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Therapeutic Technologies: Selected Tropical Diseases

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INTRODUCTION

The purpose of therapy is to alter the course of disease so that its consequences are less severe, or to make being ill more tolerable for the patient. Therapy for infections may treat symptoms, which themselves can be dangerous, or may directly attack the responsible organism.

Symptomatic treatment is quite common. Thus, for instance, it is usual to take measures against high fevers, regardless of the cause, because very high body temperatures can result in brain damage. There may or may not be treatment to eliminate the organism causing the infection, and the organism may not even be identified; nevertheless, controlling fever is important. Another symptomatic treatment that has quickly become one of the most potent tools in the tropics is oral dehydration therapy (ORT) for the dehydration that accompanies diarrheal diseases (see *Case Study A: Oral Dehydration Therapy for Diarrheal Diseases)*.

Symptomatic treatment is adequate for some infections that are self-limited. For infections that the body cannot eliminate, however, the goal of therapy is the eradication of the disease-producing organisms, not simply alleviation of symptoms, although this goal is difficult if not impossible to achieve for many tropical diseases.

In general, therapy against bacterial infections is safe, effective, and usually lasts about 1 week. Some bacterial infections (e.g., urinary tract infections) can be treated with one dose; others (e.g., those causing enlargement of the heart, endocarditis) may require 6 weeks of therapy. Prolonged treatment, usually 6 months or more, is the norm for tuberculosis, and lifetime treatment is necessary in the case of lepromatous leprosy. Many tropical diseases caused by helminths can now be adequately treated with 1 to 6 days of therapy, while for others, there is no adequate therapy. The treatment for diseases caused by protozoa is similar. The development of antiviral drugs is still in its infancy.

The mere existence of adequate therapy does not guarantee that it will be used. The availability and quality of health care varies from country to country and from one region of a country to another. Some areas in developing countries, principally the cities, have quite modern health facilities; other areas have only dispensaries or often nothing at all. This variability results in a marked inconsistency in the ability to make specific diagnoses and administer pathogen-directed treatments. In most developing countries, antimicrobial are readily available over-the-counter. The result is two common abuses of these drugs: use for conditions in which they are ineffective and use in inadequate doses. Both extensive use and underdosing promote drug resistance in the pathogens. The prevalence of organisms resistant to the antimicrobial most commonly available is high and thus poses significant therapeutic problems.

The antimicrobial that are generally available in developing countries are penicillin, chloramphenicol, various sulfonamides, tetracycline, streptomycin, isoniazid (INH), chloroquine, pyrimethamine-sulfadoxine (P/S), and some antihelminthic drugs. These are relatively inexpensive compared to other, newer agents, but have significant drawbacks. It is to these agents that resistance in some areas is widespread and growing. Alternatives are usually marketed, but frequently not available where they are needed, often because they are too expensive. Many of the older drugs, particularly the antihelminthics, are toxic to the patient. Drugs for chronic infections often require months or years of treatment, so their ef-

fective use in developing countries, particularly in rural areas, is unlikely.

Some progress is being made. Older chemotherapeutic agents are being reexamined; newer ones are being screened in the laboratory and in animals. The process of drug development is slow, however, and a decade can easily elapse before a promising chemical is marketed as an approved drug. There is a great need for safe, effective, inexpensive, oral, single dose therapies for tropical diseases. Alternatives to the present toxic agents and alternatives for use against drug-resistant organisms are particularly pressing needs. A major problem with new drug development for important pathogens in developing countries is that some diseases at-e relatively rare and others are prevalent only in areas with limited economical resources. Thus, financial incentives for the pharmaceutical companies best equipped to develop new agents are lacking.

THERAPIES: CURRENT STATUS FOR SELECTED TROPICAL DISEASES

Malaria

Human malaria is caused by four species of the genus *Plasm odium: P, falciparum, P. malariae, P. vivax,* and *P. ovale.* There are many groups of drugs available for the prevention and treatment of this disease. Their use is determined by the stage of disease, the immunologic status of the patient, and the probability that the parasite is susceptible to a particular drug (usually geographically determined). Some drugs are effective against sporozoites (the invasive stage of *Plasmodium),* some against hypnozoites (the latent stage of *P, vivax* and *P. ovale* in the liver), some against the merozoites (the erythrocytic or red blood cell stage), and still others against gametocytes (the sexual form which is picked up by the mosquito during feeding and perpetuates malaria transmission after further development in the mosquito). Some of the drugs affect more than one stage of the parasite.

Resistance of *P. falciparum* to most agents is growing. Resistance of *P. falciparum* to chloroquine has been present for some years in Panama, parts of some South American countries, India, Southeast Asia, Indonesia, China, the Republic of the Philippines, and other Pacific islands. It has spread from some parts of South America to include most parts of Bolivia, Venezuela, French Guyana, and northern Peru. There is growing prevalence of resistance in east Africa, which includes Kenya, Tanzania, eastern Zaire, Burundi, Uganda, Rwanda, Malawi, Zambia, northern Sudan, Madagascar, and the Comoro Islands (377).

In some areas, *P. falciparum* strains are also resistant to drugs other than chloroquine, such as P/S, quinine, and mefloquine (see below). Strains resistant to P/S were thought originally to be present only in Southeast Asia. Now there appear to be some resistance in Kenya, Tanzania, and the Amazon basin. Most of these are resistant to both chloroquine and P/S. Some strains in Southeast Asia are resistant to chloroquine, P/S, and mefloquine, and relatively resistant to quinine. These multiply resistant strains are mostly limited to the Thailand-Kampuchean border.

Agents for Treatment of Acute Malaria

Specific chemotherapy for acute malaria is at least 400 years old. During the 1600s, it was known that the bark of a Peruvian tree, the cinchona tree, was effective in the treatment of intermittent fever. The active ingredient, quinine, was isolated in 1820 by two French chemists, Pelletier and Caventou. Since then, new compounds have been discovered that are useful in the treatment of malaria; however, the ideal drug is yet to be discovered. The treatment of malaria becomes less satisfactory almost every year, mainly because more areas of the world report *P. falciparum* resistant to currently available drugs and drugs in clinical trials.

Quinine. -Quinine was the first medication for the treatment of malaria, and it continues to play a key role. Quinine is effective mainly against the merozoite stage of **Plasmodium** and therefore is effective in the treatment of acute malaria of all species. It was the sole specific chemotherapeutic agent for the treatment of acute malaria until World War I. As new drugs such as quinacrine (1930) and chloroquine (1934) were discovered, the importance and use of quinine diminished, With the emergence of chloroquine-resistant, quinine-sensitive strains of malaria parasites in 1959 in Venezuela (274), however, quinine has again become invaluable, and recent research has helped clarif$_y$ its proper use.

