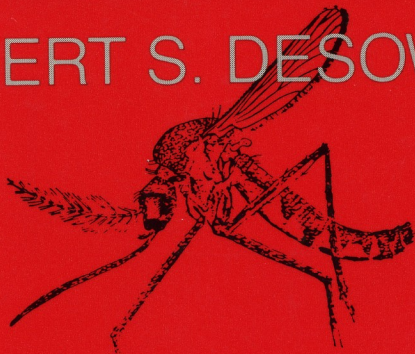


ROBERT S. DESOWITZ



New Guinea
Tapeworms
AND
Jewish
Grandmothers

TALES OF PARASITES AND PEOPLE



appropriate experimental probe. Miller is excited by the prospect that he can isolate each merozoite's specific receptor and use it as a vaccine to produce what should be a solid immunity. That isolation will be a very tricky business, but he speaks enthusiastically of exploiting the new, remarkable techniques utilizing hybridomas (certain kinds of tumor cells made into producers of specific antibodies by fusion with antibody-producing white blood cells) and recombinant-DNA technology. I'm a rather old-fashioned malariologist, and I tell Lou, who is a close personal friend, that this is Buck Rogers stuff. But in my secret heart I wish I had done those experiments.

6

THE FLY THAT WOULD BE KING

One African tyrant does not attend political councils, is not a member of the Organization of African Unity, and has not palavered with roving diplomats, and does have a personal air-transport system—the tsetse. Holding Africa in thrall since ancient times, this parasite, known as a trypanosome, is only six ten-thousandths of an inch long, but it has affected the economy, social institutions, and even the religious complexion of the continent.

During the mid-nineteenth century, Muslim Fulani cavalry swept from their near-desert West African Sahel kingdom into the savanna to the south and east, conquering and converting the animist tribes with whom they came into contact. But in their progress through woodlands and rain forests they encountered a formidable adversary, the tsetse. Swarms of these flies attacked and bit the horses, transmitting the parasite to them. It caused a lethal form of animal trypanosomiasis, and in rapid order the cavalry became a disarrayed

infantry. On foot, the Fulani were virtually powerless; their invasion was halted before it could reach the great population centers of the Benue and Niger river valleys. Thus was Islam, with its concomitant sociopolitical influences, prevented from infiltrating this vast densely peopled region of Africa for more than half a century.

The popular notion of trypanosomiasis is represented by the image of a lethargic human suffering from the "sleeping distemper," to use the words of an English observer some two hundred years ago. Not a form of distemper at all, the infection is caused in man by one of two closely related parasitic organisms, *Trypanosoma gambiense* and *T. rhodesiense*, and in animals by *T. brucei*, *T. congolense*, and *T. vivax*. (*T. gambiense* was thought to be restricted to man, but researchers have recently implicated the pig as a reservoir host.) Both animal and human trypanosomes are transmitted by the tsetse, a bloodsucking fly of the genus *Glossina*. Tsetse flies inhabit Africa only south of the Sahara, from approximately fifteen degrees north to twenty degrees south latitude, although they once had wider distribution, as evidenced by the discovery of a fossilized tsetse in the Oligocene shales of Colorado. While human trypanosomiasis continues to be a public-health problem, being responsible for some seven thousand deaths each year, it is the infection in domestic animals that has had the greatest impact on African development.

The tsetse belt encompasses more than six million square miles of land denied to livestock production, mixed farming, and in some regions, human settlement. It is an area that could potentially provide 125 million head of cattle to the protein-starved continent. The disease has forced herdsmen to concentrate their stock on the limited amount of fly-free pasturage, and this prac-

tice has led to overgrazing and attendant soil erosion. When cattle are trekked to distant markets through fly-infested country, some 25 percent may die before reaching their destination. And yet, a less anthropocentric view might hold that by preventing overexploitation of this enormous area, the tsetse and the trypanosome are the most stalwart guardians of the African ecosystem and its magnificent wild fauna.

