. Destruction of cysticerci in the brain may produce neurological complications (*see* below).

No interaction with food, alcohol or tobacco has been noted.

Uses

1. *Tapeworms*: Praziquantel administered as a single dose has achieved 90–100% cure rate in all human tapeworms. This level of efficacy is similar to that of niclosamide and even better in case of *H. nana*.

T. saginata, T. solium: 10 mg/kg single dose in the morning. It is especially valuable in case of *T. solium*, because it kills the tapeworm larvae within the cysts and there are no chances of systemic cysticercosis developing.

H. nana, D. latum: 15–25 mg/kg single dose in the morning. This is much simpler compared to 5 day treatment needed with niclosamide for eradication of *H. nana*. In case of heavy infestation, retreatment after one week is desirable.

2. *Neurocysticercosis*: The role of anthelmintics in this condition is controversial; only selected cases should be treated with them. Praziquantel was the first drug found to be effective in neurocysticercosis: 50 mg/kg daily in 3 divided doses for 15–30 days kills the larvae lodged in brain and other tissues. However, it is now the 2nd choice drug to albendazole (*see* below).
Praziquantel or albendazole are contraindicated in ocular cysticercosis.

3. *Schistosomes*: All 3 species can be treated with 40–75 mg/kg given once or in instalments over one day.

4. *Other flukes*: Praziquantel is the drug of choice for all schistosome and fluke infestations except *Fasciola hepatica*. The flukes respond to 75 mg/kg single day treatment in most cases, and on two occasions in the remaining.

CYSTICIDE 500 mg tab, DISTOCIDE 600 mg tab.

Anthelmintic treatment of neurocysticercosis

Cysticercosis of various organs, including brain, occurs in *T. solium* infestation due to migration of the larvae from the gut to various tissues *via* blood stream. Anthelmintic treatment of

neurocysticercosis may or may not be appropriate, because the cysts do not cause any problem unless the larva dies and its products induce an intense focal reaction. The anthelmintic kills the larvae and precipitates the reaction, resulting in meningeal irritation, rise in intracranial pressure, seizures and other neurological phenomena. However, it prevents future episodes due to spontaneous death of the cysticerci. The decision whether or not to give the anthelmintic may be taken depending on the number, location and viability of the cysts. Active cysts, multiple parenchymal cysts, or intraventricular cysts likely to enlarge and cause hydrocephalus are better treated. Inactive and calcified cysts may be left alone.

Out of the two anthelmintics effective in killing cysticerci, albendazole is now preferred over praziquantel for the following reasons:

- The course of treatment is shorter (8–15 day) compared to praziquantel (15–30 days).
- Cure rates in terms of resolution of symptoms and disappearance of cysts are higher (75–85% with albendazole) than praziquantel (50–60%).
- Corticosteroids (which have to be given concurrently) enhance the absorption of albendazole, but lower the blood levels of praziquantel. Phenytoin and carbamazepine also lower praziquantel levels.
- Albendazole is cheaper.

Whichever anthelmintic is used, corticosteroids (prednisolone 40–60 mg/day or dexamethasone 8–12 mg/day) must be started 2 days before and continued till 2 weeks after completing the anthelmintic course. This is necessary to suppress the inflammatory reaction to the products of killed larvae. Absorption of both albendazole and praziquantel is enhanced by ingesting them with food, particularly fatty food. For patients with seizures (as most of them are), adequate anticonvulsant treatment should be given beforehand and the fits controlled. Phenytoin and carbamazepine are the most commonly used drugs. They induce the metabolism of praziquantel, which may necessitate use of higher doses. The anticonvulsant must be continued through the course of anthelmintic medication and for an indefinite period (mostly 1–6 months) after it. While parenchymal cysts respond to albendazole in 8–15 days, intraventricular and subarachnoid cysts may require treatment for a month or longer. It is very important to kill and expel the adult worm from the gut to eliminate the source of future cysticerci.

☞ PROBLEM DIRECTED STUDY

61.1 A 40-year-old male weighing 60 kg presented with history of 2 episodes of sudden onset fits over the past 3 days. There is no past history of fits or any nervous disorder. The patient has been having headache for the last one month or so which responds to paracetamol. His wife who witnessed the fits gave a description which fitted tonic-clonic seizures. The wife also informed of noticing some behavioural changes for the last 2 months. The fits were followed by confused behaviour and drowsiness for 2–3 hours. There is no family history of fits or mental illness. MRI scan of the brain revealed 4 active cortical parenchymal cysticerci. A diagnosis of neurocysticercosis was made.

(a) Should this patient be treated with specific anthelmintic drug, or only symptomatic treatment of seizures is indicated?

(b) If anthelmintic therapy is to be given, should antiseizure drug also be given? If both are to be given, should they be given concurrently or one after the other or in overlapping manner starting with one first? What should be the sequence?

(c) If anthelmintic is to be given, which drug, dose and duration of treatment would be appropriate and why?

(d) Whether any other medication needs to be given? If so which, when, how long and why? (*see* Appendix-1 for solution)

SECTION 13

CHEMOTHERAPY OF NEOPLASTIC DISEASES

Chapter 62 Anticancer Drugs

The anticancer drugs either kill cancer cells or modify their growth. However, selectivity of majority of drugs is limited and they are one of the most toxic drugs used in therapy.

Treatment of malignant diseases with drugs is a rather recent development—started after 1940 when nitrogen mustard was used, but progress has been rapid, both in revealing pathobiology of the diseases and in discovery of new drugs. The latest innovations target growth factors, specific signaling pathways, angiogenesis, tumour antigens, etc. to introduce a different spectrum of drugs. In addition, attempts have been made to define optimal combinations, treatment strategies and patient support measures. Cancer chemotherapy is now of established value and a highly specialized field to be handled by oncology specialists supported by a multidisciplinary team. Only the general principles and an outline will be presented here.

In addition to their prominent role in leukaemias and lymphomas, drugs are used in conjunction with surgery, radiotherapy and immunotherapy in the *combined modality approach* for many solid tumours, especially metastatic. In malignant diseases, drugs are used with the aim of:

1. *Cure or prolonged remission* Chemotherapy is the primary treatment modality that can achieve cure or prolonged remission in:

Acute leukemias	in children	Choriocarcinoma
Wilm's tumour		Hodgkin's disease
Ewing's sarcoma		Lymphosarcoma
Retinoblastoma		Burkitt's lymphoma
Rhabdomyosarcoma		Testicular teratomas
		Seminoma
		Mycosis fungoides

2. *Palliation* Gratifying results are obtained (shrinkage of evident tumour, alleviation of symptoms) and life is prolonged by chemotherapy in:

Breast cancer	Chronic lymphatic leukemia
Ovarian carcinoma	Chronic myeloid leukemia
Endometrial carcinoma	Non-Hodgkin lymphomas
Myeloma	Head and neck cancers
Prostatic carcinoma	Lung (small cell) cancer

Many other malignant tumours are less sensitive to drugs—life may or may not be prolonged by chemotherapy. Tumours that are largely refractory to presently available drugs are:

Colorectal carcinoma	Malignant melanomas
Carcinoma pancreas	Bronchogenic carcinoma
Carcinoma stomach	(non small cell)
Carcinoma esophagus	Hepatoma
Renal carcinoma	Sarcoma

3. *Adjuvant chemotherapy* Drugs are used to mop up any residual malignant cells (micrometastases) after surgery or radiotherapy. This is routinely employed now and may achieve

apparent cure, especially in early breast, lung and colonic cancers.

CLASSIFICATION

A. Cytotoxic drugs

1.	*Alkylating agents*	
	Nitrogen mustards	Mechlorethamine (Mustine HCl) Cyclophosphamide, Ifosfamide, Chlorambucil, Melphalan
	Ethylenimine	Thio-TEPA
	Alkyl sulfonate	Busulfan
	Nitrosoureas	Carmustine (BCNU), Lomustine (CCNU)
	Triazine	Dacarbazine (DTIC), Temozolomide
	Methylhydrazine	Procarbazine
2.	*Platinum coordination complexes*	Cisplatin, Carboplatin, Oxaliplatin
3.	*Antimetabolites*	
	Folate antagonist	Methotrexate (Mtx) Pemetrexed
	Purine antagonist	6-Mercaptopurine (6-MP), 6-Thioguanine (6-TG), Azathioprine, Fludarabine
	Pyrimidine antagonist	5-Fluorouracil (5-FU), Capecitabine, Cytarabine (cytosine arabinoside)
4.	*Microtubule damaging agents*	Vincristine (Oncovin), Vinblastine, Vinorelbine Paclitaxel, Docetaxel Estramustine
5.	*Topoisomerase-2 inhibitors*	Etoposide
6.	*Topoisomerase-1 inhibitors*	Topotecan, Irinotecan
7.	*Antibiotics*	Actinomycin D (Dactinomycin), Doxorubicin, Daunorubicin (Rubidomycin), Epirubicin, Mitoxantrone, Bleomycins, Mitomycin C
8.	*Miscellaneous*	Hydroxyurea, L-Asparaginase, Tretinoin, Arsenic trioxide

B. Targeted drugs

1.	*Tyrosine protein-kinase inhibitors*	Imatinib, Nilotinib
2.	*EGF receptor inhibitors*	Gefitinib, Erlotinib Cetuximab
3.	*Angiogenesis inhibitors*	Bevacizumab Sunitinib
4.	*Proteasome inhibitor*	Bortezomib
5.	*Unarmed monoclonal antibody*	Rituximab, Trastuzumab

C. Hormonal drugs

1.	*Glucocorticoids*	Prednisolone and others
2.	*Estrogens*	Fosfestrol, Ethinylestradiol
3.	*Selective estrogen receptor modulators*	Tamoxifen, Toremifene
4.	*Selective estrogen receptor down regulators*	Fulvestrant
5.	*Aromatase inhibitors*	Letrozole, Anastrozole, Exemestane
6.	*Antiandrogen*	Flutamide, Bicalutamide
7.	*5-α reductase inhibitor*	Finasteride, Dutasteride
8.	*GnRH analogues*	Nafarelin, Leuprorelin Triptorelin
9.	*Progestins*	Hydroxyprogesterone acetate, etc.

GENERAL TOXICITY OF CYTOTOXIC DRUGS

Majority of the cytotoxic drugs have more profound effect on rapidly multiplying cells, because the most important target of action are the nucleic acids and their precursors, and rapid

nucleic acid synthesis occurs during cell division. Many cancers (especially large solid tumours) have a lower growth fraction (lower percentage of cells are in division) than normal bone marrow, epithelial linings, reticuloendothelial (RE) system and gonads. These tissues are particularly affected in a dose-dependent manner by majority of drugs; though, there are differences in susceptibility to individual members.

1. *Bone marrow* Depression of bone marrow results in granulocytopenia, agranulocytosis, thrombocytopenia, aplastic anaemia. This is the most serious toxicity; often limits the dose that can be employed. Infections and bleeding are the usual complications.

2. *Lymphoreticular tissue* Lymphocytopenia and inhibition of lymphocyte function results in suppression of cell mediated as well as humoral immunity.

Because of action (1) and (2) + damage to epithelial surfaces, the host defence mechanisms (specific as well as nonspecific) are broken down → susceptibility to all infections is increased. Of particular importance are the opportunistic infections due to low pathogenicity organisms. Infections by fungi (*Candida* and others causing deep mycosis), viruses (*Herpes zoster*, cytomegalo virus), *Pneumocystis jiroveci* (a fungus) and *Toxoplasma* are seen primarily in patients treated with anticancer drugs.

3. *Oral cavity:* The oral mucosa is particularly susceptible to cytotoxic drugs because of high epithelial cell turnover. Many chemotherapeutic drugs, particularly fluorouracil, methotrexate, daunorubicin, doxorubicin produce stomatitis as an early manifestation of toxicity. The gums and oral mucosa are regularly subjected to minor trauma, and breaches are common during chewing. Oral microflora is large and can be the source of infection. Neutropenia and depression of immunity caused by the drug indirectly increase the chances of oral infections. Thrombocytopenia may cause bleeding gums. Xerostomia due to the drug may cause rapid progression of dental caries.

4. *GIT* Diarrhoea, shedding of mucosa, haemorrhages occur due to decrease in the rate of renewal of the gastrointestinal mucous lining. Drugs that prominently cause mucositis are—bleomycin, actinomycin D, daunorubicin, doxorubicin, fluorouracil and methotrexate.

Nausea and vomiting are prominent with many cytotoxic drugs. This is due to direct stimulation of CTZ by the drug, as well as generation of emetic impulses/mediators from the upper g.i.t. and other areas (*see* Ch. 47).

Emetogenic potential of cytotoxic drugs

High	*Moderate*	*Mild*
Cisplatin	Carboplatin	Bleomycin
Mustine	Cytarabine	Chlorambucil
Cyclophosphamide	Procarbazine	Busulfan
Actinomycin D	Vinblastine	Fluorouracil
Dacarbazine	Doxorubicin	6-Thioguanine
Lomustine	Daunorubicin	Hydroxyurea
	Ifosfamide	Vincristine
	6-Mercapto-purine	Methotrexate
		Etoposide
	Paclitaxel	l-Asparaginase

5. *Skin* Alopecia occurs due to damage to the cells in hair follicles. Dermatitis is another complication.

6. *Gonads* Inhibition of gonadal cells causes oligozoospermia and impotence in males; inhibition of ovulation and amenorrhoea are common in females.

Damage to the germinal cells may result in mutagenesis.

7. *Foetus* Practically all cytotoxic drugs given to pregnant women profoundly damage the developing foetus → abortion, foetal death, teratogenesis.

8. *Carcinogenicity* Secondary cancers, especially leukaemias, lymphomas and histocytic tumours appear with greater frequency many years after the use of cytotoxic drugs. This may be due to depression of cell mediated and humoral *blocking factors* against neoplasia.

9. *Hyperuricaemia* This is secondary to massive cell destruction (uric acid is a product

of purine metabolism) and is especially likely to occur in leukaemias and bulky lymphomas. Acute renal failure, gout and urate stones in the urinary tract may develop. Allopurinol is protective by decreasing uric acid synthesis.

In addition to these general toxicities, individual drugs may produce specific adverse effects, e.g. neuropathy by vincristine, cardiomyopathy by doxorubicin, cystitis and alopecia by cyclophosphamide.

NOTES ON INDIVIDUAL DRUGS

ALKYLATING AGENTS

These compounds produce highly reactive carbonium ion intermediates which transfer alkyl groups to cellular macromolecules by forming covalent bonds. The position 7 of guanine residues in DNA is especially susceptible, but other molecular sites are also involved. They may react with carboxyl, hydroxyl, amino, sulfhydryl and phosphate groups of biomacromolecules. Alkylation results in cross linking/abnormal base pairing/scission of DNA strand. Cross linking of nucleic acids with proteins can also take place.

Alkylating agents have cytotoxic and radiomimetic (like ionizing radiation) actions. Most are cell cycle non-specific, i.e. act on dividing as well as resting cells. Some have CNS stimulant and cholinergic properties.

Mechlorethamine (Mustine HCl) It is the first nitrogen mustard; highly reactive and local vesicant—can be given only by i.v. route. It produces many acute effects like nausea, vomiting and haemodynamic changes. Extravasation during i.v. injection may cause sloughing. Hodgkin and non-Hodgkin lymphomas are the main indications. It has been a component of erstwhile MOPP regimen.

Dose: 0.1 mg/kg i.v. daily × 4 days; courses may be repeated at suitable intervals.

MUSTINE 10 mg dry powder in vial.

Cyclophosphamide It is inactive as such: produces few acute effects and is not locally damaging. Transformation into active metabolites (aldophosphamide, phosphoramide mustard) occurs in the liver, and a wide range of antitumour actions is exerted. It has prominent immunosuppressant property. Thus, it is one of the most popular alkylating agents useful in many solid tumours. It is less damaging to platelets, but alopecia and cystitis (due to another metabolite acrolein) are prominent. Chloramphenicol retards the metabolism of cyclophosphamide.

Dose: 2–3 mg/kg/day oral; 10–15 mg/kg i.v. every 7–10 days, i.m. use also possible.

ENDOXAN, CYCLOXAN 50 mg tab; 200, 500, 1000 mg inj.

Ifosfamide This congener of cyclophosphamide has a longer and dose-dependent t½. It has found utility in bronchogenic, breast, testicular, bladder, head and neck carcinomas, osteogenic sarcoma and some lymphomas. The dose limiting toxicity of ifosphamide is haemorrhagic cystitis. To prevent the same, *mesna* is routinely given with it. Mesna is a –SH compound that is excreted in urine—binds and inactivates the vasicotoxic metabolites of ifosfamide and cyclophosphamide. Ifosfamide causes less alopecia and is less emetogenic than cyclophosphamide.

HOLOXAN-UROMITEXAN 1 g vial + 3 amps of mesna 200 mg inj.; HOLOXAN, IPAMIDE 1 g inj.

Chlorambucil It is a very slow acting alkylating agent, especially active on lymphoid tissue: Myeloid tissue is largely spared. It is the drug of choice for long-term maintenance therapy for chronic lymphatic leukaemia; non-Hodgkin lymphoma and few solid tumours also resolve. It has some immunosuppressant property.

Dose: 4–10 mg (0.1–0.2 mg/kg) daily for 3–6 weeks, then 2 mg daily for maintenance; LEUKERAN 2, 5 mg tab.

Melphalan It is very effective in multiple myeloma and has been used in advanced ovarian cancer. Bone marrow depression is the most important toxicity. Infections, diarrhoea and pancreatitis are the complications.

Dose: 10 mg daily for 7 days or 6 mg/day for 2–3 weeks—4 weeks gap—2 to 4 mg daily for maintenance orally. Also used for regional perfusion in malignant melanoma. ALKERAN 2, 5 mg tab, 50 mg per vial for inj.

Thio-TEPA It is an ethylenimine: does not require to form an active intermediate. It has high

toxicity: seldom used now in ovarian and bladder cancer.

Dose: 0.3–0.4 mg/kg i.v. at 1–4 week intervals.

THIOTEPA 15 mg per vial inj.

Busulfan It is highly specific for myeloid elements; granulocyte precursors being the most sensitive, followed by those of platelets and RBC. It produces little effect on lymphoid tissue and g.i.t. Hyperuricaemia is common; pulmonary fibrosis and skin pigmentation are the specific adverse effects. Sterility also occurs. It is the drug of choice for chronic myeloid leukaemia.

Dose: 2–6 mg/day (0.06 mg/kg/day) orally.

MYLERAN, BUSUPHAN 2 mg tab.

Nitrosoureas These are highly lipid soluble alkylating agents with a wide range of antitumour activity. They cross blood-brain barrier—are effective in meningeal leukaemias and brain cancer. Nausea, vomiting are common and CNS effects also occur. Bone marrow depression is peculiarly delayed, taking nearly 6 weeks to develop. Visceral fibrosis and renal damage can occur:

Lomustine (CCNU): 100–130 mg/m^2 BSA single oral dose every 6 weeks; LOMUSTINE 40, 100 mg cap.

Dacarbazine (DTIC) After activation in liver, it acts by methylating DNA and interfering with its function. The most important indication is malignant melanoma; also used in Hodgkin's disease. Nausea, vomiting, flu-like symptoms, neuropathy and myelosuppression are the prominent adverse effects.

Dose: 3.5 mg/kg/day i.v. for 10 days, repeat after 4 weeks.

DACARIN 100, 200, 500 mg inj; DACARZINE 200 mg/vial inj.

Temozolamide This orally active triazine methylating agent is the drug of choice for glioma and other malignant brain tumours; also utilized in melanoma. Adverse effects are similar to dacarbazine.

Dose: 100–250 mg/day; GLIOZ 20, 100, 250 mg caps.

Procarbazine It is not a classical alkylating agent, but has similar properties. After metabolic activation (it is inactive as such), procarbazine methylates and depolymerizes DNA causing chromosomal damage. Inhibition of nucleic acid synthesis also occurs. Beause of damage to DNA, mutagenic and carcinogenic potential has been detected. It is a component of MOPP regimen for Hodgkin's and related lymphomas, and is an alternative drug for brain tumours.

Procarbazine is a weak MAO inhibitor; produces sedation and other CNS effects, and can interact with foods and drugs. Alcohol causes hot flushing and a disulfiram-like reaction in patients taking procarbazine. Males may suffer sterility. Vomiting, leucopenia, thrombocytopenia are the prominent toxicities.

Dose: 100 mg/m^2/day for 14 days in 28 days cycles.

INDICARB 20 mg cap, NEOZINE, P-CARZINE 50 mg cap.

PLATINUM COORDINATION COMPLEXES

Cisplatin It is hydrolysed intracellularly to produce a highly reactive moiety which causes cross linking of DNA. The favoured site is N^7 of guanine residue. It can also react with –SH groups of cytoplasmic and nuclear proteins. Effects resemble those of alkylating agents and radiation. It is bound to plasma proteins, penetrates tissues and is slowly excreted unchanged in urine with a t½ of about 72 hrs. Negligible amounts enter brain.

A copper transporter CTR1 is involved in the entry of platinum complexes into the tumour cells. The same are extruded from the cells by the transporter MRP1 as well as by copper efflux proteins. Resistance to cisplatin can be imparted by variation in the levels of these proteins.

Cisplatin is very effective in metastatic testicular and ovarian carcinoma. It is widely used in many other solid tumours like lung, bladder, esophageal, gastric, hepatic, head and neck carcinomas.

Cisplatin is administered by slow i.v. infusion 50–100 mg/m^2 BSA every 3–4 weeks; CISPLATIN, CISPLAT, PLATINEX 10 mg/10 ml, 50 mg/50 ml vial.

Cisplatin is a highly emetic drug. Antiemetics are routinely administered before infusing it. The most important toxicity is renal impairment which is dependent on total dose administered. Renal toxicity can be reduced by maintaining good hydration. Tinnitus, deafness, sensory neuropathy and hyperuricaemia are other problems. A shock-like state sometimes occurs during i.v. infusion.

Carboplatin It is a less reactive second generation platinum compound that is better tolerated and has a toxicity profile different from cisplatin, but mechanism of action and clinical utility are similar. Nephrotoxicity, ototoxicity and neurotoxicity are low. Nausea and vomiting is milder and is delayed: only infrequently limits the dose. The dose-limiting toxicity is thrombocytopenia and less often leucopenia. Liver dysfunction may occur. Because of less plasma protein binding, it is rapidly eliminated by the kidney with a plasma t½ of 2–4 hours. A small fraction that is bound is excreted over days. It is primarily indicated in ovarian carcinoma of epithelial origin, and has shown promise in squamous carcinoma of head and neck, small cell lung cancer, breast cancer and seminoma.