Quinine is used parenterally (b$_y$ injection) or orally as the drug of first choice in patients with falciparum malaria in areas of the world where chloroquine-resistant, P/S-resistant **P. falciparum** is prevalent. Unfortunately, it is the most toxic of all antimalarials used regularly to treat acute attacks, and this toxicity limits its use. Adverse effects from quinine are relatively common, ranging from sudden death (which is rare, but may occur from rapid intravenous infusion or hypersensitivity), to more common ringing in the ears, nausea, visual disturbance, and headache. Quinine is also associated with hypoglycemia (low blood sugar), hemolytic anemia (breakdown of red blood cells), and a decrease in clotting factors. Furthermore, increasing resistance of P. **falciparum** to quinine has recently been reported in Thailand and has been associated with treatment failures when quinine has been administered in standard doses (48).

4-Aminoquinolines. —Since quinine (and quinacrine) was in limited supply during World War 11 and was quite toxic, efforts were made to find alternatives. Through a cooperative research program in the United States during World War II, investigation of 4-aminoquinolines was undertaken after one of these compounds was reported by the French to be well tolerated and highly active.

Chloroquine. —Chloroquine is the most valuable and most extensively used of the 4-aminoquinolines. It has activity mainly against the merozoite. It continues to be the drug of first choice for treatment of acute malaria in "nonallergic" persons with chloroquine-susceptible strains of the malaria parasite and for prophylaxis for travelers in areas without chloroquine-resistant strains. Chloroquine can be given orally, intramuscularly, or intravenously and is generally available in the geographical areas where it is needed. It is well tolerated in the usual treatment and prophylactic dosages. Occasional side effects include mild transient headaches, nausea, diarrhea, visual disturbances, and pruritus (itching). Pruritis may occur in anyone, but more commonly in blacks. It probably does not cause birth defects, and is therefore presumed to be safe during pregnancy.

Amodiaquine, —Amodiaquine, another 4-aminoquinoline, was first found to be effective against nonhuman malaria in 1946. It, like chloroquine, is effective in preventing acute malaria and in treating patients with acute malaria due to all four species of **Plasmodium,** except chloroquine-resistant strains of **P, falciparurn.** Amodiaquine is slightly more effective than chloroquine against these resistant strains; however, this fact probably has little clinical significance (328). The side effects of amodiaquine are similar to, but possibly slightly less severe than, those of chloroquine. Amodiaquine is available only in an oral form, and since it does not have a bitter taste like chloroquine, it is more acceptable to children,

Pyrimethamine-Sulfadoxine .—It appeared for a short period of time that the introduction of chloroquine (1934) had brought to an end the search for malaria treatment. Then resistance to chloroquine was reported. Again an extensive search began for drugs effective against chloroquine-resistant strains of **P. falciparurn.** Many previously available drugs were screened for activity against malaria parasites. In course, it was discovered that by combining pyrimethamine with a sulfa derivative, pyrimethamine resistance could be overcome. Thus, P/S (Fansidar) was marketed as another effective regimen in the treatment and prevention of acute malaria due to all four species, excluding P/S-resistant P. falciparum strains.

P/S activity is against the merozoite. This combination was, and still is, one of the most widely

used regimens for the treatment of uncomplicated chloroquine-resistant P. *falciparum* infections. P/S is also frequently used in Africa for the treatment of chloroquine-sensitive acute malaria. Blacks frequently have itching from chloroquine and therefore use P/S as a substitute. Unfortunately, others without chloroquine-induced itching continue to use P/S when chloroquine would be adequate. Many strains of chloroquine-resistant P. *falciparum* are now resistant to P/S. This situation is thought to result partially from the indiscriminate use of P/S for prophylaxis and partially from treatment with inadequate doses.

Adverse effects are those related to pyrimethamine and sulfadoxine individually. Pyrimethamine has few side effects. Sulfadoxine has the usual adverse effects associated with any sulfa, including gastrointestinal and skin reactions which may be severe, and can be life threatening in persons with sulfa allergy. P/S has not been available in all countries, and it has only recently become available in a parenteral form.

Pyrimethamine has also been combined with other sulfas (sulfalene, dapsone) both for treatment and prophylaxis.

Trimethoprim.—Sulfas have also been combined with trimethoprim for use mainly in bacterial infections, and these combinations have been used with quinine in the treatment of uncomplicated chloroquine-resistant (known or suspected) P. *falciparum.* Trimethoprim's main activity is against the red blood cell stage of *Plasmedium.* It has relatively few side effects at doses usually given for malaria.

Tetracycline. —Tetracyclines are antibacterial agents available in various forms since 1948. They do have activity against the red blood cell form of *Plasmodium,* but this effect is extremely slow. They are not used alone, but mainly serve as adjuncts to quinine in the treatment of chloroquine-resistant, P/S-resistant *P. falciparurn* infections.

Alteration of the intestinal flora usually occurs within 48 hours following daily administration of the usual therapeutic dosages. This alteration of the normal intestinal flora increases one's susceptibility to enteric (gut) pathogenic bacteria such as *Salmonella.* Tetracycline also sensitize the skin to sunburn, besides causing nausea, vomiting, diarrhea, and discoloration of the teeth during development, the latter limiting their usefulness in children and pregnant women.

Quinacrine (Mepacrine).-Quinacrine is essentially an obsolete antimalarial because of its side effects. It is important historically because of its widespread use during World War II.

Mefloquine. —Mefloquine is one of a number of 4-quinolinemethanols developed during the 1970s by the U.S. Army Research and Development Command. This group of drugs has been studied since World War II. Mefloquine, the most active of this group, has been found effective in both prophylaxis and treatment of acute malaria due to all species, including chloroquine-resistant, P/S-resistant *P, falciparum* infections. Unfortunately, there already have been reports of resistance of *P, falciparum* strains to mefloquine both in vivo and in vitro (321). Thus, when used prophylactically, mefloquine is combined with P/s.

Agents for the Treatment of Persistent Malaria (Radical Cure)

So far, this discussion has focused on the drugs used for treating acute clinical malaria. Of the four species of *Plasmodium* that cause malaria, only two, *P, vivax* and *P. ovale,* have persistent liver stages. Plasmodial forms in the liver are called hypnozoites because they can remain quiescent for long periods, up to 3 years in cases of *P. vivax.* Following subsequent development, hypnozoites can rupture out of the liver and invade red blood cells (erythrocytes), producing clinical malaria. While hypnozoites are in the liver, patients are asymptomatic.

Quinine, chloroquine, mefloquine, and most of the other antimalarial effective in treating acute malaria have no effect on the liver stages. Since susceptible *P. falciparum* and *P. malariae* do not have liver stages, these infections can be cured by standard treatment regimens effective against the merozoites. However, since *P. vivax* and *P. ovale* do have liver stages, these infections can recur following treatment with agents effective only against the erythrocytic form.

In 1924, an 8-aminoquinoline, pamaquine, was found to be effective in the treatment of malaria. Too toxic for general use, it has been supplanted by a drug in the same family, primaquine (1950). Primaquine has good activity against the liver stages of *P. vivax* and *P. ovale* and currently is the only drug besides quinocide, another of the same family, which is effective in eliminating the hypnozoites. Although both pamaquine and primaquine also have activity against the erythrocytic stages, the necessary doses are toxic. Unfortunately, some strains require increased doses and duration of therapy for complete elimination of the hypnozoites (115).

