EMERGING DEVELOPMENTS IN THE CHEMOTHERAPY OF INFECTIOUS DISEASES

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The WHO has taken up for eradication six major tropical diseases that afflict the developing countries in major dimensions: malaria, leishmaniasis, filariasis, leprosy, schistosomiasis and trypanosomiasis. Among these, the first four are widely prevalent in India. Concerted spraying of DDT successfully suppressed the incidence of malaria in earlier years by killing the mosquito vector. A useful fallout was the lethal effect on the sand fly, which is the vector for leishmaniasis, the visceral form of which is known as Kala Azar and is mainly endemic to the eastern parts of India. However, slackness in the spraying programme and development of resistance of the vectors have resulted in large scale recrudescence of malaria as well as of Kala Azar to some extent. Apart from these, parasitic infections such as those due to intestinal worms as well as amoeba are rampant in the country. Additionally tubercular, bacterial and fungal infections also cause considerable morbidity. This lecture will survey recent advances in the treatment of these diseases and also touch upon developing trends in the dosage forms in which drugs are administered.

Chloroquine and primaquine have been the standard drugs for the treatment of Plasmodium falciparum and Plasmodium vivax respectively, the two common types of malaria prevalent in India. Fansidar, a combination of pyrimethamine and sulphadoxine, a long acting synergistic antifolate combination has now become available, but the malarial parasite builds up resistance to the drug very rapidly. Mefloquine, a quinolyl piperidyl carbiniol has been recently cleared by WHO for restricted use in resistant cases of P. falciparum. Halofantrine, a dichlorofluoro phenanthryl carbiniol is another synthetic antimalarial which has undergone successful clinical trials. Artemisinin, a sesquiterpene lactone peroxide, from the Chinese herb Qinghaosu has provided a novel and interesting lead which has led to the elaboration of derivatives like sodium artemesunate and artem ether. Inspite of worldwide efforts to develop a vaccine for malaria, a breakthrough has not yet been achieved.

The current treatment of Kala Azar depends upon the parenteral administration of toxic pentavalent antimony compounds like ureastiba-
mine, sodium stibogluconate and meglumine and amidines like penta­midine, all of which are unsatisfactory.

Diethyl carbamazine, the only drug available for the treatment of lymphatic filariasis is mainly microfilaricidal. But continuous mass treatment has been successful in reducing the load of adult worms and thus in keeping a check on the spread of filariasis. A macrofilaricidal drug would however be welcome. Amoscanate, an indigenous drug, was taken to the clinic for filaricidal screening. Two benzthiazole isothiocyanate derivatives are currently undergoing clinical trials in India for this indication. Benzimidazole carbamates also have filaricidal properties. Another type filariasis rampant in Africa causes ‘river blindness’. A derivative of amoscanate seems to be effective in its treatment, but more dramatic is the filaricidal activity of ivermectin, a semi-synthetic ionophore antibiotic which has been offered free to afflicted patients. The drug incidentally is a highly potent veterinary anthelmintic agent.

Leprosy can be combated successfully by combination therapy — dapsone, a sulphone; rifampicin, an antibiotic and clofazimine, a phenazine derivative. Some recently developed quinolone antibacterial agents have shown antileprotic activity in laboratory experiments. Antileprosy vaccines now under clinical trials carry the promise of prophylaxis.

In the area of intestinal helminths, niclosamide and praziquantel are recommended for tapeworms. The latter drug, a pyrazinoquinoline derivative, is also highly effective against schistosomiasis, a ‘WHO tropical disease’ not endemic to India. Oxamniquine, a nitroquinolyl methanol, is another effective schistosomicidal agent. Benzimidazole carbamates like mebendazole, albendazole and fenbendazole have a broad spectrum of anthelmintic activity, esp. against hookworms and roundworms; other effective drugs are : pyrantel, a thienylvinyl pyrimidine and tetramisole, an imidazothiazole. Amoscanate, a phenyl isothiocyanate, is an indigenously developed anthelmintic agent.

The treatment of amoebiasis has become simple with the advent of nitroimidazoles, mainly metronidazole and to a lesser extent, tinidazole, especially in cobination with a luminal amoebicide like diloxanide furoate, a dichloracetanilide. Satranidazole, a nitroimidazole and a dichloroacetyl quinoline are Indian developments in the field.

Nitroimidazoles have a broad range of antimicrobial properties. Metronidazole is thus widely used in the treatment of anaerobic infections. A nitroimidazooxazole has been recently found to have potent antituber-
cular properties. Modern treatment of this infection uses a combination of some of the following drugs: isoniazid, ethambutol, pyrazinamide and rifampicin. The use of the last drug has ensured rapid and satisfactory ambulatory control of TB. Quinolone antibacterials represent new leads in this direction. Norfloxacin, ciprofloxacin, oflaxacin and pefloxacin are some of the members of this class which have ushered in a new era of chemotherapy using synthetic antibacterials. These act by the novel mechanism of inhibition of the enzyme, nuclear gyrase. The field has been dominated earlier partly by cotrimoxazole, an antifolate, synergistic combination of trimethoprim and sulphamethoxazole and partly by antibiotics. In the penicillin, cephalosporin field, apart from some of the prominent earlier drugs like ampicillin and cephalaxin, combinations of a beta-lactamase inhibitor like clavulanic acid with amoxicillin (augmentin) or ticarcillin (timentin) have become popular. Subbactam is another beta-lactamase inhibitor. Newer efforts are now concentrated on developing orally active cephalaxins with a long half life and broad spectrum. Rapid advances have also been made in the subgroup of carbapenems (thienamycin) and beta-lactamase resistant monobactams (aztreonam, nocardi­cin). Glycopeptide antibiotics like vancomycin and teicoplanin are used in extreme life-threatening situations. Very recent antibacterial leads are oxazolidinones, lipopolysaccharide inhibitors and bicyclic pyrazolidinones.

Resistant fungal infections have become problematic. Available drugs beginning with clotrimazole are other imidazoles like miconazole and ketoconazole as well as triazole derivatives like terconazole and fluconazole.

Treatment of viral infections is complicated by the notorious propensity of viruses to undergo rapid mutations. Synthetic nucleosides have been partially successful — ribavirin for DNA and RNA viruses, esp. influenza A, B; vidarabine and acyclovir for the DNA virus, genital herpes and retrovird for the (in)famous retrovirus HIV, causing AIDS. Adamantane derivatives like amantadine and rimantadine have limited application in the treatment of influenza. Genetically engineered vaccines using rDNA technology are available for hepatitis.

As far as delivery of drugs is concerned, in recent years a number of formulations have been developed which take advantage of solid polymer devices to provide continuous delivery of active molecules at therapeutic levels, either by physical or by chemical control. Polymers used must be biocompatible for both categories. In the latter case, they must be biodegradable or bioerodable.