ONCOCARBIN 150 mg inj, KEMOCARB 150, 450 mg/vial inj. 400 mg/m^2 as an i.v. infusion over 15–60 min, to be repeated only after 4 weeks.

Oxaliplatin This third generation platinum complex differs significantly from cisplatin. It appears to target different biomolecules. Pathways which confer resistance to cisplatin are not operative in its case. Resistance does not easily develop to oxaliplatin, and it retains activity against tumours that have become resistant to cisplatin. Oxaliplatin is highly effective in colorectal cancer; 5-fluorouracil markedly synergises with it. Gastroesophageal and pancreatic cancers also respond.

The dose limiting toxicity is peripheral neuropathy. Sensory paresthesias involving arms, legs, mouth and throat are common. An acute form of neuropathy is usually triggered by exposure to cold. Myelosuppression is modest, but diarrhoea and acute allergic reactions are reported.

Dose: 85 mg/m^2 i.v. every 2 weeks.

KINAPLAT, OPLATIN 50 mg in 25 ml and 100 mg in 50 ml vial.

ANTIMETABOLITES

These are analogues related to the normal components of DNA or of coenzymes involved in nucleic acid synthesis. They competitively inhibit utilization of the normal substrate or get themselves incorporated forming dysfunctional macromolecules.

1. Folate antagonist

Methotrexate (Mtx)

This folic acid analogue is one of the oldest and highly efficacious antineoplastic drugs which acts by inhibiting dihydrofolate reductase (DHFRase)—blocking the conversion of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA). Utilizing the folate carrier it enters into cells and is transformed to more active polyglutamate form by the enzyme folypolyglutamate synthase (FPGS). Tetrahydrofolic acid is an essential coenzyme required for one carbon transfer reactions in *de novo* purine synthesis and amino acid interconversions. The inhibition is pseudo-irreversible because Mtx has 50,000 times higher affinity for the enzyme than the normal substrate.

Methotrexate has cell cycle specific action—kills cells in S phase; In addition to DHFRase it inhibits thymidylate synthase as well so that DNA synthesis is primarily affected. However, synthesis of RNA and protein also suffers. It exerts major toxicity on bone marrow—low doses given repeatedly cause megaloblastic anaemia, but high doses produce pancytopenia. Mucositis and diarrhoea are common side effects. Desquamation and bleeding may occur in g.i.t.

Methotrexate is absorbed orally, 50% plasma protein bound, little metabolized and largely excreted unchanged in urine. Salicylates, sulfonamides, dicumerol displace it from protein binding sites. Aspirin and sulfonamides enhance toxicity of Mtx by decreasing its renal tubular secretion.

The toxicity of Mtx cannot be overcome by folic acid, because it will not be converted to the active coenzyme form. However, *Folinic acid* (N5 formyl THFA, cirtrovorum factor) rapidly reverses the effects. Thymidine also counteracts Mtx toxicity.

Methotrexate is apparently curative in choriocarcinoma: 15–30 mg/day for 5 days orally or 20–40 mg/m^2 BSA i.m. or i.v. twice weekly.

In a dose of 2.5–15 mg/day it is highly effective in maintaining remission in children with acute leukaemias, but it is not good for inducing remission: Mtx is widely used in non-Hodgkin lymphoma, breast, bladder, head and neck cancers, osteogenic sarcoma, etc. It has prominent immunosuppressant property useful in rheumatoid arthritis, psoriasis and many other antoimmune disorders (*see* Ch. 63).

NEOTREXATE 2.5 mg tab, 50 mg/2 ml inj; BIOTREXATE 2.5 mg tab, 5, 15, 50 mg/vial inj.

The use of folinic acid *rescue* has permitted much higher doses of Mtx and has enlarged its scope to many difficult-to-treat neoplasms. A nearly 100 times higher dose (250–1000 mg/m^2 BSA) of Mtx is infused i.v. over 6 hours, followed by 3–15 mg i.v. calcium leucovorin within 3 hours, repeated as required. This procedure can be repeated weekly.

Pemetrexed This newer congener of Mtx primarily targets the enzyme thymidylate synthase. Though, it is also a DHFRase inhibitor, the pool of THFA is not markedly reduced. Like Mtx it utilizes the folate carrier to enter cells and requires transformation into polyglutamate form by FPGS for activity enhancement. Adverse effects (mucositis, diarrhoea, myelosuppression) are similar to Mtx, but a painful, itching erythematous rash, mostly involving the hands and feet, 'hand-foot syndrome' is quite common. Dexamethasone can relieve it, and pretreatment can reduce its incidence. Low dose folic acid and vit B_{12} pretreatment is recommended to limit pemetrexed induced myelosuppression. NSAIDs should be avoided as they decrease pemetrexed clearance and may increase toxicity.

In combination with cisplatin, pemetrexed is approved for treatment of mesoepithelioma and non-small cell lung carcinoma.

Dose: 500 mg/m^2 i.v. every 3 weeks.

PEMEX 500 mg vial for i.v. inj.

2. Purine antagonists

Mercaptopurine (6-MP) and thioguanine (6-TG) These are highly effective antineoplastic drugs. After synthesis in the body to the corresponding monoribonucleotides, they inhibit the conversion of inosine monophosphate to adenine and guanine nucleotides that are the building blocks for RNA and DNA. There is also feedback inhibition of *de novo* purine synthesis. They also get incorporated into RNA and DNA which are dysfunctional.

6-MP and 6-TG are especially useful in childhood acute leukaemia, choriocarcinoma and have been employed in some solid tumours as well. In acute leukaemia, both have been used in combination regimens to induce remission and 6-MP for maintaining remission as well.

All antipurines are absorbed orally (though incompletely). Azathioprine and 6-MP are oxidised by xanthine oxidase; their metabolism is inhibited by allopurinol; dose has to be reduced to ¼–½ if allopurinol is given concurrently. Thioguanine is not a substrate for xanthine oxidase; follows a different (S-methylation) metabolic path and its dose need not be reduced if allopurinol is given.

Methylation by thiopurine methyl transferase (TPMT) is an additional pathway of 6-MP metabolism. Genetic deficiency of TPMT makes the individual more susceptible to 6-MP induced myelosuppression, mucositis and gut damage, while over expression of TPMT is an important mechanism of 6-MP resistance in acute leukaemia cells. Toxicity of azathioprine is also enhanced in TPMT deficiency.

The main toxic effect of antipurines is bone marrow depression, which develops slowly. Mercaptopurine causes more nausea and vomiting than 6-TG. It also produces a high incidence of reversible jaundice. Hyperuricaemia occurs with both, and can be reduced by allopurinol.

Dose: 6-Mercaptopurine: 2.5 mg/kg/day, half dose for maintenance; PURINETHOL, EMPURINE, 6-MP, 50 mg tab. 6-Thioguanine: 100–200 mg/m^2/day for 5–20 days; 6-TG 40 mg tab.

Azathioprine This antipurine acts by getting converted to 6-MP, but has more prominent immunosuppressant action (*see* p. 882), probably because of selective uptake into immune cells

and intracellular conversion to 6-MP. This is further synthesized into the nucleic acid inhibitory neucleotides. Azathioprine primarily suppresses cell mediated immunity (CMI) and is used mainly in autoimmune diseases (rheumatoid arthritis, ulcerative colitis) as well as in organ transplantation.

Dose: Azathioprine 3–5 mg/kg/day, maintenance 1–2 mg/kg/day; IMURAN, TRANSIMUNE, AZOPRINE 50 mg tab.

Fludarabine This newer purine antimetabolite is phosphorylated intracellularly to the active triphosphate form which then inhibits DNA polymerase and ribonucleotide reductase, interferes with DNA repair as well as gets incorporated to form dysfunctional DNA. Tumour cell apoptosis is promoted by multiple mechanisms confering activity even in slow growing neoplasms. It is indicated in chronic lymphatic leukaemia and non-Hodgkin's lymphoma that have recurred after treatment. Prominent adverse effects are chills, fever, myalgia, arthralgia and vomiting after injection, myelosuppression and opportunistic infections (it is a potent suppressant of CMI).

Dose: 25 mg/m^2 BSA daily for 5 days every 28 days by i.v. infusion

FLUDARA 50 mg/vial inj.

3. Pyrimidine antagonists

Pyrimidine analogues have varied applications as antineoplastic, antifungal and antipsoriatic agents.

Fluorouracil (5-FU) is converted in the body to the corresponding nucleotide 5-fluoro-2-deoxyuridine monophosphate, which forms a covalent ternary complex with methyl-THFA and tymidylate synthase (TS) resulting in irreversible inhibition of TS. Consequently conversion of deoxyuridilic acid to deoxythymidylic acid is blocked. Selective failure of DNA synthesis occurs due to non-availability of thymidylate. Accordingly, thymidine can partially reverse 5-FU toxicity. 5-FU itself gets incorporated into RNA, interferes with RNA synthesis and function contributing to its cytotoxicity. Even resting cells are affected, though rapidly multiplying ones are more susceptible. Since inhibition of TS by 5-FU is dependednt on the prsence of THFA, concurrent infusion of leucovorin enhances the efficacy of 5-FU. Cisplatin and oxaliplatin also synergise with 5-FU. Most protocols now employ 5-FU along with leucovorin and cisplatin/oxaliplatin.

Currently, 5-FU is a commonly used anticancer drug for many solid malignancies, especially of colon, rectum, stomach, pancreas, liver, urinary bladder, head and neck. Oral absorption of 5-FU is unreliable. It is primarily used by i.v. infusion. 5-FU is rapidly metabolized by dihydropyrimidine dehydrogenase (DPD) resulting in a plasma t½ of 15–20 min after i.v. infusion. Genetic deficiency of DPD predisposes to severe 5-FU toxicity. Major toxicity of 5-FU is exerted on the bone marrow and g.i.t. causing myelosuppression, mucositis, diarrhoea, nausea and vomiting. Peripheral neuropathy (hand-foot syndrome) also occurs.

Dose: 500 mg/m^2 i.v. infusion over 1–3 hours weekly for 6–8 weeks, or 12 mg/kg/day i.v. for 4 days followed by 6 mg/kg i.v. on alternate days, 3–4 doses.

FLURACIL, FIVE FLURO, FIVOCIL 250 mg/5 ml and 500 mg/10 ml vial.

A 1% topical solution applied twice daily for 3–6 weeks has yielded gratifying results in superficial basal cell carcinoma, and in actinic keratosis.

Capecitabine It is an orally active prodrug of 5-FU. After absorption it is converted to deoxy-5-fluorouridine in the liver and released in blood. Taken up by cells, it is hydrolysed to 5-FU by thymidine phosphorylase. Because many breast and colorectal cancer cells express large quantity of this enzyme, they generate more 5-FU and suffer higher toxicity than normal cells. A combined regimen of capecitabine + oxaliplatin is frequently used in metastatic colorectal cancer. It has also been utilized in 2nd line treatment of metastatic breast cancer along with taxanes. Hand-foot syndrome and diarrhoea are prominent adverse effects, but bone marrow depression and mucositis are less marked.

Cytarabine (Cytosine arabinoside) This cytidine analogue is phosphorylated in the body to the corresponding nucleotide which inhibits DNA synthesis. The triphosphate of cytarabine is an inhibitor of DNA polymerase, as well as blocks production of cytidilic acid. However, its incorporation into DNA is now considered to be

more important for the expression of its cytotoxicity. DNA repair is also affected. Cytarabine is cell cycle specific and acts primarily during 'S' phase. Cytarabine is useful only in leukaemias and lymphomas, and is not effective in solid tumours. Primary use is induction of remission in acute myelogenous as well as lymphoblastic leukaemia in children and in adults. It is also used for blast crisis in chronic myelogenous leukaemia and non-Hodgkin's lymphoma. Because cytarabine is rapidly deaminated and cleared from plasma, it is administered either by rapid i.v. injection (100 mg/m^2) once or twice daily for 5–10 days, or by continuous i.v. infusion over 5–7 days. A high dose regimen of 1–3 g/day has also been used.

CYTABIN, CYTOSAR, BIOBIN, REMCYTA 100, 500, 1000 mg inj.

Major toxic effects are due to bone marrow suppression—leukopenia, thrombocytopenia, anaemia and mucositis, diarrhoea.

MICROTUBULE DAMAGING AGENTS

Vinca alkaloids

These are mitotic inhibitors, bind to microtubular protein—'tubulin', prevent its polymerization and assembly of microtubules, cause disruption of mitotic spindle and interfere with cytoskeletal function. The chromosomes fail to move apart during mitosis: metaphase arrest occurs. They are cell cycle specific and act in the mitotic phase. Vincristine and vinblastine, though closely related chemically, have different spectrum of antitumour activity and toxicity.

Vincristine (oncovin) It is a rapidly acting drug, very useful for inducing remission in childhood acute lymphoblastic leukaemia, but is not good for maintenance therapy. Other indications are acute myeloid leukaemia, Hodgkin's disease, Wilms' tumour, Ewing's sarcoma, neuroblastoma and carcinoma lung. Prominent adverse effects are peripheral neuropathy and alopecia. It also causes ataxia, nerve palsies, autonomic dysfunction (postural hypotension, paralytic ileus, urinary retention) and seizures. Bone marrow depression is minimal, but syndrome of inappropriate secretion of ADH (SIADH) can occur.

Dose: 1.5–2 mg/m^2 BSA i.v. weekly.

ONCOCRISTIN, CYTOCRISTIN 1 mg/vial inj.

Vinblastine It is primarily employed along with other drugs in Hodgkin's disease, Kaposi sarcoma, neuroblastoma, non-Hodgkin's lymphoma, breast and testicular carcinoma. Bone marrow depression is more prominent, while neurotoxicity and alopecia are less marked than with vincristine. SIADH has been noted. It can cause local tissue necrosis if extravasation occurs during i.v. infusion.

Dose: 0.1–0.15 mg/kg i.v. weekly × 3 doses.

UNIBLASTIN, CYTOBLASTIN 10 mg/vial inj.

Vinorelbine This is a newer semisynthetic vinblastine analogue with similar mechanism of action inhibiting microtubule assembly and causing metaphase arrest. As a single agent or combined with others, its primary indication is non-small cell lung cancer. As a second line drug, it is useful in advanced breast and ovarian carcinoma. Neutropenia is the dose limiting toxicity. Thrombocytopenia and neurotoxicity are less marked.

Dose: 25–30 mg/m^2 weekly by slow i.v. injection over 10 min.

VINOTEC, RELBOVIN 10 mg, 50 mg vial.

Taxanes

Paclitaxel It is a complex diterpin taxane obtained from bark of the Western yew tree, which exerts cytotoxic action by a novel mechanism. It binds to β-tubulin and enhances its polymerization: a mechanism opposite to that of vinca alkaloids. The microtubules are stabilized and their depolymerization is prevented. This stability results in inhibition of normal dynamic reorganization of the microtubule network that is essential for interphase and mitotic functions. Abnormal arrays or 'bundles' of microtubules are produced throughout the cell cycle. Cytotoxic action of paclitaxel emphasizes the importance of tubulin-microtubule dynamic equilibrium.

The approved indications of paclitaxel are metastatic ovarian and breast carcinoma after failure of first line chemotherapy and relapse cases. It has also shown efficacy in advanced

cases of head and neck cancer, small cell lung cancer, esophageal adenocarcinoma, urinary and hormone refractory prostate cancer. AIDS related Kaposi's sarcoma also responds.

Dose: 135–175 mg/m^2 by i.v. infusion over 3 hr, repeated every 3 weeks.

ALTAXEL, MITOTAX, ONCOTAXEL 30 mg, 100 mg, 260 mg as 6 mg/ml in cremophor (polyoxyethylated castor oil + alcohol + water) emulsion.

Acute anaphylactoid reactions occur because of the cremophor solvent. Pretreatment with dexamethasone, H_1 and H_2 antihistaminics is routinely used to suppress the reaction. The major toxicity is reversible myelosuppression (mainly granulocytopenia) and 'stocking and glove' neuropathy. Nausea, chest pain, arthralgia, myalgia, mucositis and edema can be troublesome.

Docetaxel More potent congener of paclitaxel with the same mechanism of action. It has been found effective in breast and ovarian cancer refractory to first line drugs. Small cell cancer lung, pancreatic, gastric and head/neck carcinomas are the other indications. Major toxicity is neutropenia (more than paclitaxel), but neuropathy is less frequent. Arrhythmias, fall in BP and fluid retention occur with repeated courses.

Dose: 75–100 mg/m^2 i.v. over 1 hr; repeat at 3 weeks.

DOCECAD, DOCETERE, DOXEL 20 mg, 80 mg, 120 mg/vial inj.

Docetaxel is formulated in polysorbate medium which produces less acute hypersensitivity reactions.

Estramustine It is a complex of *estradiol* with a nitrogen mustard *normustine*, which has weak estrogenic but no alkylating property. However, it binds to β-tubulin and interferes with its organization into microtubules exerting antimitotic action. Estramustine gets concentrated in prostate and the only indication is advanced or metastatic prostate cancer that is nonresponsive to hormone therapy. It is orally active, undergoes first pass metabolism in liver into active as well as inactive metabolites, which are mainly eliminated in faeces. A small amount is hydrolysed into estradiol and normustine producing myelosuppression and estrogenic adverse effects, *viz.* gynaecomastia, impotence, fluid retention, increased risk of thromboembolism and impaired glucose tolerance. Angioedema and other hypersensitivity reactions also occur.

Dose: 4–5 mg/kg orally 3 times daily.

ESMUST, ESTRAM 140 mg cap.

TOPOISOMERASE-2 INHIBITOR

Etoposide It is a semisynthetic derivative of podophyllotoxin, a plant glycoside. It is not a mitotic inhibitor, but arrests cells in the G_2 phase and causes DNA breaks by affecting DNA topoisomerase-2 function. While the cleaving of double stranded DNA is not interfered, the subsequent resealing of the strand is prevented. Etoposide is used in testicular tumours, lung cancer, Hodgkin's and other lymphomas, carcinoma bladder and stomach. Alopecia, leucopenia and g.i.t. disturbances are the main toxicity. Oral bioavailability is 50%; oral dose is double than i.v. dose.

Dose: 50–100 mg/m^2/day i.v. for 5 days, 100–200 mg/day oral.

PELTASOL 100 mg in 5 ml inj., LASTET 25, 50, 100 mg cap, 100 mg/5 ml inj, ACTITOP 50, 100 mg cap, 100 mg/5 ml inj.

TOPOISOMERASE-1 INHIBITORS

Camptothecin analogues

Topotecan, Irinotecan are two semisynthetic analogues of camptothecin, an antitumour principle obtained from a Chinese tree. They act in a manner similar to etoposide, but interact with a different enzyme (DNA topoisomerase-1). Their binding to this nuclear enzyme allows single strand breaks in DNA, but not its resealing after the strand has untwisted. They damage DNA during replication; act in the S phase and arrest cell cycle at G_2 phase.

Topotecan is used in metastatic carcinoma of ovary and small cell lung cancer after primary chemotherapy has failed. Combined with cisplatin, it has been used in cervical cancer. The major toxicity is bone marrow depression, especially neutropenia. Other adverse effects are pain abdomen, vomiting anorexia and diarrhoea.

Dose: 1.5 mg/m^2 i.v. over 30 min daily for 5 days every 3 weeks, 4 or more cycles. TOPOTEC, CANTOP 2.5 mg inj.

Irinotecan It is a prodrug which is decarboxylated in liver to the active metabolite SN-38. Cholinergic effects are produced in some patients because it inhibits AChE. These effects can be suppressed by prior atropinization. Irinotecan is primarily indicated in metastatic/advanced colorectal carcinoma; also in cancer lung/cervix/ovary and stomach. It has been combined with 5-FU and leucovorin. Dose limiting toxicity is diarrhoea. Neutropenia, thrombocytopenia, haemorrhage, bodyache and weakness are the other adverse effects.

The active metabolite SN-38 is inactivated by glucuronidation in the liver. Individuals expressing the UGT1A1*28 allele of glucuronyl transferase enzyme are more susceptible to irinotecan induced diarrhoea and neutropenia, because they fail to inactivate SN-38.

Dose: 125 mg/m^2 i.v. over 90 min, weekly for 4 weeks.

IRINOTEL, IRNOCAM 40 mg (2 ml), 100 mg (5 ml) inj.

ANTIBIOTICS

These are products obtained from microorganisms and have prominent antitumour activity. Practically all of them intercalate between DNA strands and interfere with its template function.

Actinomycin D (Dactinomycin) It is a very potent antineoplastic drug, highly efficacious in Wilms' tumour and childhood rhabdomyosarcoma. Good results have also been obtained in Mtx resistant choriocarcinoma, Ewing's sarcoma and metastatic testicular carcinoma. In addition to blocking RNA transcription (due to interference with template function of DNA) dactinomycin causes single strand breaks in DNA. Prominent adverse effects are vomiting, stomatitis, diarrhoea, erythema and desquamation of skin, alopecia and bone marrow depression.

Dose: 15 µg/kg i.v. daily for 5 days.

DACMOZEN 0.5 mg/vial inj.

Daunorubicin (Rubidomycin), Doxorubicin These are anthracycline antibiotics having antitumour activity. However, utility of daunorubicin is limited to acute myeloid as well as lymphoblastic leukaemia (in which it is highly active), while doxorubicin, in addition, is effective in many solid tumours, such as breast, thyroid, ovary, bladder and lung cancers, sarcomas and neuroblastoma. They intercalate between DNA strands and block DNA as well as RNA synthesis. They are also capable of causing breaks in DNA strands by activating topoisomerase-2 and generating quinone type free radicals. As such, they have mutagenic and carcinogenic potential. Maximum action is exerted at S phase, but toxicity is usually exhibited in G_2 phase.

Both these antibiotics produce cardiotoxicity as a unique adverse effect. This can manifest either acutely within 2–3 days, causing ECG changes, arrhythmias and hypotension, all of which are reversible; or be delayed—congestive heart failure (related to the total dose administered). CHF is due to cardiomyopathy and may be fatal. Marrow depression, alopecia, stomatitis, vomiting and local tissue damage (on extravasation) are other adverse effects. Urine may be coloured red.

Daunorubicin: 30–50 mg/m^2 BSA i.v. daily for 3 days, repeat every 3–4 weeks.

DAUNOCIN, DAUNOMYCIN 20 mg/vial inj.

Doxorubicin: 60–75 mg/m^2 BSA slow i.v. injection every 3 weeks; ADRIAMYCIN, DOXORUBICIN, ONCODRIA 10 mg, 50 mg per vial inj.