Primaquine's use is limited by gastrointestinal symptoms and hemolytic anemia. Hemolytic anemia occurs in people with a deficiency of a certain enzyme, G6PD, most frequently occurring in blacks and people of Asian or Middle Eastern descent. Hemolysis in blacks is usually self-limited; however, in Asians, hemolysis may not resolve even after primaquine is withdrawn.

Agents for Malaria Prophylaxis

Drugs that *prevent* acute malaria are said to be used as prophylaxis. Some of these, chloroquine and P/S, have already been mentioned. Chloroquine is effective in preventing multiplication of merozoites. P/S is effective against the sporozoites and merozoites. Unfortunately, again, both chloroquine and P/S are limited in geographical use because of drug resistance.

Another drug, proguanil (chloroguanide) has been available since 1945 and has been effective in the suppression and treatment of both *P. vivax* and *P. falciparum* infections. Like pyrimethamine, proguanil now has limited use because of the emergence of resistant strains of *P. fulciparum.* It is not useful for the treatment of acute attacks, but may be used as prophylaxis in areas where *P. falciparum* is susceptible to it. Not infrequently, resistance to pyrimethamine and proguanil exist together.

Recent Advances in the Supportive Treatment of Malaria

Advances in the treatment of severe malaria apart from antimalarials include the discovery of

the deleterious effect of steroids, used previously in the treatment of cerebral malaria (395), hypoglycemia associated with severe malaria and quinine therapy (148,228,403), quinine pharrnacokinetics (absorption, distribution, and excretion of the drug) (401,402), and the effectiveness of exchange transfusion for high levels of parasitemia (191).

Summary of Current Malaria Therapy and Outlook for the Future

The armamentarium of chemotherapeutic agents to be used against malaria is *barely* adequate in areas of the world where there are resistant strains of *P. falciparum.* Strains of *P. falciparum* resistant to chloroquine and P/S are spreading (327). Quinine and mefloquine resistance is emerging.

In areas where there are both chloroquine- and P/S-resistant strains of malaria parasites, no effective prophylaxis is available except for quinine and mefloquine. As these drugs are used for prophylaxis, and used in inadequate doses, as so frequently happens in developing countries, resistance to them will probably increase. Primaquine is an effective cure for the hypnozoite stage; however, the increased dosage required for some strains suggest that its effectiveness may be diminishing. (Strains such as the "Chesson strain" are thought to have *intrinsic* resistance, in contrast to resistance acquired from drug exposure.) It is clear that new effective antimalarial agents are needed as alternatives for most of the ones currently available.

Schistosomiasis

Recently, the treatment for all forms of schistosomiasis has changed significantly. Antimony potassium tartrate was initially found to be effective in 1918. It was subsequently replaced by trivalent antimonials such as stibophen, and these were largely replaced by hycanthone (1960s) and niridazole (1966), which were the drugs of choice until recently. Three agents which have been studied since about the 1970s—metrifonate, oxamniquine, and praziquantel —are effective given orally and have few adverse effects compared to hycanthone and niridazole, but are expensive. Were it not for the expense, these agents would

probably replace hycanthone and niridazole in the treatment of schistosomiasis.

Hycanthone and Niridazole.—Hycanthone is effective against **Schistosoma mansoni** and S. **haematobium,** but must be given intramuscularly in a single dose and commonly causes nausea and diarrhea. Niridazole can be given orally, is effective against S. **mansoni, S. haematobium** and somewhat against **S. japonicum,** but may cause necrologic side effects necessitating observation during therapy.

Metrifonate.—Metrifonate is effective only against S. **haematobium.** It can be administered orally, but must be given three times separated by 2-week intervals and its effectiveness varies greatly.

Oxamniquine.-Oxamniquine, effective against S. **mansoni,** maybe given orally. Side effects are usually mild. Strains of S. **mansoni** vary in susceptibility, from highly susceptible strains in the Western Hemisphere, requiring only one dose, to less susceptible strains in Africa, requiring about four times the dose given over a 2- to 3-day period.

Praziquantel.—Praziquantel is a welcome addition to the antischistosomal armamentarium. Effective against all known human schistosomes and many other trematodes, it can also be given in one oral dose and is well tolerated. Cure rates range from 70 to 95 percent with S. **mansoni** and S. **haematobium.**

Oltipraz.—Oltipraz, now undergoing clinical trials, appears to have promise for the future. It is well tolerated and has produced cure rates of greater than 80 percent with both **S. hematobium** and S. **mansoni.**

Amosconate.—Amosconate, a new antischistosomal drug, has demonstrated efficacy against S. **mansoni** and S. **japonicum** and is effective against S. **haematobium** infections of primates besides other worms. It also has some serious side effects.

Trypanosomiasis

African Sleeping Sickness (African Trypanosomiasis)

Therapy for African sleeping sickness, whether due to **Trypanosoma brucei gambiense** or to **T.b. rhodesiense,** differs depending on the stage of the disease.

The early stage of African sleeping sickness can be treated with suramin, which has been available since the 1920s. It is given on days 1, 3, 7, 14, and 21 slowly intravenously, and then weekly twice after that. Suramin has serious side effects, the immediate ones consisting of nausea, vomiting, seizures, loss of consciousness, and shock. The most important delayed effect is kidney damage. Other side effects have been reported. The drug is not effective once the pathogenic organisms have invaded the central nervous system.

Another drug that is effective in the early stage is pentamidine, which has been available since the mid-1930s. Pentamidine's use is limited by side effects which frequently result in an abbreviated course of therapy. The drug must be administered intramuscularly, resulting in pain at the injection sites. It can also cause abscesses, hypoglycemia (low blood sugar) or hyperglycemia (high blood sugar), pancreatitis, and hypotension (low blood pressure) if inadvertently given intravenously. Pentamidine is generally not as effective as suramin.

The late stage of African trypanosomiasis can be treated with melarsoprol, an arsenical first shown to have activity against trypanosomes in 1940. Melarsoprol is effective against both subspecies and both stages of disease, but its use is limited by its toxicity. This agent is used only after therapy with other agents has failed. It must be given intravenously daily, or every other day, for three doses, and then this sequence must be repeated twice more after some time has elapsed. Side effects include intensely irritating local reactions upon leakage into tissue and a potentially fatal reaction of the brain.

In summary, therapy for African sleeping sickness requires the use of toxic and frequently only partially effective drugs over an extended period of time. Hospitalization is usually required for administration and observation of intravenous therapy. Effective and appropriate treatment will require new drugs that require short courses, and are easy to administer. Such treatment is not now foreseeable.

