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The Deadly Trypanosome:

Understanding the Parasite that causes Sleeping Sickness

by Patricia E. Mancini



African sleeping sickness. Tsetse fly. Trypanosomes. To some, these words may sound exotic, menacing or even humorous, but not to me. The biochemistry and physiology of African trypanosomes, and particularly *Trypanosoma brucei*, the protozoan agent of this deadly scourge, has been the main focus of my research life and thought for almost 25 years. My current work focuses on the mechanisms by which trypanosomes attach to and interact with host cells, and the potentially toxic molecules involved in such interactions. As a new faculty member at BSC, I'd like to introduce you to this organism and the disease it causes, and point out ways in which the study of these parasites by students can offer them valuable research experience.

Training in microbiology and biochemistry prepared me well for the study of trypanosomes, but lab-bench scientific studies are only one aspect of understanding this disease and the problems it causes throughout much of the African continent. Geography, colonial history, ethnic conflicts, and cultures of the region all influence the toll this disease takes.

HISTORY AND EPIDEMIOLOGY OF AFRICAN SLEEPING SICKNESS

African sleeping sickness in humans is caused by a protozoan, *Trypanosoma brucei*, and, throughout much of sub-Saharan Africa, is transmitted by the bite of the tsetse fly. Although mortality is relatively low in numbers compared to diseases caused by other infectious agents, it is sufficient for the disease to be a major health threat and concern. *Trypanosoma brucei*, the parent species, is found in antelopes and other game animals, but these native animals (and even some local breeds of domestic cattle) can tolerate the infection without showing symptoms. However, they may serve as reservoirs of infection for the trypanosome subspecies which attack humans. We do not know what makes the wild antelope population resistant, but assume that millions of years of co-evolution have allowed it to reach a stale-mate with the parasite.

Almost as important as the disease in humans is the disease in domestic animals which, by killing animals of European (i.e., non-native) stock, prevents cultivation of, or grazing on, millions of acres of fertile land in the "tsetse belt." Some *trypanosome* species affect cattle; others, horses and camels. Together these organisms make farming and ranching difficult in the most potentially productive area of the continent. A major protein deficiency in the African diet, caused by the inability to produce sufficient food for the population, might be averted if some of this land (in an area the size of the US) could be maintained for farming and grazing.

THE VECTOR

Tsetse fly is a general name for any of the eight species of the genus *Glossina* which may carry and transmit the parasite. The flies are generally divided into two broad groups—those which live in the riverine areas of the rain forests of West Africa and are associated with the chronic form of the disease caused by *T. brucei gambiense*, and the woodland tsetse flies, which inhabit drier grasslands and forests of the east coast of Africa and are vectors for the more acute, and more rapidly fatal, form of the disease caused by *T. brucei rhodesiense*. Indigenous peoples have known for centuries that the presence of the tsetse fly is associated with high incidence of disease. Regions which are endemic for the flies are also endemic for sleeping sickness, which is essentially 100% fatal if untreated. Traditionally, native herdsman have moved their cattle away from the rivers during the tsetse season, minimizing the effects of the disease. Colonial powers actually helped spread the disease across the continent by providing host animals in their horses and cattle, so what was once a contained, endemic problem soon became widespread throughout the continent.

PATHOLOGY OF THE DISEASE
AND CURRENT DRUG TREATMENTS

After the fly bites, trypanosomes enter the mammalian host, multiply in the skin, then migrate through the tissues to the bloodstream. Most of their life cycle in the mammalian host occurs in the blood and tissues, with rapid cell division leading to high parasite levels. This is the primary stage of the disease, when available drug treatments are most likely to be effective. It is also a time when the bite of another tsetse fly can transmit these parasites to the next host. However, the disease may progress to the secondary stage when the parasites migrate from the blood into the central nervous system, including the brain and cerebrospinal fluid. Early indicators may be mild episodes of disorientation which then progress to an increasingly altered sleep cycle resulting in long periods of "sleep" and eventually coma and death.

The drugs available to treat the primary infection have not changed in 100 years. Pentamidine and suramin, which kill the parasite, are still effective against the bloodstream forms (although some strains have become resistant) but have side effects. Melarsoprol, an arsenical which until recently was the only drug for treating cerebral involvement, is toxic enough on its own to account for a 5% fatality rate. The only drug recently developed (in the 1980's) to treat secondary stage disease, eflornithine, an inhibitor of an essential pathway of parasite metabolism, was discontinued by its manufacturer after a company merger. This points up a critical problem in the development of new treatments for the disease. Pharmaceutical companies are unwilling and/or unable to devote resources to research and development of new drugs because the disease strikes in areas where the infected individuals are unable to afford the price of medication. In addition, an effective distribution system may be unavailable even if the drug is donated free of charge by the manufacturer.