Epirubicin This is a recently introduced anthracycline with mechanism of action and properties similar to doxorubicin. Epirubicin has been primarily used as a component of regimen for adjuvant therapy of breast carcinoma. Other indications are gastroesophageal, pancreatic, hepatic and bladder carcinoma. Alopecia, hyperpigmentation of skin and oral mucosa, painful oral ulcers, fever and g.i. symptoms are the common adverse effects. Urine may turn red. Cardiotoxicity is dose related.

Dose: 60–90 mg/m^2 i.v. over 5 min, repeated at 3 weeks, total dose < 900 mg/m^2 to avoid cardiotoxicity.

ALRUBICIN, EPIRUBITEC 10, 50 mg vials, for reconstitution as 2 mg/ml soln. with diluent.

Mitoxantrone It is an anthracycline derivative related to doxorubicin with lower cardiotoxicity, probably because it does not produce quinone type free radicals. However, it does bind to DNA causing strand breaks and inhibiting DNA as well

as RNA synthesis. Clinical utility is relatively narrow, restricted mostly to acute myeloid leukaemia, advanced hormone refractory prostate cancer and occasionally in breast and hepatic carcinoma, non-Hodgkin lymphoma. It has been found useful in late stage multiple sclerosis as well. Though cardiomyopathy can occur, major toxicity is marrow depression and mucosal inflammation. Discolouration of nails and eye may occur.

ONCOTRON 20 mg/10 ml inj; 14 mg/m^2 single i.v. dose, repeat at 3 weeks. For induction in acute leukaemia 12 mg/m^2/day for 5 days.

Bleomycin This is a mixture of closely related glycopeptide antibiotics having potent antitumour activity. It chelates copper or iron, produces superoxide ions and intercalates between DNA strands—causes chain scission and inhibits repair. It is highly effective in testicular tumour and squamous cell carcinoma of skin, oral cavity, head and neck, genitourinary tract and esophagus; also useful in Hodgkin's lymphoma. Rate of fluid collection in malignant pleural or peritoneal effusion can be reduced by intrapleural/intraperitoneal injection of bleomycin.

Mucocutaneous toxicity and pulmonary fibrosis, but minimal myelosuppression are the special features. Allergic and hypotensive reaction can occur after bleomycin injection. It can be injected i.m. as well.

Dose: 30 mg twice weekly i.v. or i.m. (total dose 300–400 mg); BLEOCIN, ONCOBLEO 15 mg inj.

Mitomycin C This highly toxic drug is used only in resistant cancers of stomach, cervix, colon, rectum, breast, etc. It is usually combined with 5-FU and radiation. Superficial bladder tumours are treated by intravesical instillation of mitomycin C. It is transformed intracellularly to a form which acts as an alkylating agent and crosslinks DNA. It also generates free radicals which damage DNA. Bone marrow and g.i.t. are the primary targets of toxicity. Myelosuppression is typically delayed. Injections are repeated only after 6 weeks or more. A haemolytic-uremic syndrome is reported.

Dose: 10 mg/m^2 BSA, infused i.v. in one day or divided in 5 and infused over 5 days. MITOCIN, ALMITO, LYOMIT 2, 10 mg inj.

MISCELLANEOUS CYTOTOXIC DRUGS

These drugs (except L-asparaginase) have been developed by random synthesis and testing for antitumour activity.

Hydroxyurea It blocks the conversion of ribonucleotides to deoxyribonucleotides by inhibiting the enzyme ribonucleoside diphosphate reductase—thus interferes with DNA synthesis; exerts S-phase specific action. Its primary therapeutic value is in chronic myeloid leukaemia, psoriasis, polycythaemia vera and occasionally in some solid tumours. It is also employed as a radiosensitizer before radiotherapy, and is a first-line drug for sickle cell disease in adults. Hydroxyurea is well absorbed orally and is eliminated in urine with a plasma t½ of ~ 4 hours. Myelosuppression is the major toxicity. Gastrointestinal disturbances and cutaneous reactions including pigmentation also occur.

Dose: 20–30 mg/kg daily or 80 mg/kg twice weekly; CYTODROX, HONDREA, UNIDREA 500 mg cap.

L-Asparaginase (L-ASPase) This enzyme was introduced on the basis of a difference observed between normal cells and those from childhood lymphoblastic leukaemia, *viz*. the leukaemia cells were found to be deficient in L-asparagine synthase enzyme and depended on the supply of L-asparagine from the medium. The enzyme L-ASPase (from *E. coli.*) degrades L-asparagine to L-aspartic acid, depriving the leukaemic cells of an essential metabolite, and causes cell death. L-asparaginase is a component of regimen for inducing remission in acute lymphoblastic leukaemia along with Mtx., prednisolone, vincristine, etc. However, resistance develops to L-ASPase mostly by induction of L-asparagine synthase in the leukaemic cells. Moreover, L-ASPase is antigenic, produces neutralizing antibodies which inactivate and clear the enzyme rapidly, so that clinical response is lost. A polyethylene glycol conjugated L-ASPase (Peg-asparaginase) has been produced which has very slow clearance from the body, is injected every 2 weeks and is more effective. It is also less antigenic.

Many of the typical adverse effects of anticancer drugs are not seen with L-ASPase (no leukopenia, alopecia, or mucosal damage), but it produces effects due to defective protein synthesis—hyperglycaemia, raised triglyceride levels, pancreatitis, liver damage, clotting defects and CNS symptoms. A significant number of recipients develop allergic reactions (urticaria, chills, fever, rash), including anaphylaxis; deaths are reported.

Dose: 50–200 KU/kg i.v., also i.m. daily or twice weekly for 3–4 weeks.

LEUNASE, HOILASP 10,000 KU per vial inj.

Tretinoin It is all trans-retinoic acid, a form of vit A acid (*see* Ch. 64) which acts as a differentiating agent and has recently emerged as a highly effective treatment (usually in combination with a daunorubicin or doxorubicin) for acute promyelocytic leukaemia (APL). This subtype of acute myelocytic leukaemia (AML) is associated with production of a fusion gene *PML-RARα* due to a specific chromosomal translocation. The normal retinoic acid receptor RARα-RXR dimerization needed for cell differentiation is prevented and APL is produced. Tretinoin given in relatively higher doses binds tightly to RARα-RXR diamer and prevents formation of PML-RARα dimerization. It also promotes degradation of already formed PML-RARα fusion gene. As a result, blockade of myeloid precursor cell differentiation into cells of different lineages is overcome and prolonged remission is induced in APL. Though, tretinoin alone can induce temporary remission in APL, induction therapy with tretinoin + an anthracycline produces complete remission in upto 95% patients of APL. Tretinoin has also been shown to promote stem cell renewal in bone marrow. A course of 45 mg/m^2/day tretinoin is administered till one month after remission occurs (or max. 90 days).

Adverse effects of tretinoin are dryness of skin, eye, nose, mouth, pruritus, epistaxis, rise in serum lipids, hepatic transaminases and intracranial pressure. The most serious adverse effect is 'retinoic acid syndrome' comprising of breathlessness, fever, pleural/pericardial effusion and pulmonary infiltrates. Pretreatment with dexamethasone largely prevents occurrence of this syndrome.

Arsenic trioxide Arsenic has been a traditional poison for ages. Ehrlich produced organic arsenicals for cure of syphilis, and some organic arsenicals were used in amoebiasis till 1960s. Recently, therapeutic value of small doses of arsenic trioxide in APL has been recognized. It probably acts by enhancing reactive oxygen free radical generation in APL cells. It is primarily used in resistant/relapsed cases of APL after tretinoin treatment. Lately, arsenic trioxide is also being included in the 1st line therapy of APL along with tretinoin + an anthracycline, particularly in high risk cases and in those who have initial WBC count of > 10,000/μL. With such triple therapy ~ 90% APL patients have remained in long-term remission.

Though, arsenic trioxide is absorbed orally, it is administered as 0.15 mg/kg daily i.v. infusion till remission is induced or maximum 2 months. Further treatment may be given after a gap. Adverse effects of arsenic are nausea, dizziness, malaise, fatigue, sensory disturbances, effusions, breathlessness, hyperglycaemia, Q-T prolongation, A-V block. Corticosteroid treatment provides considerable relief of these adverse effects.

TARGETED DRUGS

In the recent years fundamental studies of cancer biology and molecular mechanisms of carcinogenesis have identified several targets which can be attacked to selectively kill/inhibit cancer cells. Designing and development of drugs to attack these targets is an active area of current research. Several new drugs have been introduced while a large number are in the pipe line. These drugs are primarily of two types:

- Specific monoclonal antibodies that need to be given parenterally, and attack cell surface targets or tumour antigens.
- Synthetic compounds, given orally, which penetrate cells and affect cancer-specific enzymes or processes.

Only a sample of these drugs, especially those available in India, are presented here.

1. Tyrosine-protein kinase inhibitors

Imatinib It is the first selectively targeted drug to be introduced for treatment of a malignancy. It inhibits a specific tyrosine protein kinase labelled 'Bcr-Abl' tyrosine kinase expressed by chronic myeloid leukaemia (CML) cells and related receptor tyrosine kinases including platelet derived growth factor (PDGF) receptor that is constitutively active in dermatofibrosarcoma protuberans, stem cell receptor and *c-kit* receptor active in gastrointestinal stromal tumour (GIST) which is a rare tumour. Imatinib is found to be strickingly successful in chronic phase of CML (remission in >90% cases) and in metastatic c-kit-positive GIST, in which it is the drug of choice. A relatively higher dose may elicit response in accelerated phase of CML as well. It is also indicated in dermatofibrosarcoma protuberans. Resistance to imatinib develops by point mutations in Bcr-Abl tyrosine kinase affecting its affinity for imatinib.

Imatinib is well absorbed orally, metabolized in liver, one active metabolite is also produced. The major degrading enzyme is CYP3A4, and potential interactions can occur with inducers and inhibitors of this isoenzyme. All metabolites are excreted in faeces through bile. The t½ of imatinib is 18 hours while that of its active metabolite is double. Adverse effects are abdominal pain, vomiting, fluid retention, periorbital edema, pleural effusion, myalgia, liver damage and CHF.

Dose: 400 mg/day with meals; accelerated phase of CML 600–800 mg/day.

SHANTINIB, GLEE-VEC, IMATIB α 100 mg cap; UNITINIB 100, 400 mg cap.

Nilotinib It is a second generation Bcr-Abl, PDGF-receptor β and c-kit receptor tyrosine kinase inhibitor with 20–50 fold higher affinity for these kinases than imatinib. Thus, it can overcome resistance to imatinib due to Bcr-Abl mutation and is effective in chronic CML nonresponsive to imatinib. It is only 30% bioavailable orally, but absorption is improved by food. It is also useful in accelerated phase of CML. Thus, it is an alternative drug in imatinib nontolerant or resistant cases of CML, and has now been used as a first line drug as well. Adverse effects are similar to imatinib; Q-T prolongation has also been noted.

2. EGF receptor inhibitors

Gefitinib Epidermal growth factor (EGF) receptor is a transmembrane receptor-tyrosine-kinase which regulates growth and differentiation of epitheilal cells. Binding of ligand (EGF) to the extracellular domain of the receptor induces dimerization leading to activation of tyrosine kinase activity of the intracellular domain (*see* Fig. 4.8) → autophosphorylation of the kinase and phosphorylation of several cytoplasmic regulatory proteins which modify gene transcription to regulate growth. Certain epithelial cancers over express EGF receptor or have an active *EGFR* mutation, and their growth is critically dependent upon activation of this receptor.

Gefitinib is a synthetic compound that penetrates cells, binds to the tyrosine kinase domain of the EGF receptor (also Erbβ_1, or HER1) and prevents phosphorylation of regulatory proteins. Gefitinib has been found effective in selected patients of non-small cell lung cancer which has EGFR activating mutation. Lung cancers in non-smokers and in women are generally of this mutant type. In such cases, it has been found to be more effective than cytotoxic drugs. However, response in non-mutant type of lung cancer is disappointing. Gefitinib monotherapy has been used for locally advanced or metastatic lung cancers after cisplatin and docetaxal have failed.

Oral bioavailability of gefitinib is 60%. It is primarily metabolized by CYP3A4 with t½ of ~ 40 hours. Drug interactions with inducers/inhibitors of CYP3A4 are likely.

Dose: 250 mg/day orally;

GEFONIB, GEFTINAT 250 mg tab/cap.

The most common adverse effect is skin rash and diarrhoea. Others are nausea, anorexia, itching and rise in serum transaminase. Interstitial lung disease is an infrequent, but serious complication.

Erlotinib It is similar to gefitinib in action, pharmacokinetics, adverse effects and efficacy in a subtype of non-small cell lung cancer. It has been combined with gemcitabine for advanced/metastatic pancreatic cancer as well. Few cases of serious hepatic dysfunction have occured in patients with preexisting liver disease.

Dose: 100–150 mg OD to be taken 1 hour before or 2 hours after meal.

ERLOTEC 100, 150 mg tabs.

Cetuximab This inhibitor of EGF receptor is a chimeric monoclonal antibody directed to the extracellular domain of the EGF receptor. Binding to the receptor, it prevents transmembrane signalling resulting in blockade of cell growth, proliferation and metastasis. Survival of tumour cells is jeopardised. Infused i.v. in a loading dose followed by weekly or fortnightly maintenance doses, cetuximab is approved for advanced/metastatic squamous carcinoma of head and neck in combination with radiation and/or cisplatin based chemothrapy. EGF receptor positive metastatic colorectal cancer is another indication, either in combination with irinotecan ± cisplatin or as monotherapy in resistant cases. Adverse effects are acneform skin rash, itching, headache and diarrhoea. Anaphylactoid reactions may occur during infusion. Hypomagnesemia and interstitial lung disease are infrequent.

3. Angiogenesis inhibitors

Angiogenesis (proliferation of new blood vessels) is essential for growth and metastasis of cancers. The vascular endothelial growth factor (VEGF) is the most important stimulus for

neovascularization and increase in microvessel density within solid tumours. VEGF interacts with cell surface VEGF receptor, that is another receptor tyrosine kinase, which promotes angiogenesis by phosphorylating intracellular regulatory proteins. Several cancers over express VEGF receptor and inhibitors of this receptor have been developed as antitumour drugs.

Bevacizumab It is a humanized monoclonal antibody that binds VEGF-A and hinders its access to the VEGF receptor, interrupting angiogenic signalling. Combined with 5-FU, bevacizumab is used in metastatic colorectal cancer. Added to conventional chemotherapy, it improves survival in metastatic non-small cell lung cancer, breast cancer, clear cell renal carcinoma and glioblastoma. Deafness due to neurofibromatosis can be reversed by growth inhibitory effect of bevacizumab.

Being an antibody, bevacizumab is administered by i.v. infusion every 2–3 weeks. Adverse effects are—rise in BP, arterial thromboembolism leading to heart attack and stroke, vessel injury and haemorrhages, heart failure, proteinurea, gastrointestinal perforations, and healing defects.

Sunitinib This is a small molecular synthetic VEGF receptor-2 inhibitor, which enters cells and competitively blocks ATP binding to the tyrosine kinase domain, thereby preventing phosphorylation of angiogenic regulatory proteins. Sunitinib inhibits multiple receptor tyrosine kinases like platelet derived growth factor (PDGF) receptor α and β, c-KIT, RET, etc.). It is used in metastatic renal cell carcinoma and resistant g.i. stromal tumour (GIST). Sunitinib is administered orally daily in 4 week cycles. Adverse effects are hypertension, rashes, diarrhoea, weakness, bleeding, proteinurea, hypothyroidism, neutropenia, rarely CHF.

4. Proteasome inhibitor

Proteasomes are packaged complexes of proteolytic enzymes which degrade several intracellular signalling proteins that control cell cycle, apoptosis and survival response.

Bortezomib It is a unique boron containing compound that covalently binds to proteasome and inhibits its proteolytic activity disrupting many intracellular signalling pathways. The most important of these is nuclear factor-κB (NF-κB) mediated signalling. NF-κB is a transcription factor that normally resides in the cytoplasm bound to an inhibitory protein IκB. Hypoxia, cytotoxic drugs, DNA breaks and other stressful stimuli activate proteasome which cleaves and degrades IκB to release NF-κB which then translocates to the nucleus and transcripts certain genes to produce molecules that oppose apoptosis and promote cell proliferation. Some neoplasms overexpress NFκB which plays an important role in their survival. By inhibiting proteasome, bortezomib prevents the breakup and degradation of IκB, so that NFκB is not released to transcript survival molecules. It also causes build up of 'Bax', an apoptosis promoting protein, and affects other regulators of cell cycle.

The prime indication of bortezomib is multiple myeloma, both for first line combined therapy (along with cytotoxic drugs), as well as for relapsed disease. It is also used for refractory mantle cell lymphoma. The most prominent adverse effect is peripheral neuropathy. Others are diarrhoea, fatigue, bone marrow depression, especially thrombocytopenia.

Dose: 1.3 mg/m^2 i.v. bolus injection, 4 doses at 3 day intervals in cycles of 3 weeks.

EGYBORT 3.5 mg vial for inj.

5. Unarmed monoclonal antibodies

Monoclonal antibodies (MAbs) are sourced from hybridomas created by fusing a continuously proliferating cell line from mouse myeloma with antibody producing B lymphocytes sensitized to produce antibody against a particular antigen. This hybridoma is then cloned so that the single species antibody is obtained in large quantity. Separate hybridomas are created for each antibody. *Chimerized MAbs* are produced by substituting major portion with human IgG molecule for the mouse antibody. These MAbs are part human-part mouse. Totally human MAbs are called *humanized MAbs*. Chimerization and humanization of MAbs prolongs their sojourn in the body and reduces/eliminates their antigenicity.

Malignant cells express certain unique antigens on their surface to which MAbs could be directed. These unmodified (also called unarmed or naked) MAbs kill the target cells by several mechanisms including direct signalling of apoptosis, or antibody-dependent cellular cytotoxicity (ADCC), or complement-dependent

cytotoxicity (CDC). They could also be used as missiles to carry biological bombs (toxins) and are called immunotoxins, or a radioactive isotope as radiopharmaceuticals. These are called 'armed' MAbs.

Rituximab It is a chimerized MAb that binds to the CD20 B-cell antigen expressed on the surface of B-lymphocytes and B-cell lymphomas. Rituximab binding to the antigen promotes apoptosis through transmembrane signalling as well as by ADCC and CDC mechanisms. It is indicated in B-cell lymphoma, non-Hodgkin lymphoma and chronic lymphocytic leukaemia, both as single agent as well as in combination with cytotoxic chemotherapy. Survival benefits have been obtained both when it is used as initial therapy as well as in relapsed cases. Rituximab is also being used in some autoimmune diseases. It is administered as slow i.v. infusion weekly or at 3–4 week intervals. Maintenance doses have been given 6 monthly. Adverse effects are infusion reactions consisting of chills, fever, urticarial rashes, pruritus, dyspnoea and hypotension. Severity of the reaction varies, and is also related to rate of infusion. Pretreatment with antihistaminics dampens the reaction. Late onset neutropenia and depletion of B-lympocytes are the other problems.

Other unarmed antitumour MAbs are:
Trastuzumab, Bevacizumab, Alemtuzumab, Cetuximab

Toxin-linked MAbs are:
Ozogamicin, Gemtuzumab

Radioisotope carrying MAbs are:
Ibritumomab (^{90}Y), Tositumomab (^{131}I)

HORMONAL DRUGS

They are not cytotoxic, but modify the growth of hormone-dependent tumours. All hormones are only palliative.

Glucocorticoids They have marked lympholytic action—are primarily used in acute childhood leukaemia and lymphomas. They induce remission rapidly but relapses inevitably occur after variable intervals and gradually the responsiveness is lost. Considerable palliative effects are obtained in Hodgkin's disease. Glucocorticoids have a secondary role in some hormone responsive breast cancers.

Corticosteroids are also valuable for the control of malignany/chemotherapy associated complications like hypercalcaemia, haemolysis, bleeding due to thrombocytopenia, retinoic acid syndrome, increased intracranial tension and mediastinal edema due to radiotherapy. Moreover, they afford symptomatic relief by antipyretic and mood elevating action and potentiate the antiemetic action of ondansetron/metoclopramide. Prednisolone/dexamethasone are most commonly used; doses are high—hypercorticism may occur (*see* Ch. 20).

Estrogens They produce symptomatic relief in carcinoma prostate (*see* p. 312), which is an androgen-dependent tumour. However, relapses occur, but life is prolonged. Estrogens have been superseded in carcinoma prostate by GnRH agonists used with an antiandrogen.

Fosfestrol It is the phosphate derivative of stilbestrol; has been specifically used in carcinoma prostate.
Dose: 600–1200 mg i.v. initially, maintenance 120–240 mg orally.
HONVAN 120 mg tab, 300 mg/5 ml inj.

Selective estrogen receptor modulators
(tamoxifen)
Selective estrogen receptor down regulators
(fulvestrant)
Aromatase inhibitors (letrozole, etc).

The above three classes of drugs are the sheet anchor of adjuvant and palliative therapy of carcinoma breast, as well as for primary and secondary prevention of breast cancer (*see* Ch. 22).

Antiandrogen Flutamide and bicalutamide (*see* p. 302) antagonise androgen action on prostate carcinoma and have palliative effect in advanced/metastatic cases. Because they increase androgen levels by antiandrogenic action in pituitary, combination with orchiectomy or GnRH analogues is required to produce full therapeutic effect.

5-α reductase inhibitor Finasteride and dutasteride (*see* p. 303) inhibit conversion of testosterone to dihydrotestosterone in prostate (and other tissues), have palliative effect in advanced carcinoma prostate; occasionally used.

GnRH agonists (*see* p. 242) They indirectly inhibit estrogen/androgen secretion by suppressing FSH and LH release from pituitary and have palliative effect in advanced estrogen/androgen

dependent carcinoma breast/prostate. They are generally used in combination with antiandrogens or SERMs.

Progestins (*see* p. 319) They bring about temporary remission in some cases of advanced, recurrent (after surgery/radiotherapy) and metastatic endometrial carcinoma. High doses are needed. They have also been used in palliative treatment of metastatic carcinoma breast that has become unresponsive to tamoxifen.

GENERAL PRINCIPLES IN CHEMOTHERAPY OF CANCER

1. In cancer chemotherapy, analogy is drawn with bacterial chemotherapy; the malignant cell being viewed as an invader. However, there are two main differences—

(a) Bacterial metabolism differs markedly from that of the host, while malignant cells are in fact host cells with deranged regulation of growth and differentiation and relatively minor other differences. Therefore, selectivity of drugs is limited. A number of measures which enhance selectivity of drugs for the tumour need to be utilized. However, lately some unique tumour antigens and oncogenes (like the CML-tyrosine protein kinase gene) have been identified, which provide specific targets for drug therapy.