Chagas' Disease (American Trypanosomiasis)

Chagas' disease has two clinical stages: acute and chronic. The acute stage can be suppressed by the drug nifurtimox, which has been available since the 1970s. Following treatment with nifurtimox for 120 days, one study has claimed an 80-percent cure rate at 2 years (258). However, strains of T. *cruzi* vary in susceptibility depending on the area—strains from Argentina and Chile are more susceptible than some Brazilian strains.

Nifurtimox is fairly well tolerated, although side effects such as gastrointestinal upset and abnormalities of nerves occur in 40 to 70 percent of patients. Another drug reported to be effective in the acute stage in a large percentage of patients is benzonidazole (258). Both are given orally.

Leishmaniasis

Leishmaniasis, caused by protozoans of the genus *Leishmania,* has three major forms, depending on the species of parasite: 1) cutaneous leishmaniasis, a localized ulcer caused by one of three species, *L. tropica, L. mexicani,* or *L. braziliensis* (determined by the geographical location); 2) mucocutaneous leishmaniasis, an invasive destructive lesion caused by *L. braziliensis;* and 3) visceral leishmaniasis, a systemic disease caused by *L. donouani.* Visceral, mucocutaneous, and complicated cutaneous leishmaniasis require therapy.

Antimonials.—Antimony-containing compounds have been the mainstays of therapy for all types of leishmaniasis requiring treatment since tartar emetic was shown to be effective in 1912 (114). Sodium stibogluconate was found effective as early as 1937 and continues to be the treatment of choice along with meglumine antimonate. Both

of these drugs must be given parenterally for 10 to 30 days depending on the susceptibility of the *Leishmania* parasites.

Appropriate regimens of therapy for each strain from each geographic area have not been precisely determined. Ten-day periods of treatment are effective in the majority of patients in China, India, and the Sudan, but persons infected with Kenyan strains usually receive a 30-day course. Therapy is frequently interrupted by a rest period of 10 to 14 days.

Recently, therapy in India has been increased from 10 to 20 days, decreasing the relapse rate from 13 to 0.5 percent. Also, the pharmacokinetics of sodium stibogluconate have recently been studied, suggesting that daily doses need to be increased.

Side effects of nausea, anorexia, and malaise are generally tolerable. Antimonials do cause changes in the electrocardiogram, generally in doses higher than those used against leishmaniasis.

Amphotericin.-Amphotencin BIDD, an agent used in the United States mainly for its antifungal activity, has also been found to be effective against leishmaniasis. It must be given intravenously, usually every other day or daily, until 2.5 grams total dose is achieved. This dose takes at least 1 month to administer. Because amphotericin is extremely toxic to the kidneys, renal function must be monitored. The facilities to do this are frequently not available where the patients are in developing countries.

Pentamidine and Stilbamidine.-Another agent useful in leishmaniasis is pentamidine. As mentioned previously in relation to trypanosomiasis, its use is limited by its side effects. A similar compound, stilbamidine, maybe more effective, but its use is limited by its effects on the nervous system. Hydroxystilbamidine is also effective, but not generally available in developing countries.

Allopurinol Riboside. -Allopurinol riboside is a drug most often used in the United States to decrease uric acid excretion by the kidney in the treatment of gout. A derivative has shown some in vitro activity against *L. donovani* and is almost ready to undergo clinical trials in cutaneous leishmaniasis at the Gorgas Memorial Laboratory.

Other Agents.—The role, if any, of other agents such as cycloguanil, pyrimethamine, metronidazole, benzimidazole, rifampin, and nitrofurtimox remains to be clarified.

Summary

At present, management of leishmaniasis is usually hospital-based, since most therapy is parenteral, and side effects common and frequently serious. There is, therefore, a need for effective, safe, oral agents in the treatment of these diseases.

Filariasis

There are at least eight types of human filarial infections. The three most important are infections by **Wuchereria bancrofti, Brugia malayi,** and **Onchocerca volvulus.** The therapy for all filarial infections is similar. There is effective therapy against microfilariae (the immature worms that cause the symptoms of filariasis), but no nontoxic therapy is available against all the species of adult worms.

Diethylcarbamazine. —Diethylcarbamazine kills microfilariae and is therefore effective as prophylaxis or in treatment of symptomatic infections. It also has an effect on the adults of **W. bancrofti** and **Loa loa** (the agent of African eyeworm disease). Diethylcarbamazine can be given orally. Side effects include adverse diethylcarbamazine reactions to itself and reactions to dying worms. The latter can be severe and exacerbate eye damage.

Suramin.—Suramin is also effective against microfilariae and adults of O. **volvulus.** Following an initial test dose, there must be 1 week of observation. If no adverse reactions occur, doses may be increasea at weekly intervals. Therapy usually requires 6 weeks. Suramin must be given intravenously. Side effects include adverse reactions to the drug itself and reactions to the dying worms.

New Drugs.—New drugs undergoing evaluation are ivermectin, mebendazole, and flubendazole. The early results with ivermectin are very encouraging. A report of the first study of ivermectin in human beings with onchocerciasis (river blindness) was published in 1982 (14). The side effects that occur with the existing drugs were absent, and ivermectin cleared or greatly reduced the microfilarial load in all 32 subjects after one dose. Those results have been duplicated in at least one subsequent study (14,77). Both mebendazole and flubendazole have activity against adult worms.

Summary

In summary, there is a great need for inexpensive, well-tolerated, oral agents effective against adult worms. Of the new drugs under consideration, ivermectin may ultimately have the potential for controlling filariasis in endemic areas, but that prospect is not near at hand.

Leprosy (Hansen's Disease)

Treatment for leprosy varies depending on the severity of disease, which ranges from tuberculoid leprosy (localized lesions with few **Mycobacterium leprae** organisms) to lepromatous leprosy (which is widespread disease and infection with large numbers of **M. leprae** bacteria). The course of treatment ranges from about 3 years for some patients at the tuberculoid end of the spectrum who have relatively good immunity to lifetime treatment for patients with lepromatous leprosy who have little or no immunity.

Dapsone.—Specific chemotherapy for leprosy was not available until 1940, when dapsone, a sulfa derivative, was shown to be effective when administered by injection to patients at the U.S. Public Health Service leprosarium at Carville, LA. Dapsone was shown to be effective when given orally in 1947 and continues to be an effective, safe, inexpensive agent. Acedapsone is an injected drug which releases dapsone slowly. Both have the usual side effects of any sulfa-containing drug.

Dapsone is bacteriostatic, able to inhibit, but not kill, M. /eprae. Viable dapsone-susceptible bacilli can be isolated from patients after 10 years of treatment even though they have no evidence of active disease.

Resistance to dapsone, first reported in 1964, is now an important problem. Up to 62.5 percent of newly diagnosed and 9.3 percent of previously treated patients have resistant strains of M. **leprae.**

Resistance to dapsone develops, like resistance to many antimicrobial, when patients do not follow the prescribed treatment regimens, for whatever reasons. Irregular compliance with treatment frequently occurs as the result of unsupervised administration. It is hoped that combination chemotherapy (see below) will minimize the development of resistance. Development of widespread resistance could lead to loss of control of leprosy in a community.