The manner and degree of transmission of trypanosomes involves complex interactions of parasite, host and fly vector. With this in mind, let us consider the scenario and dramatis personae of *The Fly That Would Be King*, an African spectacular with a cast of millions.

Act 1 is set in a forest in Africa. On stage is the host—a man, a cow, or an antelope. A closer, microscopic examination reveals the second character, the trypanosome, swimming about in the blood of the host by means of an undulating membrane and a lashing flagellum. A sound of angry buzzing comes from off stage. Enter a tsetse, a brown insect not much larger than a housefly. The tsetse smells and sights the host, then strikes and bites, sucking in its trypanosome-containing blood.

Act 2 takes place inside the tsetse's gut, where the trypanosome elongates and multiplies by simple asexual division. After about four days it migrates to the fly's salivary glands; there, over the next fifteen days, further transformation takes place, until it assumes the short, stumpy appearance of the metacyclic stage—the terminal developmental form, in which it is capable of infecting a new host.

Act 3 opens in the forest twenty days after act 1. The original host lies obviously ill on the stage floor. Enter another host. The infected tsetse strikes, delivering the

metacyclic parasites to the blood stream of the new host and completing the cycle. Curtain.

While this plot is essentially the same for all African trypanosomes, the details for each species differ in important respects. In man, the disease caused by *T. gambiense* is chronic and malignant, and gives rise to the torpor and eventual coma and death classically associated with sleeping sickness.

The pathology of the disease is largely unknown. Over the course of time, the trypanosomes tend to leave the blood and enter, first, the lymphatics, and later, the spinal fluid and the tissues of the central nervous system. The patient becomes comatose during this latter phase, and dies after several years if he has not received chemotherapeutic treatment.

Whereas Gambian sleeping sickness results in a slow death, that caused by *T. rhodesiense* kills within weeks or months. The two infections differ not only in degree of virulence but in other respects as well. Gambian trypanosomiasis is essentially a human disease, cycled from person to person, while the transmission cycle of Rhodesian trypanosomiasis includes a third host—the wild antelope—which acts as a reservoir of infection. By all biological criteria, *T. rhodesiense* is a parasite of the wild ungulates, rather than man. Evolution has resulted in a state of equilibrium in which the parasite produces no overt disease in the animal host. Man, for the most part an accidental host, has not attained this accommodation, as the intense virulence of the human disease indicates. The manner by which the antelope modulates the infection remains a mystery; its elucidation might aid in devising a means of similarly stimulating a protective state in man.

The ecological setting—the landscape epidemiol-

ogy—is different for each of these disease varieties. Gambian sleeping sickness is generally restricted to the humid forests bordering the lakes and rivers of West and Central Africa, the obligatory habitat of *G. palpalis*, the tsetse species that transmits this form of the disease.

Because rural African populations rarely have the means to obtain water from distant sources, communities tend to form along the banks of rivers and lakes, and village activities—bathing, washing, drawing water, and fishing—take place at the water's edge, making for intense man-fly contact. Epidemics flare from time to time, but generally the disease level is low because this tsetse is, biologically, a relatively inefficient vector. Trypanosomes can readily multiply in *G. palpalis* only shortly after the fly emerges from the pupal stage. Very few older flies are able to act as vectors after feeding upon infected humans.

Sleeping sickness caused by *Trypanosoma rhodesiense* is endemic to the dry savanna woodlands of East and Central Africa, the habitat of both the *G. morsitans* vector and the great herds of antelope that serve as reservoir hosts. Human infections occur when people settle in the savanna or intrude to hunt, gather wood, or graze cattle. The species of vector that transmits this form of the disease is not an equal-opportunity biter; and it prefers to take a blood meal from mammals other than humans. When game becomes scarce, however, the fly will feed on humans. Apparently attracted to large, slow-moving objects, it becomes confused when these sometimes turn out to be vehicles rather than antelope, and it will feed on the passengers. In this curious way, a package tour of East African game parks occasionally includes trypanosomiasis.