(b) Infecting microorganisms are amenable to immunological and other host defence mechanisms. This is absent or minimal against cancer cells.

Human interferon α-2 (*see* p. 804) and other cytokines (interleukin-2, tumour necrosis factor, etc.) that can modify the biological responses to tumour cells are being used as adjuvants in treating neoplasms. They appear to have some direct inhibitory effect on malignant cells, in addition to reinforcing immunological defence against these.

2. A single clonogenic malignant cell is capable of producing progeny that can kill the host. To effect cure, all malignant cells must be killed or removed. Survival time is related to the number of cells that escape chemotherapeutic attack.

3. In any cancer, subpopulations of cells differ in their rate of proliferation and susceptibility to cytotoxic drugs. These drugs kill cancer cells by first order kinetics, i.e. a certain fraction of cells present are killed by one treatment.

4. Drug regimens or number of cycles of combined chemotherapy which can effectively palliate large tumour burdens may be curative when applied to minute residual tumour cell population after surgery and/or irradiation. This is the basis of the combined modality approach (*see* Fig. 62.1).

5. Whenever possible, complete remission should be the goal of cancer chemotherapy: drugs are often used in maximum tolerated doses. Intensive regimens used at an early stage in the disease yield better results.

6. Formerly cancers were treated with one drug at a time. Now a combination of 2–5 drugs is given in intermittent pulses to achieve *total tumour cell kill*, giving time in between for normal cells to recover (Fig. 62.1). However, few tumours are still treated with a single drug.

Synergistic combinations and rational sequences are devised by utilizing:

(a) Drugs which are effective when used alone.
(b) Drugs with different mechanisms of action.
(c) Drugs with differing toxicities.
(d) Empirically by trial and error; optimal schedules are mostly developed by this procedure.
(e) Drugs with different mechanisms of resistance.
(f) Drugs with known synergistic biochemical interactions.
(g) *Kinetic scheduling*: On the basis of cell cycle specificity/nonspecificity of the drugs and the phase of cell cycle (*see* box, p. 875) at which the drug exerts its toxicity.

Cytotoxic drugs are either cell cycle nonspecific (CCNS) or cell cycle specific (CCS).

(a) *Cell cycle nonspecific* Kill resting as well as dividing cells, e.g. mustine, cyclophosphamide, chlorambucil, carmustine, dacarbazine, busulfan, L-asparaginase, cisplatin, procarbazine, actinomycin D.

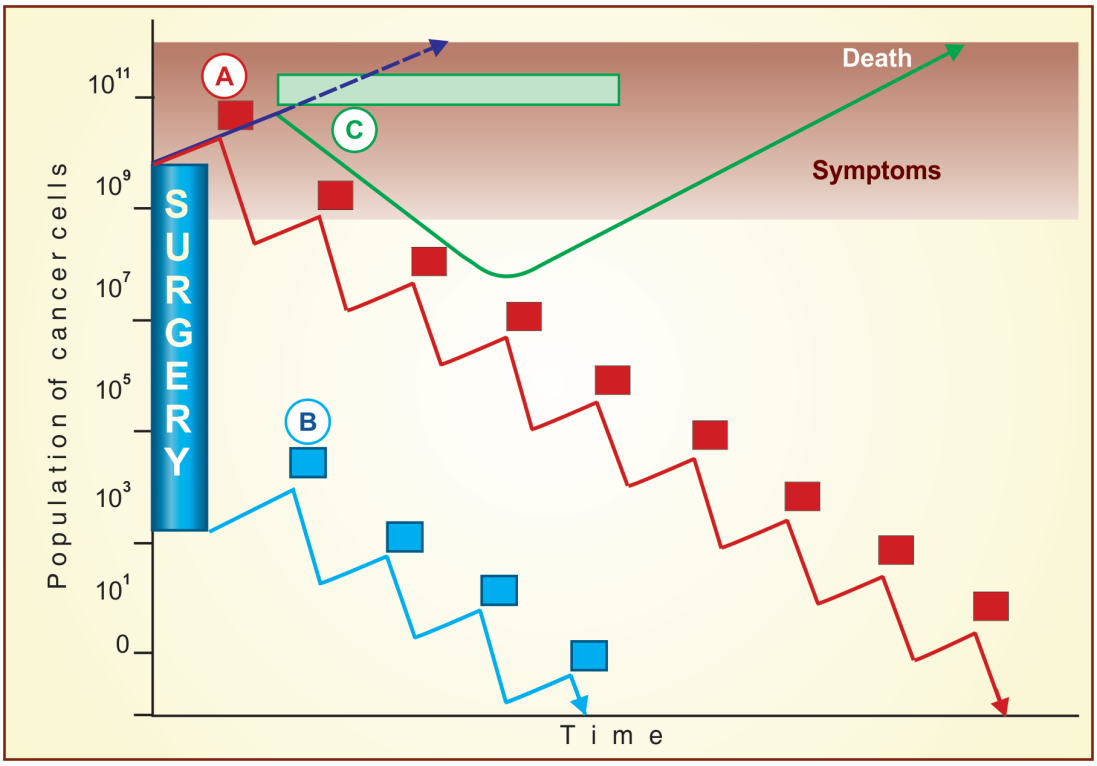


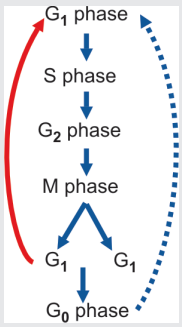
Fig. 62.1: Illustration of cancer cell dynamics with three chemotherapeutic approaches. The shaded area depicts symptoms, before which the cancer remains subclinical. The broken purple line indicates no treatment.
A. A rationally designed combination of 2–5 chemotherapeutic drugs (red bar) is given cyclically. Each cycle kills 99% tumour cells, reducing the tumour cell mass by 2 log units each time. Some regrowth occurs during the rest interval, but the rate of cell kill is more than regrowth and resistance does not develop. If the cycles are continued well beyond all symptoms disappear, cure may be achieved. Radiation may be used to supplement chemotherapy.
B. The cancer (in case of solid tumours) is resected surgically and the small number of residual cancer cells (at the primary site or in metastasis) are killed by relatively few cycles of adjuvant combination chemotherapy (blue bar). This may be supplemented by radiation (in case of radiosensitive tumours).
C. The chemotherapy is begun relatively late with a single but effective drug given continuously (green bar). It causes slower tumour cell kill, but symptom relief may occur. Resistance soon develops, and the tumour starts regrowing even with continued chemotherapy. Symptoms reappear and increase in severity. Ultimately failure of therapy and death occur.

(b) *Cell cycle specific* Kill only actively dividing cells. Their toxicity is generally expressed in S phase. However, these drugs may show considerable phase selectivity, e.g.—

G_1: Vinblastine.
S : Mtx, cytarabine, fludarabine, 6-TG, 6-MP, 5-FU, hydroxyurea, mitomycin C, doxorubicin, daunorubicin.
G_2: Daunorubicin, bleomycin, etoposide, topotecan.
M: Vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel.

It is logical to use cell cycle specific drugs in short courses (pulses) of treatment. This allows noncycling cells (which are generally less susceptible to drugs) to re-enter the cycle between drug courses. The CCS drugs are generally scheduled after a course of CCNS drug(s) to improve the cell kill. The CCS drugs are more effective in haematological malignancies and

Phases of cell cycle



Pre (nucleic acid) synthesis interval.

Synthesis of DNA occurs.

Post synthetic interval.

Mitosis occurs—two G_1 cells are produced, which either directly re-enter next cycle or pass into the nonproliferative (G_0) phase.

Nonproliferating cells; a fraction of these are clonogenic—may remain quiescent for variable periods, but can be recruited in cell cycle if stimulated later.

in solid tumours with a large growth fraction, while the CCNS drugs are effective in these as well as in solid cancers with a small growth fraction.

Many regimens have been devised by taking into consideration the above factors and by observing patient response.

Cyclic treatment is given, and for optimum remission 6–11 cycles may be needed. It has been found that maintenance therapy thereafter does not produce additional benefit.

One combination that has produced almost 100% response in Ewing's sarcoma is illustrated in Fig. 62.2.

Similarly many other regimens have been devised for different tumours.

VAMP : Vincristine + Amethopterine (Mtx) + 6-MP + Prednisolone (used in acute leukaemia).

COAP : Cyclophosphamide + Oncovin (Vincristine) + Ara-C (Cytarabine) + Prednisolone.

FOLFIRI : 5-FU + Leucovorin + Irinotecan (for colon cancer)

FOLFOX : 5-FU + Leucovorin + Oxaliplatin (for colon cancer).

ABVD : Adriamycin (Doxorubicin) + Bleomycin + Vinblastine + Dacarbazine (for Hodgkin's disease).

CHOP-R : Cyclophosphamide + Hydroxydaunorubicin (Doxorubicin) + Oncovin (Vincristine) + Prednisolone + Rituximab (for non-Hodgkin's lymphoma)

BEP : Bleomycin + Etoposide + Platinum (Cisplatin) (for testicular cancer).

7. Tumours often become resistant to any drug that is used repeatedly due to selection of less responsive cells. Such selection is favoured if low dose of a single drug is used.

Several mechanisms of tumour resistance have been recognized. Mutations altering the target biomolecule confer specific (to single drug) resistance. An important mechanism of multidrug resistance is overexpression of MDR 1 gene which increases the concentration of P-glycoprotein (an efflux transporter) on the surface of cancer cells, resulting in pumping out of the chemotherapeutic agents, especially natural products like vinca alkaloids, anthracycline antibiotics, taxanes, etc.

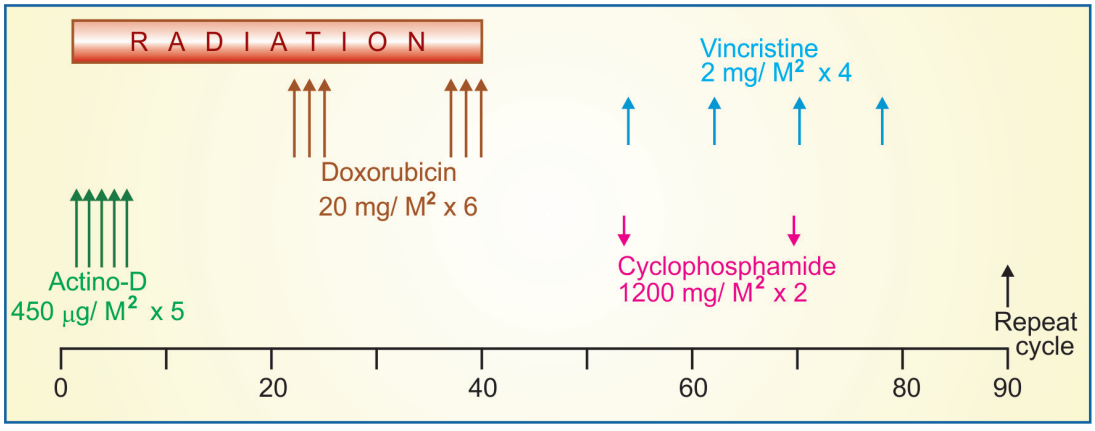


Fig. 62.2: Combined modality treatment for Ewing's sarcoma

Toxicity amelioration

High doses and intensive regimens are being employed aiming at cure of the malignancy. The associated toxicity may be ameliorated to some extent by—

1. Toxicity blocking drugs: *Folinic acid* rescue has permitted administration of > 100 fold dose of Mtx (*see* p. 863). It is professed that normal cells are rescued more than the cancer cells—therapeutic index is increased.
   - Cystitis caused by cyclophosphamide and ifosphamide can be blocked by systemically administered *mesna* and by irrigating the bladder with *acetylcysteine*. Both these are –SH containing compounds that combine with and detoxify the toxic metabolites in the bladder. Generous fluid intake and frequent bladder voiding also helps.
   - For controlling cytotoxic drug induced vomiting, *ondansetron*, a 5-HT_3 antagonist, has surpassed the efficacy of metoclopramide, which nevertheless is still used (*see* Ch. 47). Addition of dexamethasone and/or lorazepam or aprepitant further enhances the protection against vomiting.
   - The anthracycline antibiotics (doxorubicin, etc.) produce cumulative total dose related cardiotoxicity (usually at doses >300 mg/m^2). *Dexrazoxane* is an iron chelating agent which infused i.v. before doxorubicin has been found to reduce risk of such toxicity. However, it may also compromise the anticancer efficacy of doxorubicin Dexrazoxane can also be used to ameliorate anthracycline infusion site reaction due to extravasation.
2. *Amifostine* It is an organic thiophosphate which on activation by alkaline phosphatase acts as a cytoprotective against cancer chemotherapy and radiotherapy. It is particularly used for prophylaxis of cisplatin induced neuro/nephro-toxicity, and radiotherapy related xerostomia.

Dose: 910 mg/m^2 i.v. before cisplatin infusion
200 mg/i.v. before radiotherapy

CYTOFOS, NAPROFOS 500 mg/vial inj.

Short term side effects of amifostine itself are nausea, vomiting, hypotension and infusion related reaction. Delayed adverse effect is hypocalcaemia.

Vigorous hydration of the patient before, during and after cisplatin infusion also reduces nephrotoxicity.

3. Hyperuricaemia occurring as a consequence of rapid destruction of bulky tumour masses and degradation of large amount of purines can be reduced by *allopurinol*, alkalinization of urine and plenty of fluids. Corticosteroids also reduce hyperuricemia.
4. Hypercalcaemia occurring as a complication of certain malignancies like myeloma, cancer breast/prostate, etc. may be aggravated by chemotherapy. It is treated by vigorous hydration and i.v. bisphosphonates (*see* Ch. 24).
5. Drugs given in pulses with 2–3 week intervals for normal cells to recover improve the efficacy of therapy: malignant cells recovering more slowly.
6. Selective exposure of tumour to the drug by intraarterial infusion into a limb or head and neck; intrapleural/intraperitoneal injection—especially for rapidly accumulating pleural effusion or ascitis; topical application on the lesion—on skin, buccal mucosa, vagina, etc. may reduce systemic toxicity.
7. Platelet and/or granulocyte transfusion after treatment—to prevent bleeding or infection.
8. Use of *biological agents* like recombinant GM-CSF/G-CSF hastens recovery from cytotoxic drug induced myelosuppression.

Filgrastim (GRAFEEL, NEUPROGEN 300 µg/vial or prefilled syringe.

It is a human recombinant granulocyte-colony stimulating factor. Started one day after myelo-suppressive chemotherapy and injected s.c. or i.v. (5 µg/kg) daily, till neutrophil count normalizes, may be used to shorten recovery time from neutropenia.

Molgramostim (LEUCOMAX 150, 300, 400 µg/vial for s.c./i.v. inj) is a colony stimulating factor. Injected daily beginning one day after last dose of myelosuppressant chemotherapy, it hastens recovery of neutrophil count.

Interleukin-2 (Il-2) is a cytokine biological agent that itself has antitumour property by amplifying killer T-cell response.

9. Bone marrow transplantation after treatment with high doses of myelosuppressant drugs.
10. *Thalidomide* (banned in 1960 for its teratogenic effect, but reintroduced as immunomodulator, and angiogenesis inhibitor antitumour drug) has anxiolytic, antiemetic, adjuvant analgesic/antipyretic properties and has been found to counteract cancer associated cachexia and retard tumour growth by inhibiting angiogenesis. It probably acts by suppressing TNFα and by modulating IL-2. Thalidomide is also useful in erythema nodosum leprosum (ENL), (*see* p. 786).

SECTION 14

MISCELLANEOUS DRUGS

Chapter 63 Immunosuppressant Drugs

Immunosuppressants are drugs which inhibit cellular/humoral or both types of immune responses, and have their major use in organ transplantation and autoimmune diseases. The important drugs are:

1. *Calcineurin inhibitors*
   (Specific T-cell inhibitors)
   Cyclosporine (Ciclosporin), Tacrolimus
2. *m-TOR inhibitors*
   Sirolimus, Everolimus
3. *Antiproliferative drugs (Cytotoxic drugs)*
   Azathioprine, Methotrexate, Cyclophosphamide, Chlorambucil, Mycophenolate mofetil (MMF)
4. *Glucocorticoids*
   Prednisolone and others
5. *Biological agents*
   (a) *TNFα inhibitors:* Etanercept, Infliximab, Adalimumab
   (b) *IL-1 receptor antagonist:* Anakinra
   (c) *IL-2 receptor antagonists:* Daclizumab, (anti CD-25 antibodies) Basiliximab
   (d) *Anti CD-3 antibody:* Muromonab CD3
   (e) *Polyclonal antibodies:* Antithymocyte antibody (ATG), Rho (D) immune globulin.

Several other immunosuppressants and immunomodulators have also been produced.

The development of immune response and the sites of action of different immunosuppressants is summarized in Figure 63.1.

CALCINEURIN INHIBITORS
(Specific T-cell inhibitors)

Cyclosporine It is a cyclic polypeptide with 11 amino acids, obtained from a fungus and introduced in 1977 as a highly selective immunosuppressant which has markedly increased the success of organ transplantations. It profoundly and selectively inhibits T lymphocyte proliferation, IL-2 and other cytokine production as well as response of inducer T cells to IL-1, without any effect on suppressor T-cells. Lymphocytes are arrested in G_0 or G_1 phase.

The CD4 molecule associated with T cell receptor on helper T cells anchors the major histocompatibility complex class II (MHC II) carrying the antigen peptide so that it is able to activate the T cell receptor (Fig. 63.2). Stimulation of T cell receptor phosphorylates PLc, which hydrolyses PIP_2 to generate DAG and IP_3. While DAG activates PKc to produce MAPkinase dependent and other actions, IP_3 releases intracellular Ca^{2+}. After binding to calmodulin this

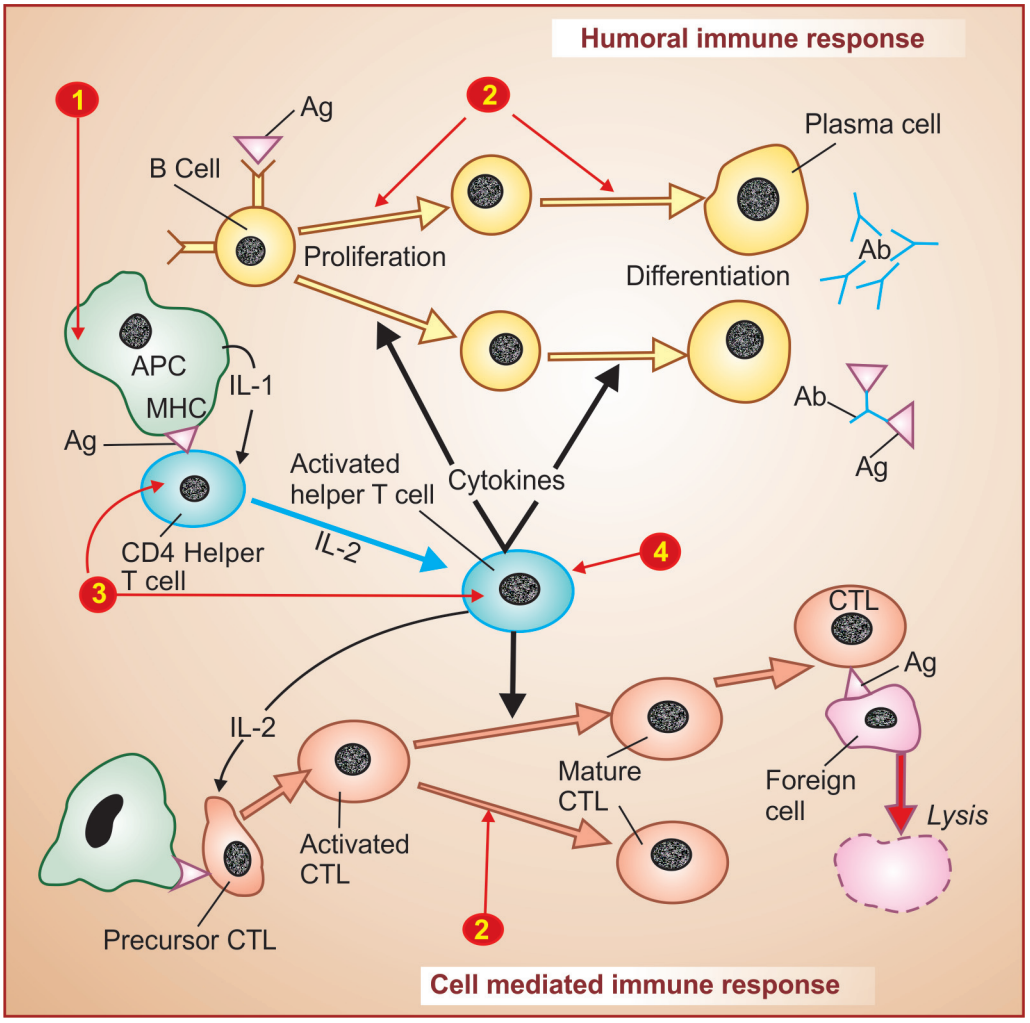


Fig. 63.1: Generation of humoral and cell-mediated immune response and sites of action of immunosuppressant drugs

The antigen (Ag) is processed by macrophages or other antigen presenting cells (APC), coupled with class II major histocompatibility complex (MHC) and presented to the CD4 helper T-cell which are activated by interleukin-I (IL-1), proliferate and secrete cytokines—these in turn promote proliferation and differentiation of antigen activated B cells into antibody (Ab) secreting plasma cells. Antibodies finally bind and inactivate the antigen.

In cell-mediated immunity—foreign antigen is processed and presented to CD4 helper T cell which elaborate IL-2 and other cytokines that in turn stimulate proliferation and maturation of precursor cytotoxic lymphocytes (CTL) that have been activated by antigen presented with class I MHC. The mature CTL (Killer cells) recognize cells carrying the antigen and lyse them.

1. Glucocorticoids inhibit MHC expression and IL-1, IL-2, IL-6 production so that helper T-cells are not activated.
2. Cytotoxic drugs block proliferation and differentiation of T and B cells.
3. Cyclosporine, tacrolimus and sirolimus inhibit antigen stimulated activation and proliferation of helper T cells as well as expression of IL-2 and other cytokines by them.
4. Antibodies like muromonab CD3, antithymocyte globulin specifically bind to helper T cells, prevent their response and deplete them.