Clofazimine. —Clofazimine is another bacteriostatic agent with a unique additional property of being anti-inflammatory. Its use is limited by its cost and side effects, consisting mainly of red skin pigmentation, nausea, and diarrhea.

Rifampin.—The only bactericidal (able to kill bacteria) agent available for the treatment of leprosy is rifampin. It is rapidly effective in reducing the number of bacteria. However, even after 5 years of treatment, viable bacteria can be recovered from patients. Its use again is limited by its cost and side effects.

Combination Chemotherapy .—Since viable bacteria can be recovered from patients treated with all of the agents mentioned above, and since dapsone resistance is quite prevalent, combinations of the above drugs are now recommended as standard treatment.

Summary

The difficulties in treating people with leprosy are readily apparent. Treatment with the agents that are currently available necessitates many years of supervised chemotherapy. Cure is virtually impossible in many patients who require lifetime treatment. When dapsone resistance develops, there are few effective alternatives. There is great need for new bactericidal agents. Since recovery from leprosy will probably not occur until the body's natural defenses against the organism are adequate, immunopotentiating agents, drugs able to stimulate the natural defenses of the body, may be the solution in the future.

Tuberculosis

It has been 40 years since the discovery that streptomycin was effective in arresting the growth of *Mycobacterium tuberculosis,* the bacterium that causes tuberculosis. Two years later, para-aminosalicylic acid (PAS) was also found to be an effective "tuberculostatic" agent, arresting the growth of the bacteria, but not killing them. With the development of M, *tuberculosis* bacteria resistant to streptomycin in 1947, PAS became the companion drug of streptomycin to prevent the growth of resistant organisms. This combination was only partially effective in eliminating resistant strains.

It was not until 1952, with the introduction of the tuberculocidal drug INH (isoniazid) that the era of effective chemotherapy for tuberculosis began. INH actually kills the organisms, rather than holding them at bay. INH is not adequate as monotherapy, however, because of the development of resistant organisms. For that reason, INH was combined with PAS or streptomycin. In 1968, with the introduction of ethambutol, another tuberculostatic agent, antituberculosis therapy seemed adequate and safe. Because the duration of therapy was long, 12 to 24 months, however, patient compliance with the treatment regimen remained a problem.

Rifampin was introduced in 1971, but its special advantage, rapid tuberculocidal activity, was not realized until the late 1970s. Rifampin helps cure the patient, and it reduces the period of time during which the patient can transmit disease to others. *M. tuberculosis* bacteria are transmitted in sputum, particularly when the patient coughs. Combining rifampin with INH rapidly clears the sputum of bacteria, decreasing the infectivity of the patient and thereby decreasing transmission of disease. The duration of therapy has been reduced from the previously recommended 18 months with INH and ethambutol to 9 months with INH and rifampin. INH is prohibitively expensive for use in many less developed countries, however, and for that reason, simply is not available where it is most needed.

Short-Course Chemotherapy .—Abbreviated courses of therapy for tuberculosis are an important goal because such courses increase patient compliance with the treatment regimen. Inadequate treatment promotes the growth of drug-

resistant organisms, and failure to achieve cure promotes spread of the disease.

In an effort to reduce the duration of therapy, various regimens of short-course combination chemotherapy have been tested in developing countries, many sponsored by the British Medical Research Council. These courses primarily involve combinations of INH, rifampin, pyrazinamide, and streptomycin. The results indicate that duration of therapy maybe reduced to 6 months or possibly even less when these drugs are used in certain combinations.

Although compliance problems are less with shorter courses of therapy, they have not been eliminated. Liver toxicity continues to occur with most drug combinations, but usually does not require discontinuing of therapy.

Problem of Resistance.—It is fortunate that agents described above are so effective in treating most patients with tuberculosis. For tuberculosis patients with resistant organisms, however, therapy is only barely adequate. For these patients, more drugs are required, resulting in more side effects, problems of compliance, and higher cost. Isolation of INH-resistant organisms from newly diagnosed cases of tuberculosis is common in the developing world, and there are some bacilli resistant to both INH and streptomycin (101).

The main limitation in these areas, however, is not drug resistance but cost. Rifampin is very expensive for most developing countries with high prevalence of tuberculosis. Rifampin treatment for an adult costs $0.44 to $1.60/day, INH $0.001 to $0.004/day, pyrazinamide $0.09 to $0.72/day (53). In a 9-month course (2 months of ethambutol, INH, and rifampin followed by 7 months of INH and rifampin), rifampin accounted for 96 percent of the cost of the regimen (121). If this regimen were used, for example, in the Philippines in 1976, it would have cost about $200/patient (121). With an estimated 141,040 persons needing therapy, the total cost of treatment would be approximately $28 million. These countries, therefore, continue to use relatively long courses of less expensive chemotherapeutic agents, with predictable compliance problems and a predictable lack of control of tuberculosis.

Summary

In summary, there is adequate treatment available now for most tuberculosis. Although effective agents are available, many countries with tropical environments are unable to benefit from them because of financial restrictions and compliance problems.

A need for new drugs, particularly to be used in combination with INH, however, remains. The current companion drugs have significant toxicities or are associated with compliance problems. There are drug-resistant strains of M. *tuberculosis.* Because some strains are resistant to more than one agent, there is a need for new effective tuberculocidal agents with rapid onset of action, especially as an alternative to INH and rifampin.

Diarrheal and Enteric Diseases

General Treatment

Until the late 1960s, treatment of moderate diarrhea required hospitalization and intravenous hydration therapy. In 1964, it was shown that patients with cholera responded well to oral dehydration with glucose, bicarbonate, potassium, and sodium chloride (276). Three years later, it was shown that glucose facilitated the absorption of these electrolytes and decreased the total stool volume (337). In 1968, oral administration of a solution containing glucose and the electrolytes mentioned above was demonstrated to be effective therapy for moderate dehydration secondary to cholera (250). Since then, much has been written concerning the role of ORT (oral dehydration therapy). WHO now has made recommendations for the composition of the oral dehydration solution. In 1983, 29 million packs containing the ingredients to be mixed with water for ORT were supplied to various countries.

ORT has made a tremendous impact on the resources needed to manage diarrheal illnesses, particularly in infants and children (see *Case Study A: Oral Dehydration Therapy for Diarrheal Diseases).* The oral dehydration solutions can be given by mothers at home and mothers can be trained by paramedical personnel, thus saving both the expense of hospitalization and time of the medi-

Photo credit: Dr. Robert .Edelrnan, National Institutes of Health

Intravenous dehydration for most cholera patients, shown here, is being replaced by the simpler, more cost-effective alternative, oral dehydration therapy (ORT).

cal personnel. About 95 percent of all patients with diarrhea given ORT respond. Those who do not can be treated with intravenous solutions. Severely dehydrated patients, however, require initial intravenous therapy. ORT is effective in diarrheas from many causes. The success of the therapy depends significantly on the cooperation of the patient and/or mother. In some areas, tradition still impedes behavioral changes necessary for successful ORT. In many areas, sanitary water is unavailable. Water must be boiled prior to making the oral dehydration solution, and mothers frequently may be reluctant to do this.

