

THE LABORATORY OF CHEMOTHERAPY FOR PARASITIC DISEASES

In the Rockefeller University's laboratory of chemotherapy for parasitic diseases, Professor Ernst A. H. Friedheim, M.D., Ph.D., doctor of tropical medicine and hygiene, is working to develop safe, effective drugs against parasites that cause debilitating diseases throughout the world.

Over the years, Dr. Friedheim has synthesized chemical compounds against several major parasitic diseases, including schistosomiasis, filariasis, onchocerciasis, and African trypanosomiasis (or sleeping sickness). After testing the compounds in laboratory animals, he has evaluated the most promising of these drugs in clinical studies conducted in Africa, Asia, Central and South America, and the Pacific islands.

Melarsoprol, the drug Dr. Friedheim developed for African trypanosomiasis, is the main drug used to treat the encephalitic stage of this disease, when the trypanosome parasites have entered and damaged the brain. Today, melarsoprol cures approximately 95 percent of lethal cases of encephalitic African trypanosomiasis and saves an estimated 15,000 lives a year. Before melarsoprol was developed, advanced cases of the East African form of this disease were incurable.

In an effort to combat parasites that invade the brain, Dr. Friedheim is studying the components of the blood-brain barrier and the relationship between the structure of various chemicals and their ability to penetrate this barrier. Much of this research focuses on a network of blood vessels known as the choroid plexus. Found in the innermost membrane of the brain, the choroid plexus secretes cerebrospinal fluid. Studies in the Friedheim laboratory have shown that the choroid plexus retains and accumulates arsenic and lead, and that concentrations of lead increase with age in at least one part of this network. These investigations suggest that the choroid plexus may serve as a kind of protective "sink" for lead and possibly other heavy metals.

Building on his extensive experience with parasitic diseases, Dr. Friedheim has recently addressed the urgent need for new drugs to fight the parasites that cause opportunistic infections in AIDS patients. *Pneumocystis carinii*, one of the parasites currently studied in the Friedheim laboratory, is responsible for a pneumonia that strikes nearly all AIDS patients during the course of their disease, often fatally.

This single-celled parasite is normally found in the lungs of healthy human beings. *P. carinii* causes no ill effects in these individuals because their immune systems are able to hold the organism in check. When the immune system is compromised by AIDS, however, the parasites are free to multiply rapidly, and pneumonia results.

The main drugs currently used for *Pneumocystis pneumonia* are trimethoprim/sulfamethoxazole and pentamidine. These drugs are helpful in treating this pneumonia, but their therapeutic use is limited by adverse side effects. Pentamidine is also the standard drug treatment for first stage African trypanosomiasis, when trypanosome parasites circulate in the blood but have not yet penetrated the brain.

Since pentamidine is less than satisfactory as a treatment for Pneumocystis pneumonia, Dr. Friedheim synthesized several other compounds, chemically different from pentamidine, that kill trypanosomes. In collaboration with Dr. Friedheim, Dr. Marilyn Bartlett of the Indiana University School of Medicine in Indianapolis investigated the effect of these drugs on *P. carinii* grown in culture (that is, outside of a living organism).

In these studies, three of Dr. Friedheim's trypanocidal drugs were highly active--in very low concentrations--against *P. carinii*. These concentrations were on the order of one part per million, lower than the concentrations of pentamidine needed to kill *P. carinii*. Dr. Friedheim has now begun to test the compounds in rats infected with *P. carinii*.

Dr. Friedheim has also focused his research on *Acanthamoeba*, which has recently been shown to cause opportunistic infections in AIDS patients. Free-living parasites found in soil and fresh water, *Acanthamoebas* cause lethal meningitis and blinding keratitis, or inflammation of the cornea, and have afflicted many contact lens wearers. As with *P. carinii*, pentamidine kills *Acanthamoeba*, but it also causes severe side effects in many patients.

Dr. Friedheim has synthesized four chemical compounds that are highly active against *Acanthamoeba* parasites grown in culture. One of these drugs kills 99 percent of three strains of the parasite, in a concentration 10,000 times smaller than the dosage tolerated in a rabbit's eye.

In collaboration with Drs. David Podell and David Gorman, ophthalmologists at Lenox Hill Hospital in New York, Dr. Friedheim has begun experiments to study the effect of these drugs on keratitis in rats. Dr. Friedheim also has studies under way to test two of the drugs in mice with amoeba meningitis.

In future studies of *P. carinii* and *Acanthamoeba*, Dr. Friedheim plans to evaluate the effect of various doses of these drugs in an increased number of laboratory animals. The expanded experiments will make it possible for Dr. Friedheim to refine the chemistry of these compounds and determine the optimum dosage needed to treat Pneumocystis pneumonia and *Acanthamoeba* infections.