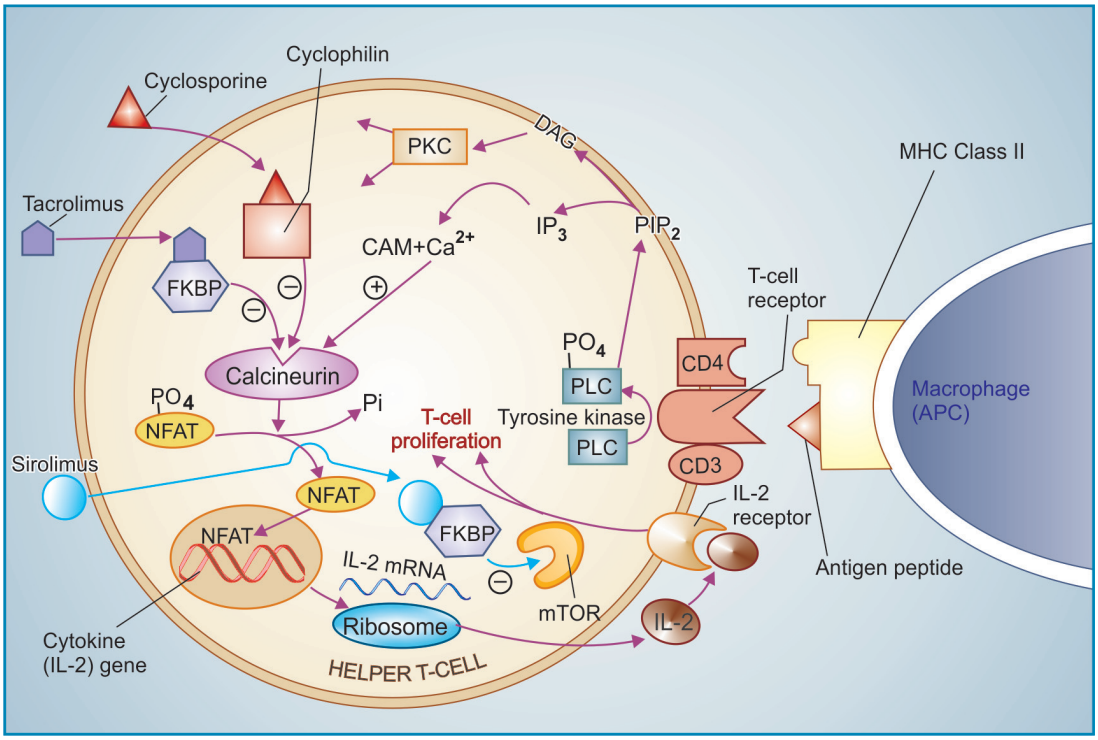


Fig. 63.2: Interaction between macrophage antigen presenting cell (APC) and helper T-cell in the immune response and mechanism of action of cyclosporine, tacrolimus and sirolimus.

Cyclosporine binds to an intracellular protein 'Cyclophilin' and this complex inhibits Ca^{2+}-Calmodulin (Ca^{2+}-CAM) activated phosphatase 'Calcineurin'. Tacrolimus also inhibits calcineurin, but after binding to a different protein FKBP (FK binding protein). Normally, after activation through T-cell receptor, calcineurin dephosphorylates a 'nuclear factor of activated T-cells' (NFAT) which translocates to the nucleus and triggers transcription of cytokine genes resulting in production of IL-2 and other cytokines. IL-2 diffuses out and acts on IL-2 receptor to stimulate T-cell proliferation and other processes, carrying forward the immune response.

Sirolimus also binds to FKBP, but this complex acts at a later stage. It binds to and inhibits a kinase termed m-TOR (mammalian target of rapamycin) which is a key factor for progression of cell proliferation.
PLC—phospholipase C; PIP_2—phosphatidyl inositol bisphosphate; DAG—diacyl glycerol; PKC—protein kinase C.

Ca^{2+} activates a membrane associated serine/threonine phosphatase called *calcineurin* which dephosphorylates regulatory protein 'nuclear factor of activated T-cell' (NFAT), permitting its intranuclear migration and transcription of cytokine genes leading to production of IL-2 along with other interleukins, GM-CSF, TNFα, interferon, etc. IL-2 is the major cytokine for T-cell multiplication and differentiation. Cyclosporine enters target cells and binds to *cyclophilin,* an immunophilin class of protein. The complex then binds to and inactivates calcineurin → response of the helper T cell to antigenic stimulation fails. Cyclosporine also enhances expression of transforming growth factor β (TGFβ), an inhibitor of IL-2 which attenuates IL-2 stimulated T-cell proliferation and production of killer lymphocytes. Cyclosporine is most active when administered before antigen exposure, but can, in addition, suppress the responses of primed helper T cells; hence useful in autoimmune diseases as well.

Cyclosporine selectively suppresses cell-mediated immunity (CMI), prevents graft rejection and yet leaves the recipient with enough immune activity to combat bacterial infection. Unlike cytotoxic immunosuppressants, it is free of toxic effects on bone marrow and RE system. Humoral immunity remains intact. However, it is nephro-

toxic—the major limitation, and impairs liver function. Other adverse effects are sustained rise in BP, precipitation of diabetes, anorexia, lethargy, hyperkalaemia, hyperuricaemia, opportunistic infections, hirsutism, gum hyperplasia, tremor and seizures.

Cyclosporine is the most effective drug for prevention and treatment of graft rejection reaction. It is routinely used in renal, hepatic, cardiac, bone marrow and other transplantations. For induction it is started orally 12 hours before the transplant and continued for as long as needed. When graft rejection has started, it can be given i.v., because oral bioavailability is low, dependent on presence of bile and is highly variable. Blood level monitoring is required for effective therapy. It is concentrated in WBCs and RBCs, metabolized in liver by CYP3A4 and excreted in bile. The plasma t½ is biphasic 4–6 hr and 12–18 hr.

Dose: 10–15 mg/kg/day with milk or fruit juice till 1–2 weeks after transplantation, gradually reduced to maintenance dose of 2–6 mg/kg/day. Therapy may be started with 3–5 mg/kg i.v. infusion.

IMUSPORIN 25, 50, 100 mg soft gelatin cap. Absorption from this preparation is slower and more variable. A newer microemulsion formulation SANDIMMUN NEORAL, PANIMUN BIORAL 25, 50, 100 mg caps, has more consistent bioavailability. For i.v. use cyclosporine is dispersed in cremaphor emulsion: SANDIMMUN, PANIMUN 100 mg/ml inj in 1 ml, 5 ml, 50 ml vial, which is diluted and infused over 4–6 hours. An acute reaction consisting of chills, fever, bodyache and dyspnoea often occurs because of the solvent; i.v. cyclosporine is used only in emergency, and is substituted by oral medication as soon as possible.

Cyclosporine is a second line drug in autoimmune diseases, like severe rheumatoid arthritis, uveitis, bronchial asthma, inflammatory bowel disease, dermatomyositis, etc. and in psoriasis, especially to suppress acute exacerbations. It is generally used along with corticosteroids or Mtx. Good results have been obtained in some cases of aplastic anaemia. For these conditions, lower doses (2–5 mg/kg/day) are needed and adverse effects are milder. However, it is not curative and relapses occur when the drug is withdrawn.

Drug interactions Cyclosporine can interact with a large number of drugs. All nephrotoxic drugs like aminoglycosides, vancomycin, amphotericin B and NSAIDs enhance its toxicity. By depressing renal function, it can reduce excretion of many drugs. Phenytoin, phenobarbitone, rifampin and other enzyme inducers lower its blood levels so that transplant rejection may result. On the other hand, CYP3A4 inhibitors erythromycin, ketoconazole and related drugs inhibit its metabolism to increase bioavailability and cause toxicity. Potassium supplements and K^+ sparing diuretics can produce marked hyperkalaemia in patients on cyclosporine.

Tacrolimus (FK506) This immunosuppressant is chemically different from cyclosporine, but has the same mechanism of action, and is ~100 times more potent. It binds to a different cytoplasmic immunophilin protein labelled 'FK 506 binding protein (FKBP)', but the subsequent steps are the same, i.e. inhibition of helper T cells *via* calcineurin.

Tacrolimus is administered orally as well as by i.v. infusion. Oral absorption is variable and decreased by food. It is metabolized by CYP3A4 and excreted in bile with a t½ of 12 hour. Therapeutic application, clinical efficacy as well as toxicity profile are similar to cyclosporine. Tacrolimus also requires blood level monitoring for dose adjustment. However, due to higher potency and easier monitoring of blood levels, it is generally preferred now for organ transplantations. Tacrolimus may be useful in patients whose rejection reaction is not suppressed by cyclosporine. It is particularly valuable in liver transplantation because its absorption is not dependent on bile. Being more potent, it is also suitable for suppressing acute rejection that has set in.

Tacrolimus has been used in fistulating Crohn's disease. A 10 week course may induce remission. Topically, it is useful in atopic dermatitis. Hypertension, hirsutism, gum hyperplasia and hyperuricaemia are less marked than with cyclosporine, but tacrolimus is more likely to precipitate diabetes, cause neurotoxicity, alopecia and diarrhoea. Dose limiting toxicity is renal.

Dose: 0.05–0.1 mg/kg BD oral (for renal transplant), 0.1–0.2 mg/kg BD (for liver transplant). It can also be given i.v. (no i.v. preparation is available in India); 0.03–0.1% topically.

TACROMUS, PANGRAF 0.5, 1.0, 5.0 mg caps; TACRODERM, TACREL 0.03, 0.1% oint.

mTOR INHIBITORS

Sirolimus This new and potent immunosuppressant is a macrolide antibiotic (like tacrolimus), which was earlier named Rapamycin. It binds to the same immunophillin FKBP as tacrolimus, but the sirolimus-FKBP complex inhibits another kinase called 'mammalian target of rapamycin' (mTOR), and does not interact with calcineurin (Fig. 63.2). The mTOR is an important link in the cascade of signalling pathways which lead to proliferation and differentiation of T-cells activated by IL-2 and other cytokines. Sirolimus arrests the immune response at a later stage than cyclosporine.

Sirolimus is absorbed orally, but fatty meal reduces absorption. It is extensively metabolized, mainly by CYP3A4, so that systemic bioavailability is only 15–20%. Elimination occurs primarily by the biliary route; the t½ is ~60 hours. Inhibitors and inducers of CYP3A4 significantly alter its blood level, which needs to be monitored. Cyclosporine shares the same isoenzyme and raises the blood level of sirolimus. For prophylaxis and therapy of graft rejection reaction, sirolimus can be used alone, but is generally combined with lower dose of cyclosporine/tacrolimus and/or corticosteroids and mycophenolate mofetil. The latter combination avoids use of a calcineurin inhibitor, and is particularly suitable for patients developing renal toxicity with cyclosporine. Sirolimus is effective in some steroid refractory cases, and has been used in stem cell transplant as well. However, it is not recommended for liver transplant. Sirolimus coated stents are being used to reduce the incidence of coronary artery restenosis, by inhibiting endothelial proliferation at the site.

Significantly, sirolimus is not nephrotoxic, but it can suppress bone marrow, mainly causing thrombocytopenia. Rise in serum lipids is common. Other adverse effects are diarrhoea, liver damage and pneumonitis.

Dose: Initially loading dose 1 mg/m^2 daily, followed by titrated lower doses for maintenance.

RAPACAN 1 mg tab.

Everolimus It is similar to sirolimus in mechanism, clinical efficacy, doses, toxicity and drug interactions, but is better absorbed orally and has more consistent bioavailability. The t½ is shorter (~40 hours) so that steady state levels can be reached earlier.

ANTIPROLIFERATIVE DRUGS

(Cytotoxic immunosuppressants)

Certain cytotoxic drugs used in cancer chemotherapy exhibit prominent immunosuppressant property, mainly by preventing clonal expansion of T and B lymphocytes (*see* Fig. 63.1).

Azathioprine (*see* p. 863) It is a purine antimetabolite which has more marked immunosuppressant than antitumour action. The basis for this difference is not clear, but may be due to its selective uptake into immune cells and intracellular conversion to the active metabolite 6-mercaptopurine, which then undergoes further transformations to inhibit *de novo* purine synthesis and damage to DNA. It selectively affects differentiation and function of T cells and inhibits cytolytic lymphocytes; CMI is primarily depressed.

The most important application of azathioprine is prevention of renal and other graft rejection, but it is less effective than cyclosporine; generally combined with it or used in patients developing cyclosporine toxicity. Relatively lower doses (1–2 mg/kg/day) are used in progressive rheumatoid arthritis (*see* p. 211), and it is frequently employed for maintening remission in inflammatory bowel disease (*see* p. 685). It may be an alternative to long-term steroids in some other autoimmune diseases as well.

Methotrexate (Mtx. *see* p. 862) This folate antagonist is a potent immunosuppressant which markedly depresses cytokine production and cellular immunity, and has antiinflammatory property. It has been used as a first line drug in many autoimmune diseases like rapidly progressing rheumatoid arthritis (*see* p. 210), severe psoriasis, pemphigus, myasthenia gravis, uveitis, chronic active hepatitis. Low dose Mtx maintenance therapy is relatively well tolerated.

Cyclophosphamide (*see* p. 860) This cytotoxic drug has more marked effect on B cells and humoral immunity compared to that on T cells and CMI. It has been particularly utilized in bone marrow transplantation in which a short course with high dose is generally given. In other organ transplants it is employed only as a reserve drug. In rheumatoid arthritis, it is rarely used, only when systemic manifestations are marked. Low doses are occasionally employed for maintenance therapy in pemphigus, systemic lupus erythematosus and idiopathic thrombocytopenic purpura.

Chlorambucil It has relatively weak immunosuppressant action which is sometimes utilized in autoimmune diseases and transplant maintenance regimens.

Mycophenolate mofetil (MMF) It is a newer immunosuppressant; prodrug of mycophenolic acid which selectively inhibits *inosine monophosphate dehydrogenase,* an enzyme essential for *de novo* synthesis of guanosine nucleotides in the T and B cells (these cells, unlike others, do not have the purine salvage pathway). Lymphocyte proliferation, antibody production and CMI are inhibited. As 'add on' drug to cyclosporine + glucocorticoid in renal transplantation, it has been found as good or even superior to azathioprine, but should not be combined with azathioprine. It can help to reduce the dose of cyclosporine and thus its toxicity. MMF + glucocorticoid + sirolimus is a non-nephrotoxic combination that is utilized in patients developing renal toxicity with cyclosporine/tacrolimus. MMF is rapidly absorbed orally and quickly converted to the active metabolite mycophenolic acid. This is then slowly inactivated by glucuronidation with a t½ of ~ 16 hours. The glucuronide is excreted in urine. Vomiting, diarrhoea, leucopenia and predisposition to CMV infection, g.i. bleeds are the prominent adverse effects.

Dose: 1.0 g BD oral; CELLMUNE, MYCEPT, MYCOPHEN 250, 500 mg tab/cap.

Glucocorticoids (*see* Ch. 20)

Glucocorticoids have potent immunosuppressant and antiinflammatory action, inhibit several components of the immune response (*see* p. 286). They particularly inhibit MHC expression (Fig. 63.1) and activation/proliferation of T lymphocytes. Expression of several IL and other cytokine genes is regulated by corticosteroids and production of adhesion molecules is depressed. The short-lived rapid lymphopenic effect of steroids is due to sequestration of lymphocytes in tissues. Accordingly, they have marked effect on CMI but little effect on humoral immunity.

The corticosteroids are widely employed as companion drug to cyclosporine or other immunosuppressants in various organ transplants. In case graft rejection sets in—large doses of corticoids i.v. are employed for short periods. They are used in practically all cases of severe autoimmune diseases, especially during exacerbation. Long-term complications are the greatest limitations of steroid use; and it is maintenance of remission for which other immunosuppressants often prove safer.

BIOLOGICAL AGENTS

These are biotechnologically produced recombinant proteins or polyclonal/monoclonal antibodies directed to cytokines or lymphocyte surface antigens which play a key role in immune response. They are important recent additions, mostly as supplementary/reserve drugs for severe and refractory cases of autoimmune diseases and graft versus host reaction.

TNFα inhibitors

TNFα is secreted by activated macrophages and other immune cells to act on TNF receptors ($TNFR_1$, $TNFR_2$) which are located on the surface of neutrophils, fibroblasts, endothelial cells as well as found in free soluble form in serum and serous fluids. TNFα amplifies immune inflammation by releasing other cytokines and enzymes like collagenases and metalloproteinases. The TNFα inhibitors are mainly used in autoimmune diseases, and are briefly described with disease modifying drugs for rheumatoid arthritis in Ch.15.

Etanercept This fusion protein of human TNF receptor and Fc portion of human IgG_1 neutralizes both TNFα and TNFβ. It prevents activation of macrophages and T-cells

during immune reaction. It is used mostly in combination with Mtx in rheumatoid arthritis patients who fail to respond adequately to the latter (*see* p. 212). It is also approved for severe/refractory ankylosing spondylitis, polyarticular idiopathic juvenile arthritis and plaque psoriasis.

Infliximab It is chimeral monoclonal antibody against TNFα which binds and inactivates TNFα. Used by s.c. injection every 4–8 weeks along with Mtx and other conventional therapy, it has proven useful in refractory rheumatoid arthritis, fistulating Crohn's disease, ulcerative colitis, psoriasis and ankylosing spondylitis.

Adalimumab It is fully human recombinant anti-TNFα antibody indicated in the same range of autoimmune diseases as infliximab, and like the latter, does not bind TNFβ, but is less antigenic. It can be added to Mtx or other conventional drugs for additional benefit.

IL-1 receptor antagonist

Stimulated macrophages and other mononuclear cells elaborate IL-1 which activates helper T-cells and induces production of other ILs, metalloproteinases, etc. An endogenous IL-1 receptor antagonist has been isolated and several of its recombinant variants have been produced for clinical use.

Anakinra This recombinant human IL-1 receptor antagonist prevents IL-1 binding to its receptor and has been approved for use in refractory rheumatoid arthritis (*see* p. 212) not controlled by conventional DMARDs. Anakinra along with continued Mtx has been used alone as well as added to TNFα antagonists, because its clinical efficacy as monotherapy appears to be lower.

IL-2 receptor antagonist

The CD-25 molecule is expressed on the surface of immunologically activated, but not resting T-cells. It acts as a high affinity receptor for IL-2 through which cell proliferation and differentiation are promoted. Some anti CD-25 antibodies have been developed as IL-2 receptor antagonist to specifically arrest the activated T-cells.

Daclizumab It is a highly humanized chimeric monoclonal anti CD-25 antibody which binds to and acts as IL-2 receptor antagonist. Combined with glucocorticoids, calcineurin antagonists and/or azathioprine/MMF, it is used to prevent renal and other transplant rejection reaction. The plasma t½ of daclizumab is long (3 weeks), and it has also been used in combination regimens for maintenance of graft.

Basiliximab This is another anti CD-25 antibody with higher affinity for the IL-2 receptor, but shorter plasma t½ (1 week). Clinical use of basiliximab is similar to that of daclizumab.

Both daclizumab and basiliximab can cause anaphylactic reactions and promote opportunistic infection.

Anti-CD3 antibody

Muromonab CD3 It is a murine monoclonal artibody against the CD3 glycoprotein expressed near to the T cell receptor on helper T cells (*see* Fig. 63.2). Binding of muromonab CD3 to the CD3 antigen obstructs approach of the MHCII-antigen complex to the T-cell receptor. Consequently, antigen recognition is interfered, and participation of T-cells in the immune response is prevented. Following antibody binding, the T-cell receptor is internalized and the T-cells get rapidly depleted from blood, partly by cytolysis and partly by their migration to non-lymphoid organs. An immune blocked state results.

Muromonab CD3 is the oldest (developed in the 1980s) monoclonal antibody that is still occasionally used clinically, though newer humanized anti CD3 monoclonal antibodies have been produced which are less antigenic. Muromonab CD3 is now primarily used for acute transplant rejection reaction, particularly in steroid-resistant cases. Daily i.v. injection of muromonab CD3 is given for 2 weeks along with corticosteroids and other immunosuppressants. Subsequent courses are not recommended, because the first course produces antibodies against mouse protein which neutralise it. Use of muromonab CD3 for induction therapy of organ transplantation is infrequent now, since better alternatives are available. It has also been used to deplete T cells from the donor bone marrow before transplantation.

Initial doses of muromonab CD3 are associated with 'cytokine release syndrome' with flu-like symptoms, *viz*. chills, rigor, high fever, wheezing, malaise, etc. which is due to release of TNFα, ILs and interferon. The symptoms decrease in severity with subsequent doses. Occasionally aseptic meningitis, intragraft thrombosis, life-threatening pulmonary edema, seizures and a shock-like state are produced. High-dose corticosteroid pretreatment attenuates the reaction, and is a part of the usual protocol while administering muromonab CD3.

Polyclonal antibodies

Antithymocyte globulin (ATG) It is a polyclonal antibody purified from horse or rabbit immunized with human thymic lymphocytes which contains antibodies against many CD antigens as well as HLA antigens. It binds to T lymphocytes and depletes them. It is a potent immunosuppressant

and has been used primarily to suppress acute allograft rejection episodes, especially in steroid-resistant cases, by combining with other immunosuppressants, including steroids. It can also be used in induction regimens, but this has the potential to produce serum sickness or anaphylaxis.
LYMPHOGLOBULIN (equine) 100 mg/vial inj.; 10 mg/kg/day i.v.;
THYMOGLOBULIN (rabbit) 25 mg/vial inj.; 1.5 mg/kg/day.
ATG 100 mg inj; 200 mg i.v./day.

Anti-D immune globulin It is human IgG having a high titer of antibodies against Rh (D) antigen. It binds the Rho antigens and does not allow them to induce antibody formation in Rh negative individuals. It is used for prevention of postpartum/post-abortion formation of antibodies in Rho-D negative, DU negative women who have delivered or aborted an Rho-D positive, DU positive baby/foetus. Administered within 72 hours of delivery/ abortion, such treatment prevents Rh haemolytic disease in future offspring. It has also been given at 28th week of pregnancy.
Dose: 250–350 µg i.m. of freez dried preparation.
RHESUMAN, RHOGAM, IMOGAM 300 µg per vial/prefilled syringe.

Higher doses (1000–2000 µg) are needed for Rh negative recipients of inadvertantly administered Rh positive blood. It should never be given to the infant or to Rho-D positive, DU positive individuals.

IMMUNOSUPPRESSION IN ORGAN TRANSPLANTATION

Use of immunosuppressants is essential for successful organ transplantation. In general 3 types of regimens are used depending upon the stage of transplantation.