Treatment for Specific Organisms

Viruses. -Viruses cause a significant amount of diarrheal illnesses in the tropics. Viral agents of diarrheal diseases include rotavirus and Norwalk agent, possibly the two most important agents, adenoviruses, enteroviruses, etc., as well as other agents which have not been specifically identified.

There is no effective specific therapy for any of the viral agents of diarrhea] diseases. None of the generally available antiviral agents are useful in treating diarrheal illnesses. Interferon, a molecule which can protect host cells from viruses, and interferon inducers are being studied

in some viral illnesses. In general, prevention of viral illnesses through vaccination is the hope for the future.

Bacteria.—Many bacteria have been identified as the cause of diarrheal illness, and the list is growing as laboratory methods for identification improve. Other bacteria have been isolated from patients with and without diarrhea, and some of these are clearly pathogenic. In many areas, the facilities to identify etiologic agents of diarrhea are unavailable.

Most episodes of bacterial diarrhea are self-limited and specific. There are effective antibacterial agents for most of the pathogenic organisms, but these agents are frequently unavailable or too expensive. Alternatives in special situations (e.g., allergy to an agent or resistance) often are not readily available. Resistance to drugs by many enteric bacterial pathogens is growing.

Vibriocholerae. —Tetracycline has been the drug of choice for treating cholera, but it has several drawbacks. It causes staining of teeth in children, the group in which most diarrheal illness occurs. Tetracycline also sensitizes the skin to sunburn and is not recommended for pregnant women during the stages of bone and teeth development. Alternatives to tetracycline are furazolidone, chloramphenicol, and trimethoprim/sulfamethoxazole (T/S).

Cholera strains had remained almost universally susceptible to tetracycline until 1977, when 76 percent were found resistant after 5 months of an epidemic Tanzania (226). In December 1980, 18 percent of strains of *Vibriocholerae* isolated in Bangladesh were multiply resistant to tetracycline, ampicillin, kanamycin, streptomycin, and T/S (131). Some of these strains are able to transfer their resistance factors to *Escherichia coli* (131).

Shigella.—Many species of *Shigella* cause diarrhea. *Shigella* usually cause endemic diarrhea, but may cause epidemics. In general, effective agents such as ampicillin, chloramphenicol, and T/S are available to treat shigellosis, but there is a growing problem with resistance. Sulfonamide resistance was described in Japan in the *1950s* and was described subsequently elsewhere (185). Areas which had previously had uniformly sensitive strains began to have consistently resistant strains.

Subsequently, strains were isolated that were resistant to more than one antimicrobial. Investigators discovered that these *Shigel/a* were probably acquiring resistance factors from other organisms present in the gastrointestinal tract, specifically E, *coli.* The transfer of resistance factors between bacilli has become an important complication of the treatment of many bacterial infections; some of these are mentioned later in this chapter.

The exact reason for the increase in the incidence of resistance factors in *Shigella* is not entirely clear, but is, in general, thought to result from the widespread use of therapeutic agents in a population, especially when they are used indiscriminately or in inadequate dosages. Such use frequently occurs when the agents are available over-the-counter, as they are in many developing countries. *Shigella* resistance not only is a problem in the developing world, but also has been reported in Washington, DC (294). Up to 93 percent of strains in some areas have been resistant to more than one drug (294).

Salmonella, —For many years, chloramphenicol has been the most reliable drug in the treatment of typhoid and typhoid-like enteric fever (infection due to nontyphi species of *Salmonella).* With the development of new antimicrobial, alternatives such as ampicillin, amoxicillin, amdinocillin, and T/S have become available.

Drug resistance in *Salmonella* was not much of a problem before 1972. Since then, there have been outbreaks of disease with resistant organisms in more than one country (128). Strains of both typhi and nontyphi species have been found to be resistant (30). More importantly, multiply resistant strains of S. *typhi* have been isolated. Occasionally, these strains are resistant to both cloramphenicol and ampicillin (38). More recently, strains resistant to chloramphenicol, ampicillin, and T/S have been isolated (188). Again, some of these resistant strains are able to transfer resistance factors to other bacteria (187).

Escherichia coli. —Antimicrobials are ineffective in decreasing the duration or volume of diarrhea associated with *E. coli* infection, but are sometimes recommended if the patient's diarrhea continues beyond 3 days or if the patient has bac-

teremia (bacteria in the bloodstream). Various strains of *E. coli* vary in their susceptibility to drugs, but they may be susceptible to ampicillin, chloramphenicol, and T/S.

Enterotoxigenic strains of *E. coli* (those that cause disease by a toxin produced by the bacterium) frequently cause diarrhea in travelers. A number of antimicrobial have been shown to be effective prophylactically including doxycycline, minocycline, trimethoprim, and T/S. Doxycycline-resistant strains have been isolated from Peace Corps volunteers in Thailand (102). Besides nausea, the possibility of skin photosensitivity from doxycycline and minocycline exist, although reactions to these agents are less frequent than those due to tetracycline.

Campylobacter. —The diarrhea resulting from *Campylobacter* infections frequently lasts only a few days, and therapy usually is not necessary. *Campylobacter* are generally susceptible to erythromycin, tetracycline, furazolidone, chloramphenicol, and clindamycin; erythromycin continues to be the drug of choice. In some areas, strains are resistant to tetracycline (113).

Other Causes. —Other bacterial causes of diarrhea are species of *Aeromonas, Pleisiomonas, Yersinia, Vibrio* (noncholera), *Staphylococcus, Clostridium difficile,* and C. *perfringens. Aeromonas* produces a toxin that causes diarrhea that is usually self-limited; it can usually be treated with erythromycin, tetracycline, and chloramphenicol, but is resistant to ampicillin. *V. parahemolyticus* is one of the noncholera vibrios which cause diarrhea. Treatment is usually unnecessary. S. *aureus* and C. *perfringens* are common causes of food-borne outbreaks of gastroenteritis which are self-limited, and no treatment is advocated. C. *difficile* is an important cause of antibiotic-induced colitis in developed countries, although the incidence of this disease is not known, since detection methods are not available. The preferred drug is vancomycin, but the cost of one course of therapy is $200 to percent 500, more than most citizens of developing countries can afford. Metronidazole, bacitracin, and cholestyramine are cheaper alternative agents.

Protozoa.—Giardia lamblia and *Entameba histolytica* are common causes of diarrhea world-

wide, but are particularly prevalent in countries with tropical environments. Giardiasis usually responds to either quinacrine, metronidazole, or tinidazole, and these agents are fairly well tolerated in the doses required. Therapy is not always effective, however, and retreatment may be necessary.