STRATEGIES FOR PREVENTION AND CONTROL

Although the latest World Health Organization statistics record only about 40,000 reported cases, this is probably a gross under-representation. As many as half a million people may currently be infected, but most

cases go unreported and untreated because the rural populations which are most at risk may have minimal contacts with healthcare personnel. Also, infected individuals may seek treatment only at later stages of the disease or not at all. Many are children who die of trypanosomiasis without ever causing a blip on the surveillance radar.

Surveillance and screening of infected individuals in local areas have been successful strategies for control in the past, almost eradicating the disease in the half century prior to the 1970's. Unfortunately, surveillance as a control measure relies on successful administrative infrastructures and

economics because it is a labor-intensive activity. Surveillance teams must cover vast areas to diagnose the disease where infection rates are highest, must take blood samples from individuals in villages where, in some cases, 70% of the population may be infected, and finally, must arrange for contact with healthcare delivery systems which are often inadequate. Patients must be transported to hospitals where the drugs are generally administered intravenously. This removal of infected persons from a community has the public health effect of removing a reservoir of infection, and may help cut down on transmission but may be a "hard sell" to families of infected individuals. In the past, successful control strategies have also involved the labor-intensive collection and removal of the flies when they are active during the daylight hours. Broader strategies such as spraying insecticides or converting riverine areas and woodlands into farmland have also been effective. However, these are often threatening to the delicate ecological balance of an area and, in any case, also rely upon an administrative infrastructure and a robust economy.



Dr. Mancini
with students

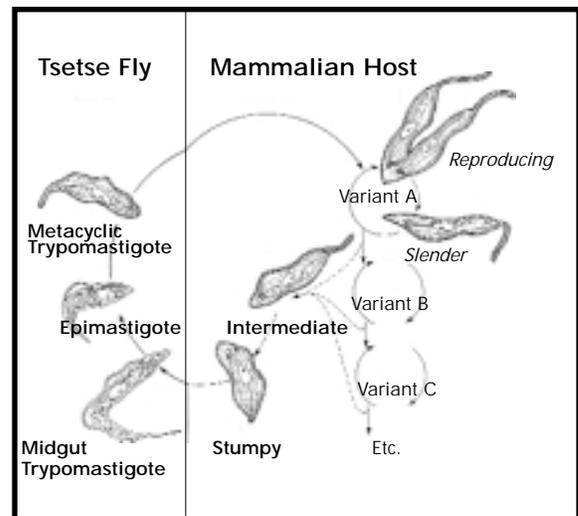
THE GEOPOLITICS AND DEVASTATING CONSEQUENCES OF THE DISEASE

In the past 40 years the legacy of colonial rule has resulted in economic and political changes, ethnic unrest, civil wars, population migrations due to famine and other non-biological events which have subjected the population in sub-Saharan Africa to reduced levels of surveillance, minimal treatment, and subsequent dramatic increases in the incidence and mortality of sleeping sickness. The boundaries of countries which are affected by these problems, including (but not limited to) the Democratic Republic of the Congo, Sudan, Uganda and Angola, can be superimposed upon recent data recording epidemic resurgence of this disease. Even countries with stable political and economic structure are at risk of increased incidence due to the thousands of refugees who may carry the disease across national borders. Few countries are equipped to deal with the magnitude of such a problem.

HOW UNDERGRADUATES BENEFIT FROM RESEARCH ON MICROBIAL SYSTEMS

Laboratory research with trypanosomes provides a meaningful experience for undergraduate students for several reasons. Trypanosomes offer a system for study very similar to that of other biological systems: non-infectious laboratory strains of the parasites can now be studied using all the methods of modern biochemistry and molecular biology to grow and manipulate trypanosomes, and these methods are applicable to research on other organisms. Students entering the job market directly after college will be well prepared with “hands-on” experience for jobs in biotechnology or pharmaceutical companies, or in academic research, hospital and/or government labs. And some undergraduate research is almost always a prerequisite for admission to good graduate and professional programs. Admissions committees are impressed by the level of technical expertise and commitment exemplified by students who do “bench level” research. Additionally, the ability to think logically in order to design, execute, analyze and write up experiments is useful for many future scientific or nonscientific endeavors. Studies on trypanosomes overlap with research in genetics, cell and molecular biology, immunology and biochemistry currently being undertaken in the Biology and

The life cycle of the African trypanosome in the mammalian host and in the tsetse fly host. Shown are the various morphological forms seen in each, as well as the phenomenon of antigenic variation (altered surface proteins) seen in the mammalian host. Figure courtesy of Dr. James E. Strickler © 1980. Modified with permission.