1. *Induction regimen* This is given in the perioperative period: starting just before the transplant to about 2–12 weeks after it. Accelerated rejection develops in the first week, while acute rejections are most likely from 2–12 weeks. The most common regimens include triple therapy with cyclosporine/tacrolimus/sirolimus + prednisolone + MMF/azathioprine. The sirolimus + prednisolone + MMF combination avoids risk of renal toxicity. Two drug and single drug regimens are also used. Many experts do not give cyclosporine preoperatively, and try to delay its induction as far as possible to avoid nephrotoxicity, particularly in renal transplantation. If no rejection develops, the doses are gradually reduced after 2 weeks and this phase merges imperceptably with maintenance phase.

2. *Maintenance regimen* This is given for prolonged periods, may be life-long. Triple drug regimen consisting of maintenance doses of any three of the following choices—cyclosporine/tacrolimus, sirolimus, prednisolone, azathioprine/MMF are generally favoured, because each component is needed in lower doses—reduces toxicity and cost. Nephrotoxicity is often the limiting factor with cyclosporine/tacrolimus, while long-term steroid therapy has its own problems. The component which produces toxicity in a given patient is curtailed or dropped. Two drug and one drug regimens are also used, but are associated with more episodes of acute rejection. After 1 year, cyclosporine is generally dropped, but its continuation is associated with fewer acute rejections. In case of intolerance to the first line drugs *viz.* cyclosporine, tacrolimus, sirolimus, MMF, azathioprine and prednisolone, the second line drugs like cyclophosphamide, chlorambucil or daclizumab are substituted.

3. *Antirejection regimen* This is given to suppress an episode of acute rejection. Steroid pulse therapy (methylprednisolone 0.5–1 g i.v. daily for 3–5 days) is effective in majority of cases. In case of no response, muromonab CD3/ATG is given as rescue therapy or the antibodies are combined with steroids. Tacrolimus, sirolimus, MMF have also been used in rescue therapy of steroid resistant rejection. If the maintenance regimen had not included cyclosporine, its addition can treat acute rejection, but can be damaging to the transplanted kidney.

Adverse effects The two general untoward effects of immunosuppressant therapy are:
(a) Increased risk of bacterial, fungal, viral (especially CMV) as well as opportunistic infections.
(b) Development of lymphomas and related malignancies after a long latency.

Chapter 64 Drugs Acting on Skin and Mucous Membranes

A variety of drugs applied topically to the skin or mucous membranes produce therapeutic effects localized to the site of application. They act primarily by virtue of their physical/mechanical/chemical/biological attributes and may be divided into several categories designated by the most prominent action.

DEMULCENTS

Demulcents are inert substances which sooth inflamed/denuded mucosa or skin by preventing contact with air/irritants in the surroundings. They are, in general, high molecular weight substances and are applied as thick colloidal/viscid solutions in water. Some, like *gum acacia, gum tragacanth* produce foam with water, reduce surface tension and act as suspending/emulsifying agents.

Glycyrrhiza is a sweet tasting root (liquorice); used in cough lozenges to sooth the throat and as sweetening/flavouring agent in mixtures. It contains a glycoside *glycyrrhizin* which has steroid like salt retaining action when taken orally.

Methylcellulose It is a synthetic cellulose derivative used as bulk purgative, in nose drops and contact lens solutions.

CADILOSE 0.5% drops in 10 ml bottle.

Propylene glycol is a clear, viscous liquid, miscible with water as well as some oils that is used in cosmetics and as occlusive dressing for ichthyosis, etc.

Glycerine is a clear, sweet, viscous liquid. Undiluted glycerine has dehydrating property—produces a warm sensation and irritates mucous membranes. Applied to anal canal as suppository it induces evacuation. Applied to dry skin and cracked lips (50% in water) it acts as emollient and is a popular vehicle for gum/throat paints. It is also used orally/per rectum (50–75%) or intravenously (10%) to reduce intraocular/intracranial tension.

EMOLLIENTS

Emollients are bland oily substances which sooth and soften skin. They form an occlusive film over the skin, preventing evaporation, thus restoring elasticity of cracked and dry skin. Olive oil, arachis oil, sesame oil, cocoa butter, hard and soft paraffin, liquid paraffin, wool fat, bees wax and spermaceti are the commonly employed emollients. They are also used as vehicles for topically applied medicaments and as ointment bases.

Wool fat may cause allergy in some patients.

ADSORBANTS AND PROTECTIVES

Adsorbants are finely powdered, inert and insoluble solids capable of binding to their surface (adsorbing) noxious and irritant substances. They are also called protectives because they afford physical protection to the skin or mucosa. Other protectives form a continuous, adherent and flexible occlusive coating on the skin. Demulcents and emollients also serve as protectives.

Magnesium/zinc stearate They have very smooth surface—prevent friction, and are not water wettable—can be used on exuding surfaces because they allow evaporation of water and do not form a crust.

Talc It is native hydrous magnesium silicate, which spreads easily—used in talcum/face powders. Entering raw surfaces, it can form granulomas—should not be sprinkled on wound or used for surgical gloves.

Calamine It is native zinc carbonate tinted pink with ferric oxide. Calcined calamine is zinc oxide.

It has mild astringent and antiseptic action and is a good soothing and protective agent. Used in calamine lotion along with zinc oxide and bentonite (native hydrated aluminium silicate) which have similar properties, as cosmetic, on sunburn, insect bite, urticaria and contact dermatitis.

CALACREME 5% cream, CALAMINOL 5% and CALAMYL 10% emulsion, CALAK 15% with zinc oxide 5%, bentonite 3% sodium citrate 0.5%, glycerol 5% (calamine lotion).

Starch It is used in dusting powders and for surgical gloves, but should not be used on exuding surfaces because it absorbs moisture, crusts on drying and encourages fermentation.

Boric acid It is a smooth and fine powder: has mild antiseptic (*see* Ch. 65), antipruritic and deodorant actions. It is a common ingredient of prickly heat powders.

Aloe vera gel It is a mucilaginous preparation from the fleshy leaves of *Aloe vera* plant with soothing and moisturising property, widely included in cosmetic and skin care products. Therapeutic claims in acne, psoriasis and many other conditions have been made.

ALOVIT: Aloe extract 10% + vit E 0.5% cream.

Polyvinyl polymer On drying its solution forms an occlusive pellicle-like coating on abraded skin. Used as a spray on abrasions and minor cuts, it protects from dust and exposure.

HEALEX SPRAY: 2.5% + benzocaine 0.36% as aerosol wound dressing.

Feracrylum It is a water-soluble biodegradable polymer which forms gel-like complexes on coming in contact with blood. Applied to fresh abrasions, it stops oozing of blood and protects the wound by acting as a physical barrier. A mild antiseptic action is also exerted.

SEPGARD GEL: 1% gel, to be applied as a thin film on the abrasion/wound.

Dimethicone (Dimethyl polysiloxane, Simethicone) It is a silicone polymer—a viscous, amphiphilic liquid. It is pharmacologically inert, has water repellent and surface tension reducing properties (collapses froth). Applied to the skin, it adheres and protects it; special use—to prevent maceration and excoriation of skin due to soiling with urine (suprapubic cystostomy). Also used on bedsores, ulcers and burns.

BARRIER-SF: Dimethiocone 15%, vit E 0.18% cream.

Sucralfate (topical) This aluminium salt of sulfated sucrose used primarily as peptic ulcer protective (*see* p. 656), has been formulated as a topical gel. Applied on burns, bedsores, diabetic/radiation/aphthous ulcers, excoriated skin, sores, etc. it adheres and serves to protect damaged tissue—facilitates healing.

PEPSIGARD LIGHT GEL 10% gel; to be applied on the ulcer 3-4 times a day.

ASTRINGENTS

Astringents are substances that precipitate proteins, but do not penetrate cells, thus affecting the superficial layer only. They toughen the surface making it mechanically stronger and decrease exudation. Drugs are:

Tannic acid and tannins Tannic acid is present in many plants but is generally obtained from nutgalls of oak. Tannins are found in tea, catechu, nutmeg, areca nut (betel nut), etc. They denature proteins forming protein tannate. Uses are:

Bleeding gums—as glycerine of tannic acid.

Bleeding piles—as tannic acid suppository.

Alkaloidal poisoning—precipitates ingested alkaloids as tannates.

(Its use on burns has been abandoned because it forms a crust under which bacteria could grow. Sufficient systemic absorption often occurred to cause centrilobular necrosis of the liver.)

Alcohol Ethanol and methanol are good astringents at 50–90% concentration. Denatured spirit rubbed on the skin prevents bedsores, but should not be applied on the sores once these have formed, as it is highly irritating to raw surfaces. Ethanol is also used as after-shave and on minor cuts.

Mineral astringents Heavy metal ions are astringent and antiseptic. Alum has been used as after-shave and as local haemostatic on minor cuts. Other aluminium, zinc and zirconium salts

are used as antiperspirants. They diffuse through the sweat ducts, reduce secretion from glands and partially block the ducts as well. Their antibacterial action prevents decomposition of sweat by bacteria, reducing body odour.

IRRITANTS AND COUNTER-IRRITANTS

Irritants stimulate sensory nerve endings and induce inflammation at the site of application. Depending on their nature, concentration and sensitiveness of the site, they produce cooling sensation or warmth, pricking and tingling, hyperaesthesia or numbness and local vasodilatation. Irritants which cause local hyperemia with little sensory component are called *Rubefacients*. Stronger irritants which in addition increase capillary permeability and cause collection of fluid under the epidermis (forming raised vesicles) are termed *Vesicants*. Certain irritants also produce a remote effect which tends to relieve pain and inflammation in deeper organs—called *Counter-irritants*.

Mechanism of counterirritation Cutaneous sensations are precisely localized. Deeper sensations from muscles, joints and viscera are perceived more diffusely. A spinal segment, receiving afferent impulses from the surface as well as from deeper organs, modulates them—preferentially conducting the former to the higher centers. When a counter-irritant is applied to the area of skin supplied by nerves from the same segment as the deeper organ from which pain impulses are coming, the cutaneous impulses obscure the deeper sensation.

Irritation of afferent nerve endings produces arteriolar dilatation in the adjoining areas of skin by axon reflex (which mediates flare in triple response). Through segmental association of afferents, vasodilatation also occurs in the corresponding deeper organ. Increased blood supply helps to fight the cause of pain and inflammation in the deeper organ.

Counterirritants are generally massaged to relieve headache, muscular pain (torticollis, backache, sprain), joint pain, pleural/peritoneal pain, colics, etc. Drugs are:

Volatile oils (essential oils) are terpene hydrocarbons of plant origin having a characteristic odour. They have variable properties, but all are irritants. Stearoptenes are solid volatile oils.

Turpentine oil Obtained by distilling *Pinus* oleoresin; used as counterirritant in the form of liniment or 'stupes'.

Clove oil Applied by cotton swab for toothache.

Eucalyptus oil Used in pain balms.

Camphor It is obtained from the bark of *Cinnamomum camphora* or produced synthetically. Produces cooling sensation on skin and is mildly anaesthetic—relieves itching. It is added in liniments and pain balms. Taken internally—small doses produce a warm and comforting sensation in epigastrium; large doses are emetic. Systemically it produces excitement and convulsions (especially in children).

Thymol Obtained from *Thymus vulgaris*, has a pungent taste. It is included in pain balms.

Menthol From mint or prepared synthetically, has cooling and soothing action. It is added to pain balms, throat paints, throat lozenges and inhalers for relief of nasal congestion. It is also a carminative.

Mustard seeds It contains a glycoside *sinigrin* and an enzyme *myrosin*. When ground seeds are soaked in water, myrosin hydrolyses sinigrin to release *allyl isothiocyanate* which is a strong irritant. Mustard plaster has been used as rubefacient and counterirritant. As a suspension in water 4–8 g of ground seeds are emetic.

Capsicum (Chillies) It is a powerful irritant, hot in taste. The active principle is *capsaicin*. It is a popular condiment in Indian cooking, and is included in some counterirritant preparations. After initial stimulation, capsaicin depletes afferent nerve endings of the transmitter substance P; may relieve post-herpetic neuralgia on local application.

Canthridin A crystalline solid obtained from Spanish fly. It is a strong irritant, higher concentrations damage the epithelium and cause vesication—has been used to remove warts, etc. It is added to hair tonics—claimed to increase vascularity of scalp and promote hair growth.

Methyl salicylate (oil of wintergreen) In contrast to other salicylates, it is not used internally (induces vomiting, gastritis and systemic toxicity). It is combined with other irritants in liniments and ointments for muscle and joint pain.

Alcohol Produces rubefaction when rubbed on skin and is a vehicle for liniments.

Some counterirritant combinations

ALGIPAN: Capsicum oleoresin 0.1%, histamine 0.1%, methyl nicotinate 1%, glycol salicylate 5% cream.

ARJET SPRAY: Methyl salicylate 875 mg, menthol 1.6 g, camphor 1.5 g, benzyl nicotinate 20 mg, squalance 250 mg, glycol salicylate 875 mg per 50 ml spray.

RELISPRAY: Winter green oil 20%, clove oil 1%, menthol 4%, nilgiri oil 6%, camphor 10%, cinnamon oil 0.5%, turpentine oil 10% spray.

EUTHERIA: Eucalyptol 7.2%, menthol 4.7%, methylsalicylate 11.25% balm.

MEDICREME: Methylsalicylate 8%, menthol 2%, adrenaline 0.03%, mephenesin 2.5%, chlorpheniramine 0.2%, cream.

RELAXYL: Capsicum oleoresin 0.05%, mephenesin 10% methyl nicotinate 1% ointment.

VICKS VAPORUB: Menthol 2.8%, camphor 5.25%, thymol 0.1% turpentine oil 5.5% ointment.

IODEX: Methylsalicylate 5%, iodine 4% nonstaining ointment.

AMRUTANJAN: Eucalyptus oil 17%, camphor 10%, thymol 1%, menthol 4.5%, methylsalicylate 7% ointment.

CAPSIGYL-D: Capsaicin 0.075%, methyl salicylate 20%, menthol 10%, camphor 5%, eucalyptus oil 5%, diclofenac 1% gel.

CAUSTICS AND ESCHAROTICS

Caustic means corrosive and *Escharotic* means cauterizer. These chemicals cause local tissue destruction and sloughing. An escharotic, in addition, precipitates proteins that exude to form a scab—gets fibrosed to form a tough scar. They are used to remove moles, warts (including genital warts) condylomata, papillomas and on keratotic lesions. Care is needed in their application to avoid ulceration. It is believed that all micro-organisms are killed during cauterization, but this is not always so.

Podophyllum resin As 10–25% alcoholic solution or suspension in mineral oil.

PODOWART 20% paint; CONDYLINE 0.5% podophyllotoxin soln.

Silver nitrate As toughened silver nitrate sticks or pencils.

Phenol As 80% w/w solution.

Trichloroacetic acid As crystals or 10–20% solution to cauterise adenoids; dilute solution is used to promote peeling of frackled skin.

Glacial acetic acid Undiluted.

KERATOLYTICS

Keratolytics dissolve the intercellular substance in the horny layer of skin. The epidermal cells swell, soften and then desquamate. These drugs are used on hyperkeratotic lesions like corns, warts, psoriasis, chronic dermatitis, ringworm, athletes foot, etc.

Salicylic acid As 10–20% solution in alcohol or propylene glycol for dissolving corns. More effective when applied under occlusive dressing. *Propylene glycol* is hygroscopic. Applied under polyethylene occlusive dressing, it causes maceration of skin and acts as a keratolytic, supplementing the action of salicylic acid.

CORNAC 16.5% liquid, CORN CAP 40% oint in adhesive tape.

Lower concentrations (3–5%) are used in other conditions, e.g. in Whitfield's ointment.

RINGCUTTER 3% ointment with 5% benzoic acid.

It is also mildly antiseptic and antifungal.

Resorcinol Has antiseptic, antifungal, local irritant and keratolytic properties; 3–10% is used in eczema, seborrheic dermatitis, ringworm, etc.

Urea Applied at a concentration of 5–20% in cream/ointment base, urea acts as a humectant by its hygroscopic and water retaining property. It causes softening and solubilization of keratin, facilitating its removal from hyperkeratinized lesions like ichthyosis, lichen planus. Inclusion

of urea enhances the penetration of the concurrently applied topical steroid.

ANTI-SEBORRHEICS

These are drugs effective in seborrheic dermatitis which affects areas rich in sebaceous glands (scalp, face, trunk) and is characterized by erythematous, scaling lesions. Dandruff is the commonest complaint. A causal role of the yeast *Pityrosporum ovale* has been shown, but various trigger factors like change in quantity and composition of sebum, increase in alkalinity of skin (due to increased sweating), external local factors, emotional stress, genetic predisposition appear to be needed to transform the yeast from a commensal to a noninvasive pathogenic organism. Drugs used are:

Selenium sulfide Applied to the scalp as a 2.5% lotion or shampoo, it slows epidermal proliferation and scaling. It is also antikeratolytic and fungicidal to *P. ovale*. Dryness, folliculitis and dandruff are benefited, but > 50% patients relapse on discontinuation. Systemic absorption and toxicity can occur if it is applied to inflamed or damaged skin. Some individuals develop sensitivity reactions.

SELSUN 2.5% susp., SELDRUFF PLUS 2.5% susp. with clotrimazole 1%.

Zinc pyrithione It reduces epidermal turnover and inhibits *P. ovale*. Weekly shampoo (1%) reduces dandruff, but symptoms do not resolve completely.

It is often combined with ketoconazole.

SCALPE: Zinc pyrithione 1%, Ketoconazole 2% shampoo.

Corticosteroids Massaged in the scalp as a lotion, topical steroids are highly effective in relieving symptoms of seborrheic dermatitis including dandruff. Pityrosporal yeasts are reduced in the affected skin. However, relapse rates are high on discontinuation and prolonged use can produce adverse effects like atrophy, poor healing, purpura, etc.

Imidazole antifungals Among several of these compounds, ketoconazole (KTZ) was found to be the most effective against *P. ovale*. Orally (200 mg/day for 4 weeks) it has been found to improve seborrhoea. But because this is often a chronic relapsing condition and prolonged oral KTZ therapy is considered unwarranted, KTZ has been formulated into 2% cream/shampoo/scalp gel. Good to excellent results have been obtained with these preparations without skin irritation, contact sensitivity, phototoxicity or systemic adverse effects.

KETOVATE, NIZRAL, OCONA 2% cream, 2% shampoo.

Clotrimazole 1% solution may be used in its place.

Sulfur, Resorcinol, Coaltar, Ammoniated mercury These drugs are mildly effective. They have minimal antiyeast action: may benefit seborrhoea by keratolytic and antiseptic properties.

Salicylic acid It is keratolytic, has mild effect in seborrhoea, probably by removing the scales and by improving penetration of other drugs.

MELANIZING AGENTS

Melanizing agents are drugs that increase sensitivity to solar radiation and promote repigmentation of vitiliginous areas of skin. Psoralens are furocoumarins which on photoactivation stimulate melanocytes and induce their proliferation.

Psoralen It is obtained from fruit of *Ammi majus*.

MANADERM 10 mg tablet, 1% ointment, PSORLINE 5 mg tablet, 0.25% solution and ointment.

Methoxsalen (MACSORALEN 10 mg tab, 1% solution, MALANOCYL 10 mg tab, 0.75% soln.) and ***Trioxsalen*** (NEOSORALEN 5 mg, 25 mg tablets and 0.2% lotion) are synthetic psoralens.

They sensitize the skin to sunlight which then induces erythema, inflammation and pigmentation. They are applied topically as well as given orally. Methoxsalen is absorbed better, undergoes less first pass metabolism and is more effective than trioxsalen. Their plasma t½ is short (~ 1 hr); sensitization of skin is maximal at 1–2 hours, but lasts for 8 hours or more.

Topical therapy The solution/ointment is carefully painted on the small well defined vitiliginous lesion—which is then exposed to sunlight for 1 minute and then occluded by bandage or sun screen ointment. Weekly treatment with longer exposures is given. Pigmentation usually begins to appear after a few weeks; months are needed for satisfactory results. Then periodic maintenance treatment may be needed. This therapy should be undertaken only under direct supervision of physician because longer exposure causes burning and blistering.

Oral therapy On alternate days after 2 hours of a 0.3–0.6 mg/kg (usually 20 mg) oral dose of a psoralen, skin is exposed to sunlight (or artificial UV light), initially for 15 minutes—gradually increasing to 30 minutes over days. Eyes, lips and other normally pigmented areas should be protected during exposure to sunlight.

DRUGS FOR PSORIASIS

Psoriasis is an immunological disorder manifesting as localized or widespread erythematous scaling lesions or plaques. There is excessive epidermal proliferation attended by dermal inflammation. Periodic flareups are common. Drugs can diminish the lesions, but cannot cure the disease. Therapy has to be prolonged and adjusted to the severity of disease. Topically applied emollients, keratolytics, antifungals afford variable symptomatic relief, but *topical corticosteroids* are the primary drugs used. They are very effective in mild-to-moderate disease, and initially even in severe cases. Most patients respond within 3 weeks, and the response may be hastened by applying the steroid under occlusion. Therapy is started with a potent steroid which is substituted after improvement by either weekly application or by a milder preparation. However, they carry their own local and systemic adverse effects, and lesions may progressively become refractory. Systemic therapy with corticosteroids and/or immunosuppressants is reserved for severe and refractory cases. Other topically used drugs are:

Calcipotriol It is a synthetic nonhypercalcaemic vit D analogue effective topically in plaque type psoriasis. It binds to the intracellular vit D receptor in epidermal keratinocytes and suppresses their proliferation while enhancing differentiation. On absorption through the skin, it is inactivated rapidly by metabolism so that little systemic effect on calcium metabolism is exerted. Benefit in psoriasis is slow; but most cases respond in 4–8 weeks. Response is maintained till treatment is continued. Efficacy of calcipotriol in psoriasis is rated comparable to a moderate potency topical steroid. Combination with a steroid is more effective than either drug alone. Side effects are skin irritation, erythema and scaling. Hypercalcaemia is rare. It is a safe and effective alternative to steroids, but expensive.

DAIVONEX 0.005% oint; apply over psoriatic lesions twice daily.

Tazarotene This synthetic retinoid applied as a topical gel (0.05–0.1%) is moderately effective in psoriasis. It is a prodrug which is hydrolysed in the skin to tezarotenic acid that exerts antiproliferative and antiinflammatory action by binding to the intracellular retinoic acid receptor and modification of gene function. Combination with a topical steroid/calcipotriol may benefit refractory cases. Skin irritation, burning sensation, peeling are common. These can be minimized by careful application to the plaques only. It is teratogenic.