Symptomatic and asymptomatic intestinal ameba infections (amebiasis) respond to a number of drugs that are given orally and are well tolerated. Amebic liver abscess responds to a group of drugs known as "imidazoles," which includes metronidazole and tinidazole, and to more toxic drugs such as emetine, dihydroemetine, and chloroquine. Metronidazole in high oral doses causes abdominal cramps, nausea, and bloating and therefore is not tolerated by some people. Tinidazole is better tolerated and as effective. In patients who may not tolerate metronidazole and tinidazole, emetine and dihydroemetine are alternatives. Emetine and tinidazole may cause many adverse effects, including abnormalities of the heart rhythm, however, and it is recommended that patients receiving either of these drugs remain hospitalized.

Four other protozoa should be mentioned as the cause of diarrhea: ***Balantidium coli, lsospora belli, Cryptosporidium*** spp., and ***Sarcocystis*** spp. Balantidiasis responds to tetracycline and paromomycin. There is little information available on the proportion of diarrhea in tropical populations caused by the other three, and data on the effectiveness of treatment are only now becoming available. Furazolidine, T/S, and pyrimethamine-sulfa have been reported to be effective.

Helminths.—There area number of nematodes (roundworms) implicated as causes of diarrhea, including ***Ancylostoma duodenale*** and ***Necatur americanus*** (hookworms), ***Capillaria phillippinensis, Strongyloides stercoralis*** (threadworms), and ***Trichuris trichura*** (whipworms). For many of these, treatment may not be recommended the worm burden is not heavy and the risk of reinfection, is high, as is often the case in developing countries. For most roundworms, effective, safe, short-duration therapy is available.

Hookworms can usually be treated with bephenium, pyrantel pamoate, levamisole, or me-

bendazole in one or two doses for 3 consecutive days. Frequently, however, only the more toxic drug tetrachloroethylene is available.

S. *stercoralis* usually responds to thiabendazole, but this is one drug which is toxic and frequently causes anorexia, nausea, vomiting, diarrhea, and vertigo. Furthermore, thiabendazole is not always effective. Mebendazole is better tolerated, but still less effective.

T, *trichura* infections were a problem until the advent of mebendazole in 1971; now over 80 percent of these infections can be cured by a twice daily course for 6 days. Other alternatives effective against trichuriasis are oxantel, flubendazole, and albendazole.

Infection with C. *philippinensis* is a continuing problem. Mebendazole and thiabendazole are sometimes effective after 20 and 30 days respectively.

Praziquantel has revolutionized the treatment of trematodes (parasitic flatworms), many of which are associated with diarrhea: ***Fasciolopsis buski, Echinostoma itocanum,*** heterophyids, clonorchids, opisthorchids, and schistosomes. Virtually all of these respond to praziquantel.

Summary

Most cases of diarrhea can be treated successfully by treating the patient's symptoms with ORT. ORT **is** of particular benefit to infants and children, who may otherwise die from the dehydration that accompanies bouts of diarrhea. There are also safe, effective drug treatments for most of the bacterial infections that cause diarrhea, but not for viral infections. Protozoa and helminths that cause diarrhea can usually be eliminated with drugs, but the drugs are often toxic and not entirely effective. In general, however, the worldwide impact of these specific treatments, even if applied universally and successfully, would not approach the worldwide benefit of ORT if ORT were universally applied.

Acute Respiratory Infections (ARIs)

ARIs due to bacteria or viruses are usually either the major cause of death or second only to diarrheal disease in tropical environments. They

are a major cause of morbidity everywhere. From a clinical point of view, infections are divided between the upper respiratory tract infections (URTIS) and lower respiratory tract infections (LRTIs), though the causative agents overlap to some degree. URTIS are infections that occur in and around the teeth, gums, sinuses, throat, tonsils, epiglottis, middle ear, larynx, and trachea. The most important LRTIs result in pneumonias. In many tropical countries, the methods necessary to make the cause-specific diagnosis of respiratory infections are not available. Many areas in developing countries do not have bacteriology or serology, not to mention the more sophisticated facilities necessary for culturing and identifying viruses.

Viruses

Most of the URTIS in tropical countries appear to be viral in origin, usually caused by the same viruses caused by disease in temperate environments—rhinoviruses, coronaviruses, adenoviruses, Ebstein-Barr virus, cytomegalovirus, influenza, parainfluenza viruses, etc. Most of these infections are self-limited, and although there is some morbidity resulting in loss of workdays, there is little mortality in adults. In children, there can be acute mortality associated with the development of a cycle of infection and malnutrition.

Many of the viruses that cause URTI also cause LRTI. The viruses that may cause severe pneumonia and death are measles, respiratory syncytial virus, and influenza. These generally cause death from overwhelming pulmonary involvement and respiratory failure. In many localities, the oxygen therapy that frequently is necessary is unavailable.

Antiviral chemotherapy is still in its infancy. Amantidine and rimantadine are effective in reducing the incidence and severity of symptoms due to infection with influenza A if given prophylactically or within the first 48 hours after the onset of symptoms. These agents are fairly well tolerated, but they are generally unavailable in the developing countries and relatively expensive.

There is no treatment available for the other common viral causes of URTI. Enviroxime is an antiviral agent available in Europe but not in the United States, and evidently effective against rhinovirus, one of the causes of the common cold.

Bacteria

Upper Respiratory Tract Infections (URTIs).—Four bacterial causes of URTI deserve specific mention. One, ***Corynebacterium diphtheria,*** causes diphtheria, an acute, life-threatening pharyngitis. Another, ***Bordetella pertussis,*** is the cause of pertussis (whooping cough). The treatment of diphtheria is with antitoxin and penicillin or erythromycin. Antimicrobial are not effective in changing the course of pertussis. Both of these diseases can be prevented by immunization.

Streptococcus pyogenes, a Group A streptococcus known best as the organism precipitating rheumatic fever, is a common cause of pharyngitis. The disease is responsive to penicillin and erythromycin, among other antimicrobial.

Haemophilus influenzae causes ear infections, bronchitis, sinusitis, infection of the epiglottis, and meningitis, primarily in children. Ampicillin has generally been the drug of choice, although T/S and tetracycline also may be effective. Many strains of ***H. influenza*** are now resistant to ampicillin. The preferred drug for serious infections involving ampicillin-resistant strains is chloramphenicol.

Lower Respiratory Tract Infections (LRTIs).—Effective antimicrobial are available for most of the pathogens causing pneumonia acquired in the community, although the variety of drugs is usually limited. Hospital-acquired pneumonias (nosocomial infections) in developing countries, just as in the developed countries, are often caused by drug-resistant bacilli or ***Staphylococcus aureus.***

Streptococcus pneumonia, —***S. pneumonia,*** the cause of pneumococcal pneumonia, is one of the most common causes of bacterial pneumonia, affecting almost all ages in both tropical and temperate climates. Pneumococcal pneumonia continues to be a frequent cause of mortality in some groups of patients worldwide even though effective antimicrobial are usually available and even though these patients are treated (13). ***S. pneu-***

moniae is generally responsive to oral penicillin, cephalosporins, tetracycline, erythromycin, or chloramphenicol, as well as other antimicrobial. Patients who are very ill must receive these drugs by injection.