Chemistry departments at BSC. This promotes a level of camaraderie here among undergraduate researchers which is useful when they enter the professional world.

But there is a more important reason for doing research on any parasite agent of diseases which afflict primarily developing countries. Microorganisms have always affected the course of human society—consider the effects of plague, typhus, typhoid, dysentery, and tetanus during wars, or cholera epidemics in cities and rural areas, or the Irish potato famine, which brought so many individuals to the United States during the mid-19th century. Students at BSC studying trypanosomes learn valuable lessons in public health. Increased awareness of public health and environmental issues both locally and worldwide helps them understand the interplay between individual actions within the society and the spread of microorganisms and disease, as well as the effect that microorganisms have on the course of a soci-

ety's progress as a whole. Ultimately the control and eventual eradication of African sleeping sickness and its companion diseases, malaria, hookworm, leishmaniasis, schistosomiasis, and more, will depend both on the science and on the social factors which influence how individuals in a community or a country interact with one another and with the disease agent.

WHAT TO DO? STRATEGIES FOR UNDERSTANDING THE PARASITE AS A MEANS OF COMBATING THE DISEASE

Understanding the parasite's physiology and biochemistry (in other words, "know thine enemy"), can help researchers to develop a rational approach to prevention or therapy. Trypanosomes have so far evaded most attempts to control and understand them. Through millions of years of co-evolution with their mammalian hosts, the parasites which survive rely on "immunoconfusion" and "immunoevasion," mechanisms which allow them to be overlooked by the immune system. In addition, the metabolism of the parasite closely mimics the metabolism of its mammalian hosts, another survival advantage, so drugs for treating the disease have a very narrow window of effectiveness for eradicating the parasite without causing damage to the patient.

In order to develop new and effective drugs, we will have to find an Achilles' Heel in the parasite, i.e., a metabolic variation found only in the parasite and not in the host, which might be exploited for drug therapy without damage to the host physiology. A thorough knowledge of the parasite's physiology and biochemistry is one way to find this difference, but even this straightforward approach has been hampered for many years by the inability to study the parasite effectively. Once removed from the host animal, the trypanosome is a fragile creature, difficult to keep alive in the lab. In recent years there have been advances in the ability to culture the parasite and to study its genes and their expression or activation using molecular biological techniques in addition to traditional biochemical and immunological methods. This has allowed us to produce sufficient quantities of this organism or its protein components to examine their functions more carefully, a first step in designing specific drugs to block those functions and kill the parasite. However, we still have few clues as to how the parasite actually kills its host. Is its simple presence in large numbers sufficient to interfere with the host's own metabolism? Does it produce

toxic substances that directly kill host cells, damaging functions of critical organs? Does it actively inhibit certain components of the immune system? How does it migrate through tissues to the small capillaries of the bloodstream, and from there to the brain? These are some of the questions which need to be addressed by studying the biochemistry of the trypanosome's components and how they work.

Any projects undertaken by BSC students must be safe, and there are now culture systems which use a form of the parasite which is non-infectious for humans. These allow growth of sufficient numbers of cells for students to study their interactions with mammalian or insect cells in culture. Special dyes can now be used to stain different physiological states of parasite or host to assess adherence or production of toxic substances. In addition, students can learn how to clone and detect specific parasite genes and produce their proteins in the lab to help in identifying novel drugs to inhibit well known proteins, or to find unique proteins as novel drug targets in the parasite. Newer purification methods allow both isolation of the proteins and identification of their functions, providing many potential projects for student focus. In the past ten years, several types of cell surface enzymes, receptor molecules, adhesion proteins, stress-related proteins and other important molecules have been identified in trypanosomes as potential targets. Unraveling the components of the parasite provides enough work for many students to participate in helping us to understand and control this disease.

—*Patricia E. Mancini is Assistant Professor of Biological Sciences*