LATEZ 0.05%, 0.1% gel; TAZRET 0.05% gel, 0.1% cream; 0.05–0.1% application once daily in the evening.

Coaltar This crude preparation containing many phenolic compounds exerts a phototoxic action on the skin when exposed to light, especially UVA, and retards epidermal turnover. Applied as ointment or alcoholic solution on psoriatic plaques (generally with salicylic acid) and exposed to sunlight daily, it induces resolution of psoriatic lesions in majority of cases, but relapses are common. Its use has declined now because of strong smell, cosmetic unacceptability, skin irritation, allergy, and potential for photosensitivity and carcinogenicity.

EXETAR: coaltar 6%, salicylic acid 3%, sulfur ppt. 3%, oint. TARSYL: coaltar 1%, salicylic acid 3% lotion. IONAX-T: coaltar 4.25%, salicylic acid 2% scalp lotion.

Photochemotherapy (PUVA: Psoralen ultraviolet A) Photoactivated psoralen undergoes O_2 independent as well as O_2 dependent reactions and binds to pyrimidine bases—interferes with DNA synthesis and epithelial cell turnover. PUVA therapy has produced gratifying results in severely debilitating psoriasis, but relapses occur when treatment is stopped. Oral methoxasalen is followed 1–2 hours later by UVA exposure on alternate days. There are serious concerns regarding potential of PUVA to cause skin cancer, cataracts and immunological damage. Being inconvenient and carrying risks, it is reserved for severe cases of psoriasis only.

Psoralens have also been used to accelerate tanning—a maximum of 2 weeks treatment has been advised for this purpose. Other applications of PUVA are in lichen planus, urticaria pigmentosa, atopic dermatitis and cutaneous T cell lymphoma.

Adverse effects: Mottling, erythema, burns, blistering, premature ageing of skin, gastric discomfort, nervousness and insomnia.

Acitretin It is a synthetic retinoid for oral use in psoriasis, lichen planus, severe ichthyosis, etc. It acts by binding to 'retinoic acid receptor' in epidermal cells and regulating their proliferation and maturation. Inflammation is suppressed. Because of frequent and potentially serious adverse effects, use of acitretin is restricted to recalcitrant, pustular and other forms of severe psoriasis. Combination with topical antipsoriatic drugs is advised.

Dose: 0.5–0.75 mg/kg/day oral;

ACITRIN, ACETEC, ACERET 10, 25 mg tab.

Dryness of skin and eyes, gingivitis, erythema and scaling of skin, alopecia, arthralgia, myalgia, lipid abnormalities and liver damage are the important adverse effects. Elimination of acitretin is very slow (taking months) because of accumulation in body fat. It is highly teratogenic. Women taking acitretin must not conceive during and till 3 years after stopping it. Drinking alcohol should be prohibited during and till 3 months after acitretin use.

Etanercept It is a TNFα inhibitor immunosuppressive drug, also used in psoriasis. It is described in Ch. 15 and Ch. 63.

DEMELANIZING AGENTS

They lighten hyperpigmented patches on skin.

Hydroquinone It is a weak hypopigmenting agent. It inhibits tyrosinase and other melanin forming enzymes, decreases formation of and increases degradation of melanosomes. Regular application (as 2–6% lotion or cream) for months is required in melasma, chloasma of pregnancy, etc. The response is often incomplete and pigmentation may recur when it is discontinued, especially if exposed to sunlight; sunscreens are frequently combined. Skin irritation, rashes and allergy are possible. Care is to be taken to avoid its entry in eyes.

EUKROMA 4% cream, MELALITE: Hydroquinone 2% with glycerylester of PABA 2.8% cream. BRITE: hydroquinone 4%, glyceryl PABA 2.8% cream.

Monobenzone A derivative of hydroquinone; potent demelanizing agent—destroys melanocytes and may cause permanent depigmentation. Full effect takes 4–6 months; treated areas should be protected from sunlight by a sunscreen. Its bleaching action is somewhat irregular: ugly depigmented patches can appear. Erythema and eczema may also result. Therefore, its use should be restricted to patients with widespread vitiligo—to reduce the colour contrast between pigmented and nonpigmented areas and for post-inflammatory melasma; 5% lotion or 20% ointment is applied 2–3 times daily.

BENOQUIN 20% ointment.

Azelaic acid It is a drug for acne (*see* p. 894) that is also effective in hyperpigmentary disorders including melasma. It appears to act by inhibiting the melanin forming enzyme tyrosinase. However, it is a weak demelanizing agent with reversible hypopigmentary action.

Azelaic acid is used as a 10%, 20% cream. The only side effect is mild and transient local irritation.

AZIDERM 10%, 20% cream.

SUNSCREENS

Sunscreens are substances that protect the skin from harmful effects of exposure to sunlight.

(a) Chemical sunscreens They absorb and scatter UV rays that are responsible for sunburn and phototoxicity, but allow longer wave lengths to penetrate, so that tanning occurs.

Efficacy of a sunscreen formulation is quantified by its 'Sun protection factor' (SPF) which is the ratio of the dose of UVB radiation that will produce minimal erythema on protected skin to the dose required for the same on unprotected skin. Most commercial preparations have a SPF of 15. Period for which they remain effective depends on the vehicle.

Para-aminobenzoic acid (PABA) and its esters: glyceryl mono amino benzoate. They absorb UVB (290–320 nm). PABA is used as 5% solution in alcohol/propylene glycol (PABALAK) or as 10% cream (PARAMINOL).

Benzophenones (such as oxybenzone 2–6%) block UVA (320–400 nm); are highly protective; thus higher concentrations prevent tanning also.

Cinnamates (such as octyl methoxy cinnamate) are included in sunscreens.

SUNSHIELD: Octyl methoxy cinnamate 5%, vit E 0.25% lotion. EUKROMA-SG: Oxybenzone 3%, Octylmethoxy cinnamate 5%, hydroquinone 2% cream.

Uses Chemical sunscreens are used as adjuncts in vitiligo therapy, drug induced phototoxicity and to facilitate tanning while preventing sunburn. There is some evidence that they can prevent skin cancer and premature ageing of skin.

(b) Physical sunscreens Heavy petroleum jelly, titanium dioxide, zinc oxide and calamine are opaque substances that stop and scatter not only UV but also visible light. They are also called 'sun shades' and have to be applied as a thick lotion/cream which may be cosmetically disagreeable. They withhold longer wave lengths also, which are mostly involved in photoallergy. Not only sunburn, but tanning as well is prevented.

Chloroquine taken orally is effective in actinic eruptions, but should be reserved for severe cases only.

DRUGS FOR ACNE VULGARIS

Acne vulgaris is the most common skin disease in adolescent boys and girls. Under androgenic stimulation the sebaceous follicles of face and neck produce excess of sebum and get colonized by bacteria and yeast (*Propionibacterium acnes, Staph. epidermidis, Pityrosporum ovale*). Bacterial lipases produce fatty acids which irritate the follicular ducts causing retention of secretions and hyperkeratosis— 'comedones' are formed which may rupture into the dermis causing inflammation and pustulation.

1. Topical Therapy

1. Benzoyl peroxide It is one of the most effective and widely used drugs in acne: gradually liberates oxygen (in the presence of water) which kills bacteria, especially anaerobic/microaerophilic ones: used almost exclusively for acne because of its high efficacy against *P. acnes* and additional keratolytic and comedolytic properties. *P. acnes* or other bacteria do not develop resistance to benzoyl peroxide. It induces mild desquamation, the comedone caps are shed and production of irritant fatty acids in the sebum is reduced. Benzoyl peroxide is a mild irritant of the skin—burning and stinging sensation is often felt initially, localized erythema may occur. Most patients gradually develop tolerance to these actions; if not, use should be discontinued. Avoid contact with eyes, lips, mucous membranes and denuded skin. It can bleach hair and coloured fabric.

Adverse effects are excessive dryness of skin, marked scaling, erythema, edema and contact sensitization (in 1–2% patients). It is used as 5–10% cream, gel or lotion; duration and frequency of application is guided by the degree of irritation produced and tolerated; start with 15 min once daily.

PERSOL, PERNOX, BENZAC-AC 2.5% and 5% gel; in PERSOL FORTE 10% cream with sulfur ppt. 5%.

2. Retinoic acid (all trans vitamin A acid, Tretinoin) It is a potent comedolytic: promotes lysis of keratinocytes, prevents horny cells from binding to each other, hence comedones, which are horny impactions in follicles, cannot form. Epidermal cell turnover is stimulated resulting in peeling. No antibacterial action is exerted. It is highly efficacious in acne, but response is delayed (may take 6–10 weeks). Tretinoin has the potential to irritate the skin; start with the lower concentration applied once daily.

Side effects are feeling of warmth, stinging, excessive redness, edema and crusting. Used as a 0.025–0.05% gel or cream, it can be alternated with benzoyl peroxide (one in the morning the other at night), but both should not be applied together because benzoyl peroxide accelerates degradation of tretinoin. Teratogenic risk with topical retinoic acid is minor because of low blood levels produced; but it should be used during pregnancy only if essential.

Tretinoin has been shown to prevent photoageing of skin. Dry scaly surface, mottling, wrinkles, rough and leathery texture, sagging of loose skin that develop due to excessive exposure to sun are arrested and pigmented spots tend to fade. However, the risk-benefit ratio of long-term prophylactic therapy is not clear.

EUDYNA 0.05% cream. RETINO-A 0.025% and 0.05% cream.

3. Adapalene It is a newer synthetic tretinoin-like drug which binds directly to the nuclear retinoic acid receptor and modulates keratinization and differentiation of follicular epithelial cells. It also exerts antiinflammatory action; comedone formation is suppressed. In acne vulgaris it is as effective but less irritating than tretinoin. It remains stable in the presence of benzoyl peroxide; can be combined with it.

ADAFERIN, ADAPEN, ADAPLE, ACLENE 0.1% gel; apply once daily at bed time.

Tazarotene (*see* p. 891) is another topical retinoid with therapeutic effect in acne vulgaris in addition to that in psoriasis.

4. Topical antibiotics Clindamycin, erythromycin and tetracyclines are less effective against *P. acnes* than benzoyl peroxide. They are appropriate for cases with inflamed papules, rather than in non-inflamed comedones. They do not irritate skin but can cause sensitization.

Erythromycin: ACNEDERM 2% lotion and oint; ERYTOP 3% lotion and cream; ACNESOL 4% gel, 2% lotion, ACNELAK-Z 4% lotion and gel with zinc acetate 2%.
Clindamycin: CLINDAC-A, CLINCIN 1% gel.

Nadifloxacin is a newer topical quinolone broad-spectrum antibiotic which has exerted therapeutic benefit in inflamed acne and folliculitis.

NADIBACT, NADOXIN 1% cream for topical application.

5. Azelaic acid It is a natural product from *Pityrosporum ovale* that has been developed for topical treatment of acne. Many aerobic and anaerobic microorganisms, especially *P. acnes* present on acne bearing skin are inhibited. Azelaic acid reduces cutaneous bacterial density, free fatty acid content of skin surface lipids and proliferation of keratinocytes. Used as 10%, 20% cream, its efficacy in acne approaches that of benzoyl peroxide, but response is delayed. It has also benefited melasma (p. 892).

AZIDERM 10%, 20% cream

II. Systemic Therapy

Systemic use of drugs in acne is indicated only in severe cases with cysts and pustules which are likely to form scars.

1. Antibiotics Tetracycline, minocycline or erythromycin have been used. After initial control, smaller maintenance doses may be continued for months. However, long-term systemic antibiotic therapy has its own complications. Recently risk of intracranial hypertension after use of tetracyclines for > 2 months has been emphasized.

2. Isotretinoin (13-cis retinoic acid) is an orally administered retinoid that reduces production of sebum (skin bacteria decrease secondarily), corrects abnormal keratinization of follicles and causes dramatic improvement. A 20 week course of 0.5–1 mg/kg daily brings about remission in most cases of cystic acne. Relapses

occur after variable intervals; can be treated similarly. Side effects are frequent—cheilitis, dryness of skin, eyes, nose and mouth, epistaxis, pruritus, conjunctivitis, paronychia, rise in serum lipids and intracranial tension, and musculoskeletal symptoms. Therefore, it should be reserved for unresponsive cases of severe acne.

Isotretinoin is highly teratogenic; upto 25% exposed foetuses had birth defects—craniofacial, heart and CNS abnormalities (ACCUTANE embryopathy). It is contraindicated in women likely to become pregnant during therapy and one month after. The t½ of isotretinoin is ~18 hours, and it is not accumulated like other retinoids. ISOTROTIN, SOTRET 10, 20 mg cap, IRET 20 mg cap.

Isotretinoin is also effective in the prevention and treatment of skin cancers. Oral leucoplakia, actinic keratoses and other premalignant lesions can be treated, but benefit-risk ratio is not clear.

TOPICAL STEROIDS

Glucocorticoids are used topically for a large variety of dermatological conditions. They benefit by virtue of their antiinflammatory, immunosuppressive, vasoconstrictor and antiproliferative (for scaling lesions) actions. The intensity of action depends on the extent of absorption to the deeper layers, thus lipophilicity of the compound determines potency to a great extent. Fluorinated compounds and lipid soluble esters, e.g. hydrocortisone butyrate are potent. The available preparations may be roughly graded as:

Potent

Beclomethasone dipropionate	0.025%	BECLATE cream.
Betamethasone benzoate	0.025%	TOPICASONE cream, oint.
Betamethasone valerate	0.12%	BETNOVATE cream, oint. BETASONE cream.
Halcinonide	0.1%	CORTILATE, HALOG, cream
Clobetasol propionate	0.05%	LOBATE, TENOVATE, DERMOTYL cream
Dexamethasone sod. phosphate	0.1%	DECADRON cream (with Neomycin 0.35%).
Dexamethasone trimethyl-acetate	0.1%	MILLICORTENOL cream.
Fluocinolone acetonide	0.025%	FLUCORT oint., LUCI oint.
Fluocortolone	0.5%	ULTRALAN oint.
Triamcinolone acetonide	0.1%	LEDERCORT oint.

Moderately potent

Fluocinolone acetonide	0.01%	FLUCORT-H oint. and skin lotion.
Clobetasol butyrate	0.05%	EUMOSONE cream
Fluocortolone	0.25%	COLSIPAN oint.
Mometasone	0.1%	MOMATE, CUTIZONE oint, cream
Fluticasone propionate	0.05%	FLUTIVATE, MOLIDERM cream
Prednicarbate	0.1-0.25%	DERMATOP, STEROTOP cream
Triamcinolone acetonide	0.05%	DESOWEN, DESONIDE cream/ lotion
Hydrocortisone + urea 12%	1%	COTARYL-H cream.
Hydrocortisone acetate	2.5%	WYCORT oint.

Mild

Hydrocortisone acetate	0.1–1.0%	LYCORTIN 1% oint., in CORTOQUINOL 1% with quiniodochlor 4% cream, GENTACYN-HC TOPICAL 1% with gentamicin 0.1%. CORTISON-KEMICETINE 0.5% with chloramphenicol 0.5%.
Hydrocortisone butyrate	0.001%	LOCOID cream

General guidelines for the use of topical steroids

(i) Penetration of the steroid at different sites differs markedly—high at axilla, groin, face, scalp and scrotum; medium at limbs and trunk: low at palm, sole, elbow and knee. Areas of high penetration easily develop adverse effects—potent preparations should be avoided. Areas of low penetration do not generally respond to milder agents.

(ii) Absorption into the skin also depends on the nature of lesion—high in atopic and exfoliative dermatitis, low in hyperkeratinized and plaque

forming lesions. Milder drugs should be used on acute lesions, stronger ones reserved for chronic lesions.

(iii) Choice of vehicle is important. Lotions and creams (to some extent) are better for exudative lesions—they allow evaporation, have a cooling, drying and antipruritic effect. Sprays and gels are appropriate for hairy regions. Ointments form an occlusive film and are good for chronic, scaly conditions.

(iv) Occlusive dressing markedly enhances absorption of the steroid (as much as 10 fold), retains moisture and results in maceration of the horny layer. Chronic, hypertrophied lesions may be occluded intermittently (12 hours at a time). Continuous occlusion promotes bacterial and fungal growth.

(v) Absorption is greater in infants and young children—milder agents should be used.

(vi) Routine use of potent steroids is not justified. Very potent preparations should be restricted to severe inflammatory conditions, unresponsive eczema, psoriasis, etc., and that too only for short periods till the lesion resolves. The mildest preparation that will control the lesion should be used.

(vii) Use of potent preparations should be short term or intermittent to prevent adverse effects and tachyphylaxis. Sudden discontinuation should be avoided. Upon improvement a less potent preparation may be substituted or the steroid may be alternated with an emollient till the lesion resolves.

(viii) More than 2 applications a day do not afford additional benefit. Generally twice daily application is satisfactory.

A combination of steroid with an antimicrobial may be used for—impetigo, furunculosis, secondary infected dermatoses, napkin rash, otitis externa, intertriginous eruptions.

Indications for topical steroids

Lesions that usually respond well	*Lesions requiring potent steroids, respond slowly*
Atopic eczema	Cystic acne
Allergic contact dermatitis	Alopecia areata
Lichen simplex	Discoid LE
Primary irritant dermatitis	Hypertrophied scars, keloids
Seborrheic dermatitis	Lichen planus
Psoriasis of face, flexures	Nail disorders
Varicose eczema	Psoriasis of palm, sole, elbow, knee

Local adverse effects of topical steroids

Thinning of epidermis
Dermal changes—atrophy
Telangiectasia, Striae
Easy bruising
Hypopigmentation
Delayed wound healing
Fungal and bacterial infections

} Related to the potency of preparation and duration of treatment; skin of face is more susceptible. Potent halogenated steroids not to be used on face.

Systemic adverse effects of topical steroids

Adrenal pituitary suppression can occur if large amounts are applied repeatedly. Infants and children are particularly susceptible. Rarely, Cushing's syndrome has been reported. With proper use, the systemic risks are minimal.

Popular combinations are:

Containing Neomycin (0.3–0.5%): BECLATE-N, BETASONE-N, COLSIPAN-N, DECADRON, KENACOMB, KENALOG-S SKIN, TOPICASONE.

Containing Chinoform or Quiniodochlor (3–4%): BECLATE-C, BETASONE-C, BETNOVATE-C, CORTOQUINOL, FLUCORT-C

Containing Gentamicin (0.1%): GENTICYN-HC TOPICAL, DERMOTYL-G, LOBATE-G

Containing Chloramphenicol (1%): CORTISON-KEMICETINE

Containing Providone iodine (1%): ECZO-BETADINE

Containing Miconazole (2%): FLUCORT-MZ, TENOVATE-M

Containing Clotrimazole (1%): CLOBEN

Chapter 65 Antiseptics, Disinfectants and Ectoparasiticides

ANTISEPTICS AND DISINFECTANTS

The terms *antiseptic* and *disinfectant* connote an agent which inhibits or kills microbes on contact. Conventionally, agents used on living surfaces (skin, mouth) are called *antiseptics* while those used for inanimate objects (instruments, privies, water supply) are called *disinfectants*. There is considerable overlap and many agents are used in either way. A practical distinction between the two on the basis of a *growth inhibiting versus direct lethal* action is futile because these are often concentration dependent actions. The term *Germicide* covers both category of drugs.

There, however, is difference between 'disinfection' and 'sterilization'. While sterilization means complete killing of all forms of microorganisms, disinfection refers to reduction in the number of viable pathogenic microbes to a level that they do not pose a risk to individuals with normal host defence. The terms 'sanitization' and 'decontamination' also have similar connotation. Thus, in ordinary usage, disinfectants do not eliminate all microbes.

The era of antiseptics and disinfectants was heralded by Semmelweiss (washing of hands in chlorinated lime) and Lister (antiseptic surgery by the use of phenol) in the 19th century. These germicides differ from systemically used antimicrobials by their low parasite selectivity—are too toxic for systemic use. However, many systemic antimicrobials are applied topically as well, and some antibiotics (bacitracin, neomycin) are restricted to topical use, but are generally not enumerated with the antiseptics. A strict distinction is thus impossible.

A good antiseptic/disinfectant should be:

(i) Chemically stable.
(ii) Cheap.
(iii) Nonstaining with agreeable colour and odour.
(iv) Cidal and not merely static, destroying spores as well.
(v) Active against all pathogens—bacteria, fungi, viruses, protozoa.
(vi) Require brief time of exposure.
(vii) Able to spread through organic films and enter folds and crevices.
(viii) Active even in the presence of blood, pus, exudates and excreta.

A disinfectant in addition should not corrode or rust instruments and be easily washable. An antiseptic in addition should be:

- Rapid in action and exert sustained protection.
- Nonirritating to tissues, should not delay healing.
- Nonabsorbable, produce minimum toxicity if absorbed.
- Nonsensitizing (no allergy).
- Compatible with soaps and other detergents.

Spectrum of activity of majority of antiseptic-disinfectants is wide, reflecting nonselectivity of action. However, some are rather selective, e.g. hexachlorophene, chlorhexidine, quaternary ammonium antiseptics, gentian violet and acriflavin are more active on gram-positive than gram-negative bacteria; silver nitrate is highly active against gonococci and benzoyl peroxide against *P. acnes*.

Mechanisms of action of germicides are varied, but can be grouped into:

(a) Oxidation of bacterial protoplasm.
(b) Denaturation of bacterial proteins including enzymes.
(c) Detergent like action increasing permeability of bacterial membrane.

Factors which modify the activity of germicides are:

- Temperature and pH.

- Period of contact with the microorganism.
- Nature of microbe involved.
- Size of innoculum.
- Presence of blood, pus or other organic matter.

Potency of a germicide is generally expressed by its *phenol coefficient* or *Rideal Walker coefficient*, which is the ratio of the minimum concentration of test drug required to kill a 24 hour culture of *B. typhosa* in 7.5 minute at 37.5°C to that of phenol under similar conditions. This test has only limited validity, particularly in relation to antiseptics which have to be tested on living surfaces.

Therapeutic index of an antiseptic is defined by comparing the concentration at which it acts on microorganisms with that which produces local irritation, tissue damage or interference with healing.