In 1967, a drug-resistant strain of S. *pneumonia* was isolated from a patient in Australia (147). Subsequently, relatively resistant strains have been isolated from many parts of the world, especially South Africa and New Guinea, and some of these strains are multiply resistant with relative resistance to penicillin, tetracycline, and chloramphenicol. Patients with these strains have not responded to the usual doses of penicillin (394).

Streptococcus pyogenes, —S. pyogenes is a cause of pneumonia as well as URTI and is frequently associated with complications such as empyema (infection between the inside of the chest and the outside of the lung causing a collection of pus in that site). It responds to penicillin, but hospitalization and parenteral therapy are often required, at least initially.

Staphylococcus aureus, —Staphylococcal pneumonia not infrequently complicates recovery from viral infections, especially in children. Hospitalization is recommended with parenteral administration of semisynthetic enzyme-resistant penicillins or cephalosporins for about 2 weeks. Antistaphylococcal antimicrobial are effective and generally available.

Haemophilus influenza. —Besides causing ear infections and meningitis, *H. influenza* may cause pneumonia, most frequently in children. Most strains are sensitive to ampicillin, chloramphenicol, T/S, and the newer cephalosporins. However, drug resistance is prevalent in some tropical environments. Some strains are resistant to ampicillin, but occasionally there is resistance to both ampicillin and chloramphenicol, the antimicrobial most commonly recommended for treatment (40).

Klebsiella pneumonia and Escherichia col.—*K. pneumonia* and *E. coli* are less common than S. *aureus* or H. *influenza* as causes of community-acquired pneumonia. These organisms are usually susceptible to aminoglycosides such as gentamicin. Aminoglycosides must be given parenterally and are toxic to the kidney. Frequently, aminoglycosides are not available in developing countries.

Pseudomonas pseudomallei. —This organism causes melioidosis, a spectrum of disease ranging from acute to chronic pneumonitis, soft tissue infection, and other manifestations. Most cases have been reported from Southeast Asia. Treatment consists of tetracycline, chloramphenicol, and/or T/S.

Yersinia pestis.—Y. pestis is the etiologic agent of plague. It may cause fulminant pneumonia, which *is* highly contagious. Streptomycin is the drug of choice. Alternatives may be chloramphenicol, tetracycline, or T/S.

Others. —Other less common kinds of bacterial pneumonias are associated with brucellosis, leptospirosis, anthrax, glanders, salmonellosis, typhus, and Q fever. These pneumonias are usually only one manifestation of a more generalized illness. If the diagnosis can be made, treatment is usually available.

Mycoplasma

Mycoplasma are bacteria-like organisms that usually cause URTIS and atypical pneumonia in adolescents and young adults. Tetracycline and erythromycin are effective therapy and usually do not have significant adverse effects.

Protozoa

Pneumocystis carinii is a protozoan which causes pneumonitis in immunosuppressed patients in developing countries, mainly in malnourished children. In the United States, it is common among patients with acquired immunodeficiency syndrome (more commonly known as "AIDS"). The drug of first choice, a combination of trimethoprim and sulfamethoxazole, or a sulfa with pyrimethamine is effective in about 75 percent of cases. The alternative, pentamidine, is not readily available and is not entirely effective either. It must be given parenterally and has some serious adverse effects.

Amebiasis can sometimes cause acute and chronic pulmonary disease, but usually responds well to oral metronidazole.

Fungi

There are a number of fungi that cause acute and/or chronic pneumonitis and pleural disease in tropical environments. Most are responsive to amphotericin B. Amphotericin is toxic to the kidney, must be given parenterally, and is frequently unavailable in developing countries. Amphotericin-induced kidney failure is difficult to manage without the aid of dialysis, which also is frequently unavailable.

Helminths

Most adult helminths in developing countries do not initially infect the respiratory tract, but cause disease if the larval forms migrate through the lungs. Most of the time, this stage of the infection is self-limited and does not need treatment.

Echinococcus granulosus and other related species are "tapeworms. " The larval worms form cysts in various organs, including the lungs. There is no effective medical treatment for tapeworm infection of the lung. Recently, a new drug, albendazole, has been demonstrated effective in a small number of patients. *Paragonirnus westermani,* a fluke that causes small pulmonary cysts, has recently been shown to respond to praziquantel. The eggs of S. *mansoni* and S. *japonicum* can end up in the lung, causing a buildup of fibrous tissue around them. There is no available treatment for this stage of the disease.

Summary

Drug therapy is available for most bacteria, but not viral ARIs. Even with treatment, however, mortality rates from ARIs are high, especially among children. The general state of good health of the population that keeps mortality from ARIs low in the United States and other developed countries, is probably the most important factor lacking in developing countries.

Arboviral and Related Viral Infections

The 80 or so arboviruses known to infect humans cause four basic types of clinical conditions. Two are generally benign and self-limited, consisting of: 1) fevers of short duration, with or without a rash; and 2) painful joints and rash of short duration. Complications can develop from either of these two conditions, but they are the exception. The two more serious clinical syndromes caused by arboviruses are: 1) acute central nervous system disease usually with inflammation of the brain (encephalitis), ranging in severity from mild aseptic meningitis to coma, paralysis, and death; and 2) hemorrhagic fevers, with extensive hemorrhaging, and associated with shock and high case fatality rates (liver damage and jaundice accompany these symptoms in yellow fever).

There have been no specific treatments available for any of these viral illnesses. Management of the more serious conditions is exclusively supportive, directed toward alleviating major symptoms and preventing spread. Correction of fluid and electrolyte imbalance, oxygen, and blood transfusions are the most common measures.

Immune therapy with monoclinal antibodies has been effective in protecting mice against *Sindbis* virus and arboviruses (311). Plasma containing antibodies to one hemorrhagic fever virus, given to patients before the eighth day of illness, reduced mortality from 16.5 to 1.1 percent. However, these patients had more frequent relapses (211). Similar results were obtained with immune therapy in monkeys experimentally infected with Machupo virus (211). Immune therapy and ribavirin, a broad spectrum antiviral, is effective in decreasing the mortality from Lassa fever in monkeys (172). Both are undergoing clinical trials in Sierra Leone (219).

SUMMARY

This chapter has briefly outlined the present therapy available for the selected tropical diseases covered in this report. For some diseases, there has been, and continues to be, effective therapy, although there is a growing problem of drug resistance in diseases ranging from P. falciparurn malaria to leprosy and other bacterial infections. For other diseases, therapy is available, but quite toxic. For still others, such as most viral infections, no therapy is available at all. Although tremendous progress has been made, the deficiencies are great, and much work remains to be done.