CLASSIFICATION

1. *Phenol derivatives*: Phenol, Cresol, Hexylresorcinol, Chloroxylenol, Hexachlorophene.
2. *Oxidizing agents*: Pot. permangnate, Hydrogen peroxide, Benzoyl peroxide.
3. *Halogens*: Iodine, Iodophores, Chlorine, Chlorophores.
4. *Biguanide*: Chlorhexidine.
5. *Quaternary ammonium (Cationic):* Cetrimide, Benzalkonium chloride, Dequalinium chloride.
6. *Soaps*: of Sod. and Pot.
7. *Alcohols*: Ethanol, Isopropanol.
8. *Aldehydes*: Formaldehyde, Glutaraldehyde.
9. *Acids*: Boric acid, Acetic acid.
10. *Metallic salts*: Silver nitrate, Silver sulfadiazine, Mild silver protein, Zinc sulfate, Calamine, Zinc oxide.
11. *Dyes*: Gentian violet, Acriflavine, Proflavine.
12. *Furan derivative*: Nitrofurazone.

1. PHENOLS

Phenol (Carbolic acid) It is one of the earliest used antiseptics and still the standard for comparing other germicides. It is a relatively weak agent (static at 0.2%, cidal at >1%, poor action on bacterial spores). It is a general *protoplasmic poison*, injuring microbes and tissue cells alike—at higher concentrations causes skin burns and is a caustic. It acts by disrupting bacterial membranes and denaturing bacterial proteins. Organic matter diminishes its action slightly while alkalies and soaps do so profoundly (carbolic soaps are not more germicidal than soap itself). It is now seldom employed as an antiseptic, but being cheap, it is used to disinfect urine, faeces, pus, sputum of patients and is sometimes included in antipruritic preparations because of its mild local anaesthetic action.

Cresol It is methyl-phenol; more active (3–10 times) and less damaging to tissues. Used for disinfection of utensils, excreta and for washing hands.

LYSOL is a 50% soapy emulsion of cresol.

Hexylresorcinol It is a more potent derivative of the phenolic compound resorcinol that is odourless and nonstaining; used as mouthwash, lozenge and as antifungal.

Chloroxylenol It has a phenol coefficient of 70; does not coagulate proteins, is noncorrosive, nonirritating to intact skin, but efficacy is reduced by organic matter. It is poorly water soluble; the commercial 4.8% solution (DETTOL) is prepared in 9% terpinol and 13% alcohol; used for surgical antisepsis. A 0.8% skin cream and soap, 1.4% lubricating obstetric cream (for vaginal examination, use on forceps, etc.), and a mouthwash (DETTOLIN 1% with menthol 0.45%) are also available. These preparations lose activity if diluted with water and kept for a time.

Hexachlorophene This chlorinated phenol acts by inhibiting bacterial enzymes and (in high concentration) causing bacterial lysis. It is odourless, nonirritating and does not stain. Its activity is reduced by organic matter but not by

soap. It is commonly incorporated in soap and other cleansing antiseptics for surgical scrub, patient's skin, etc., but is narrow spectrum; kills gram-positive but not gram-negative bacteria or spores. The degerming action is slow but persistent due to deposition on the skin as a fine film that is not removed by rinsing with water. Incorporated in toilet products, it is a good deodorant.

Use of a 3% solution for baby bath markedly reduced the incidence of staphylococcal infections, but produced brain damage (especially in premature neonates). Around 1970 several fatalities occurred in USA. Since then use of preparations containing > 2% hexachlorophene have been banned.

2. OXIDIZING AGENTS

Potassium permanganate It occurs as purple crystals, highly water soluble, liberates oxygen which oxidizes bacterial protoplasm. The available oxygen and germicidal capacity is used up if much organic matter is present—the solution gets decolourised. A 1:4000 to 1:10,000 solution (Condy's lotion) is used for gargling, douching, irrigating cavities, urethra and wounds. The action is rather slow and higher concentrations cause burns and blistering—popularity therefore has declined.

It has also been used to disinfect water (wells, ponds) and for stomach wash in alkaloidal poisoning (except atropine and cocaine which are not efficiently oxidized). It promotes rusting and is not good for surgical instruments.

Hydrogen peroxide It liberates nacent oxygen which oxidizes necrotic matter and bacteria. A 3.0% solution produces 10 volumes of oxygen, much of which escapes in the molecular form. Catalase present in tissues speeds decomposition resulting in foaming—helps in loosening and removing slough, ear wax, etc. Hydrogen peroxide has poor penetrability and a weak, transient action. It loses potency on keeping. Use therefore is much restricted.

Benzoyl peroxide It is specifically active against *P. acnes* and used on acne vulgaris (*see* p. 893).

3. HALOGENS

Iodine It is a rapidly acting, broad-spectrum (bacteria, fungi, viruses) microbicidal agent; has been in use for more than a century. Acts by iodinating and oxidizing microbial protoplasm. A 1 : 20,000 solution kills most vegetative forms within 1 min. Even bacterial spores are killed with higher concentrations/longer contact. Organic matter retards but does not abolish its germicidal action.

Solid iodine is corrosive, stronger solutions (> 5%) cause burning and blistering of skin. *Tincture iodine* (2% in alcohol) stings on abrasions. It is used on cuts, for degerming skin before surgery, and to treat ring worm, etc. *Mandel's paint* (1.25% iodine dissolved with the help of Pot. iodide forming soluble I_3^--ions) is applied on sore throat. A *nonstaining iodine ointment (*IODEX 4%*)* is popular as antiseptic and counterirritant. Some individuals are sensitive to iodine—rashes and systemic manifestations occur in them.

Iodophores These are soluble complexes of iodine with large molecular organic compounds that serve as carriers—release free iodine slowly. The most popular—*Povidone (Polyvinyl-pyrrolidone) iodine*: is nonirritating, nontoxic, nonstaining and exerts prolonged germicidal action. Treated areas can be bandaged or occluded without risk of blistering. It is used on boils, furunculosis, burns, otitis externa, ulcers, tinea, monilial/trichomonal/ nonspecific vaginitis and for surgical scrubbing, disinfection of endoscopes and instruments.

BETADINE 5% solution, 5% ointment, 7.5% scrub solution, 200 mg vaginal pessary; PIODIN 10% solution, 10% cream, 1% mouthwash; RANVIDONE AEROSOL 5% spray with freon propellant.

Chlorine A highly reactive element and a rapidly acting potent germicide, 0.1–0.25 ppm kills most pathogens (but not *M. tuberculosis*) in 30 sec. However, the degerming action is soon exhausted, and it lacks substantivity. It is used to disinfect urban water supplies. Organic matter binds chlorine, so that excess has to be added to obtain free chlorine concentration of

0.2–0.4 ppm. This is known as the 'chlorine demand' of water. Chlorine is more active in acidic or neutral medium.

Chlorophores These are compounds that slowly release hypochlorous acid (HOCl). Because of ease of handling, they are used in preference to gaseous chlorine.

(i) *Chlorinated lime (bleaching powder)* It is obtained by the action of chlorine on lime; resulting in a mixture of calcium chloride and calcium hypochlorite. On exposure, it decomposes releasing 30–35% W/W chlorine. It is used as disinfectant for drinking water, swimming pools and sanitizer for privies, etc.

(ii) *Sodium hypochlorite solution* Contains 4–6% sodium hypochlorite. It is a powerful disinfectant used in dairies for milk cans, other equipment and for infant feeding bottles. It is unstable and too irritant to be used as antiseptic, except for root canal therapy in dentistry.

4. BIGUANIDE

Chlorhexidine A powerful, nonirritating, cationic antiseptic that disrupts bacterial cell membrane. A secondary action is denaturation of microbial proteins. It is relatively more active against gram-positive bacteria. Like hexachlorophene it persists on the skin. Present in SAVLON (*see* below), it is extensively used for surgical scrub, neonatal bath, mouthwash, obstetrics and as general skin antiseptic.

Chlorhexidine is the most widely employed antiseptic in dentistry. As 0.12–0.2% oral rinse or 0.5–1% toothpaste, it is highly active in preventing/treating gingivitis. Twice daily chlorhexidine oral rinse markedly reduces oral infections in immunocompromised patients, including AIDS. However, it may leave an unpleasant after taste, and repeated application causes brownish discolouration of teeth.

5. QUATERNARY AMMONIUM (CATIONIC) ANTISEPTICS

These are detergents; cidal to bacteria, fungi and viruses. However, many gram-negative bacteria (especially *Pseudomonas*), *M. tuberculosis* and bacterial spores are relatively resistant. They act by altering permeability of cell membranes and denaturing of bacterial proteins. Soaps, being anionic, neutralize their action, while alcohol potentiates. They spread through oil and grease, have cleansing and emulgent properties. They are nonirritating and mildly keratolytic. However, the germicidal action is rather slow and bacteria may thrive under a film formed by them on the skin. Pus, debris and porous material like cotton, polyethylene reduce their activity. Occasionally sensitization occurs. These disadvantages not withstanding, they are widely used as sanitizers, antiseptic and disinfectant for surgical instruments, gloves, etc, but should not be considered sterilizing.

Cetrimide A soapy powder with a faint fishy odour. Used as 1–3% solution, it has good cleansing action, efficiently removing dirt, grease, tar and congealed blood from road side accident wounds. Alone or in combination with chlorhexidine, it is one of the most popular hospital antiseptic and disinfectant for surgical instruments, utensils, baths, etc.

CETAVLON CONCENTRATE: Cetrimide 20%
SAVLON LIQUID ANTISEPTIC: Chlorhexidine gluconate 1.5% + Cetrimide 3%.
SAVLON/CETAVLEX CREAM: Chlorhexidine HCl 0.1% + Cetrimide 0.5%.
SAVLON HOSPITAL CONCENTRATE: Chlorhexidine gluconate 7.5% + Cetrimide 15%.

Benzalkonium chloride (Zephiran) It is highly soluble in water and alcohol. A 1:1000 solution is used for sterile storage of instruments and 1 in 5000 to 1 in 10,000 for douches, irrigation, etc.

Dequalinium chloride Has been used in gum paints and lozenges.
DEQUADIN 0.25 mg lozenges.

6. SOAPS

Soaps are anionic detergents; weak antiseptics, affect only gram-positive bacteria. Their usefulness primarily resides in their cleansing action. Washing with soap and warm water is one of the most effective methods of preventing transmission of infection by removing/diluting

pathogenic bacteria. Soaps can be medicated by other antiseptics.

7. ALCOHOLS

Ethanol It is an effective antiseptic and cleansing agent at 40–90% concentration. The rapidity of action increases with concentration upto 70% and decreases above 90%. It acts by precipitating bacterial proteins. A cotton swab soaked in 70% ethanol rubbed on the skin kills 90% bacteria in 2 min.; has been used before hypodermic injection and on minor cuts. Low concentrations enhance the antiseptic activity of iodine and chlorhexidine when used as solvent for these. It is an irritant and should not be applied to mucous membranes or to delicate skin (scrotum), ulcers, etc. On open wounds it produces a burning sensation, injures the surface and forms a coagulum under which bacteria could grow. It is a poor disinfectant for instruments—does not kill spores and promotes rusting.

Isopropanol It is less volatile; can be used in place of ethanol.

8. ALDEHYDES

Formaldehyde It is a pungent gas—sometimes used for fumigation. A 37% aqueous solution called *Formalin* is diluted to 4% and used for hardening and preserving dead tissues. It denatures proteins and is a general protoplasmic poison, but acts slowly. A broad-spectrum germicide, but use as antiseptic is restricted by its irritating nature and pungent odour. It is occasionally employed to disinfect instruments and excreta. Those who handle formalin can develop eczematoid reactions. The urinary antiseptic methenamine acts by releasing formaldehyde in acidic urine (*see* p. 760). Formaline is also used to precipitate *toxoids* from toxins.

Glutaraldehyde It is less volatile, less pungent, less irritating and better sterilizing agent than formalin, but needs to be activated by alkalinization of the solution. It exerts broad-spectrum activity against bacteria, fungi and viruses. Organic matter does not inactivate it. A 2% solution is used to disinfect surgical instruments and endoscopes, but prolonged contact is needed. Repeated application on skin can cause sensitization. The alkalinized solution has a short shelf life (2 weeks) unless stablilizing agents are added.

9. ACIDS

Boric acid It is only bacteriostatic and a very weak antiseptic. But being nonirritating even to delicate structures, saturated aqueous solutions (4%) have been used for irrigating eyes, mouthwash, douche, etc. Boroglycerine paint (30%) is used for stomatitis and glossitis. A 10% ointment (BOROCIDE) is available for cuts and abrasion. It is included in prickly heat powders and ear drops. However, boric acid is not innocuous; systemic absorption causes vomiting, abdominal pain, diarrhoea, visual disturbances and kidney damage. Hence its use for irrigating bladder, large wounds, as ointment on extensive burnt areas, liberal use of powder for infants is not recommended.

Acetic acid It is a relatively weak antiseptic, bactericidal only above 5%. *Pseudomonas* is especially susceptible. It is occasionally used for burn dressing and for douche in 1–3% strength.

10. METALLIC SALTS

Silver compounds These are astringent and caustic. They react with SH, COOH, PO_4 and NH_2 groups of proteins.

(i) Silver nitrate rapidly kills microbes, action persisting for long periods because of slow release of Ag^+ ions from silver proteinate formed by interaction with tissue proteins. Tissues get stained black due to deposition of reduced silver. Silver nitrate touch is used for hypertrophied tonsillitis and aphthous ulcers. It is highly active against gonococci—1% solution is used for ophthalmia neonatorum.

(ii) Silver sulfadiazine (*see* p. 706) is highly active against *Pseudomonas* and has been used on burns.

Zinc salts They are astringent and mild antiseptics.

(i) Zinc sulfate: is highly water soluble, 0.1–1% is used for eyewash and in eye/ear drops (Zinc-boric acid drops—in ZINCO-SULFA 0.1% eye drop). Applied to skin, it decreases perspiration. *White lotion* containing 4% each of zinc sulfate and sulfurated potash has been used for acne and impetigo; (THIOSOL 2.5%, THIOSOL FORTE 4% lotion).

(ii) Calamine and zinc oxide: are insoluble. In addition to being mildly antiseptic, they are popular dermal protectives and adsorbants.

11. DYES

Gentian violet (crystal violet) A rosaniline dye active against staphylococci, other gram-positive bacteria and fungi, but gram-negative organisms and mycobacteria are insensitive. Aqueous or alcoholic solution (0.5–1%) is used on furunculosis, bedsores, chronic ulcers, infected eczema, thrush, Vincent's angina, ringworm, etc. It has become unpopular due to deep staining.

Acriflavine and Proflavine These are orange-yellow acridine dyes active against gram-positive bacteria and gonococci. Their efficacy is not reduced by organic matter and is enhanced in alkaline medium. Solutions lose efficacy on exposure to light—store in amber bottles. They are nonirritant and do not retard healing—particularly suitable for chronic ulcers and wounds. Bandage impregnated with acriflavine-vaseline is used for burn dressing;
ACRINOL 0.1% acriflavine cream.

The *triple dye lotion* contains gentian violet 0.25% + brilliant green 0.25% + acriflavine 0.1% (TRIPLE DY), has been used for burns and for dressing umbilical stump in neonates.

12. FURAN DERIVATIVES

Nitrofurazone (Nitrofural) It is cidal to both gram-positive and negative, aerobic and anaerobic bacteria, even in high dilutions, but activity is reduced in the presence of serum. Acts by inhibiting enzymes necessary for carbohydrate metabolism in bacteria. It is highly efficacious in burns and for skin grafting. Its local toxicity is negligible—but sensitization occurs frequently.
FURACIN 0.2% cream, soluble ointment, powder.
Nitrofurantoin and Furazolidone are other furan derivatives used for urinary and intestinal infections respectively.

ECTOPARASITICIDES

These are drugs used to kill parasites that live on body surface. Lice (*Pediculus sp.*—wingless insects) and mites (*Sarcoptes/Acarus scabiei*—arachnids) are minute arthropods infesting human skin and hair.

Scabies It is highly contagious; the mite burrows through the epidermis, laying eggs which form papules that itch intensely. Lesions may get secondarily infected requiring systemic antimicrobial therapy. The finger webs are the preferred sites of entry, but may soon spread to forearms, trunk, genitals and lower legs. Other members of the patient's family should be treated concurrently; garments and bed linen should be washed in hot water and put in sun to prevent cross infection and re-infection.

Pediculosis The lice thrive on head (*P. capitis*), body (*P. corporis*) or pubic region (*P. pubis*). They cause itching, suck blood and transmit typhus and relapsing fever. The eggs called *nits* get attached to the hair and clothing by a chitin like cement.

Drugs used are:

Permethrin	Sulfur
Lindane (BHC)	Dicophane (DDT)
Benzyl benzoate	Ivermectin
Crotamiton	

1. Permethrin This broad-spectrum and potent pyrethoid insecticide is currently the most efficacious and most convenient drug for both scabies and lice. It causes neurological paralysis in insects, probably by delaying depolarization. Toxicity of permethrin in humans is very low; apparently 40–400 times lower than that of lindane. After application, permethrin persists on the skin for days; systemic absorption is minimal. Nearly 100% cure rates have been obtained in

scabies and pediculosis; comparative studies have found it to be more effective than lindane, benzyl benzoate and crotamiton. Single application is needed in most cases. Resistance to permethrin is very rare and it is effective in lindane nonresponsive cases. Few patients may experience mild and transient burning, itching, tingling, erythema or rash.

For scabies: PERMITE, OMITE, NOMITE 5% cream; apply all over the body except face and head; wash after 8–12 hours. SCABERID 5% cream, 1% soap; SCABPER 5% lotion.

For head lice: PERLICE, KERALICE 1% cream rinse, ELICE 5% lotion, SCALTIX 1% lotion; massage about 30 g into the scalp, washoff after 10 min.

Thus, permethrin is now the 1st choice drug for scabies and pediculosis

2. Lindane (Gamma benzene hexachloride, BHC) Another broad-spectrum insecticide which kills lice and mites by penetrating through their chitinous cover and affecting the nervous system. Lindane is highly effective in treating headlice (67–92% cure) and scabies (84–92% cure) by single treatment. However, efficacy is lower than permethrin. Both lice and mites can develop resistance to lindane. Combining it with benzyl benzoate precludes resistance and improves cure rate to nearly 100%.

GAB 1% lotion, ointment; GAMADERM, SCABOMA 1% lotion; GAMASCAB 1% lotion, cream; ASCABIOL 1% emulsion with cetrimide 0.1%; BENZO 1% lotion, 1% soap.

For pediculosis: apply to scalp and hair (taking care not to enter eyes), leave for 12–24 hr. (a shower cap may be used for long hair) and then wash off. If lice are still present, repeat treatment after 1 week.

For scabies: the lotion/cream is rubbed over the body (below neck) and a scrub bath taken 12–24 hr later. Single treatment suffices in most patients; can be repeated only after a week, if the mite is still present.

The disadvantages of lindane are:

Being highly lipid soluble it can be absorbed through the skin (especially from oily vehicles and in small children)— can produce systemic toxicity —CNS stimulation, vertigo, convulsions (especially in children) and cardiac arrhythmias.

Absorbed lindane is widely distributed in the body, especially in fat; is metabolised and eliminated with a t½ ~24 hr. It can induce CYP isoenzymes in liver and affect metabolism of many drugs.

Though well tolerated by most patients if instructions are followed, it is less favoured for treatment of scabies—because application over large body surface is required—possibility of systemic absorption is more. It should be avoided in infants, young children and during pregnancy. Skin irritation is not prominent.

3. Benzyl benzoate It is an oily liquid with faint aromatic smell; has been popular for treatment of scabies. The emulsion is applied all over except face and neck after a cleansing bath. A second coat is applied next day which is washed after 24 hours. The treatment is convenient and does not interfere with routine activities. It has achieved 76–100% cure in scabies. Benzyl benzoate is minimally absorbed through the skin; systemic toxicity is low, but neurological symptoms have occurred in children—contraindicated in them. Skin irritation is common, especially in children. Contact dermatitis is possible.

BENZYLBENZOATE APPLICATION 25% lotion; DERMIN 25% lotion; SCABINDON 25% oint with DDT 1% and benzocaine 2%

For pediculosis, it can be applied to the scalp, taking care not to enter eyes, and is washed off after 24 hours. Benzyl benzoate is now a 2nd choice drug for scabies and seldom used for pediculosis. Its combination with lindane is highly effective.

4. Crotamiton It is an effective scabicide, pediculocide and antipruritic, but has produced lower cure rates (60–88%) in scabies. Better results have been obtained by extended 5 day application in children. It is less prone to cause skin irritation and has low systemic toxicity despite absorption through the skin—may be preferred for children. It is applied twice at 24 hr interval and washed off day after that.

CROTORAX, CROTON 10% cream, lotion

Because of lower efficacy and need for repeat application, it is a second choice drug for scabies and pediculosis.

5. Sulfur It is the oldest scabicide and weak pediculocide, antiseptic, fungicide and keratolytic. Applied to skin it is slowly reduced to H_2S and oxidized to SO_2 and *pentathionic acid.* These, especially the latter, dissolve the

cuticle of itch mite and kill it. The reactions are carried out by epidermal cells and the arthropods themselves.

Sublimed sulfur or precipitated sulfur is used as a 10% ointment. After a warm scrubbing bath (to open the burrows) the ointment is massaged over the entire body (below the neck) for 3 consecutive days, followed by soap water bath on the fourth day. It is cheap but has disadvantages:

(a) Treatment is messy.
(b) Produces bad odour—socially unacceptable —may interfere with patient's vocation.
(c) Repeated applications are required.

Sulfur has been superseded by better drugs.

6. Dicophane (DDT) It has been a popular insecticide for mosquitoes, flies and other pests. For this purpose, it is used in the dust or watery suspension form, which is poorly absorbed through skin. For pediculosis and scabies a 1–2% lotion or ointment is applied and washed off after 12–24 hours. It penetrates through the exoskeleton and acts as a neurotoxin for the arthropods. When oily vehicles are used, significant amounts may be absorbed through the skin and cause rashes, muscle weakness, tremor. Very high doses produce BHC like convulsions. It gets stored in body fat and induces microsomal enzymes. Combination with benzyl benzoate (SCABINDON oint) is more effective. It is rarely used.

7. Ivermectin This anthelmintic drug (*see* p. 854) has been found highly effective in scabies and pediculosis as well. It is the only orally administered drug used for ectoparasitosis. A single 0.2 mg/kg (12 mg in adults) dose has cured upto 91–100% patients of scabies. AIDS patients with scabies also respond. Most cases of head/body lice have been successfully treated.

Ivermectin is very well tolerated by scabies/pediculosis patients, with few if any side effects. However, it is not to be given to children < 5 yr, pregnant and lactating women. Only limited use of ivermectin has been made in scabies and pediculosis because of the availability of efficacious topical agents.