There is, then, an intimate relationship between the

nature of the ecosystem and the epidemiology of trypanosomiasis. The history of Africa, however, is characterized by continuous ecological change—with felled rain forests succeeded by grasslands and savanna woodlands, an advancing or retreating desert, and shifting distribution or concentration of human inhabitants and wild fauna. These environmental changes have played a crucial role in the epidemiological patterns of the Gambian and Rhodesian forms of trypanosomiasis, particularly where their ranges overlap in east-central Africa.

The activities and diseases of both Africans and colonial expatriates have also contributed to the epidemiological status of trypanosomiasis. Before the nineteenth-century colonial period, trypanosomiasis was confined to a relatively few smoldering foci. Internecine warfare and lack of roads restricted communication and prevented the spread of the infection. The rapid dissemination of sleeping sickness can be traced to the opening up of Africa by the colonial powers. It was the *Pax Britannica* as much as the tsetse that was responsible for the broadcast of infection. How this complex of changing environmental and human factors has influenced epidemicity of the two types of human trypanosomiasis is illustrated, par excellence, by the events that have occurred along the Kenya and Uganda shores of Lake Victoria.

Prior to human settlement, the lake was surrounded by a tropical high forest. Primitive farmers migrated to the lake's shores and felled forest tracts for their shifting agriculture. Forest-inhabiting tsetse were present, but human trypanosomiasis was absent. Eventually, deforestation progressed to such a degree that grassland replaced large areas of forest. The grassland then

attracted a second wave of migration—Nilotic pastoralists (that is, herders who originated in the Nile basin) and Bantu cultivators. The combined pressures of grazing and agriculture suppressed forest regeneration and thus maintained a fly-free area beyond the forest that fringed the lake.

In the nineteenth century the society along the lake was devastated by the twin pestilences of smallpox and rinderpest, and agricultural activity diminished. Before the population had time to recover, savanna woodland succeeded the grassland. At the close of the nineteenth century the ecological stage was set for sleeping sickness. The shores of the lake were bordered by a rain forest infested with *G. palpalis*, the tsetse vector of *T. gambiense*. Beyond the forest *G. morsitans*, the vector of *T. rhodesiense*, inhabited the savanna woodland. Still the trypanosome had not made its debut.

The parasite is thought to have been introduced when Sir Henry Morton Stanley, employed at that time in the Congo by the Belgians, mounted an expedition in 1887 to the area of Lake Victoria. Natives in Stanley's retinue, probably infected with *T. gambiense*, may have carried the seeds of the epidemic that was to decimate the population for the next ten years.

By 1910, when the Gambian sleeping sickness began to burn itself out, the number of inhabitants in the area had declined from 300,000 to 100,000. Before the epidemic, the large size and number of human settlements had had the effect of suppressing the faunal population; but as people died of the disease or fled the stricken area, the game reservoirs of *T. rhodesiense* increased and moved into the adjacent savanna woodland. The final epidemiological link in the chain of Rhodesian sleeping sickness—from game to man through

woodland-dwelling fly—was now present, to complete the cycle. When government-inspired resettlement was attempted in the 1940s, the migrants rapidly became infected with this highly lethal disease, and once again the inhabitants deserted the land. Today, this potentially rich region is virtually abandoned, occupied only by a few fishermen who are at high risk of contracting the infection.

When I joined the West African Institute for Trypanosomiasis Research in 1951, the entire infected population of Nigeria lay, so to speak, before me, but I was to be introduced to the human disease in a much more personal way and under circumstances that gave me a first glimpse into the meshing of the fly, the trypanosome, the ecosystem, and human behavior.

My friend Dan Quaddo, a Rukuba and in the epithets of that unregenerate colonial era, a pagan (being neither Christian nor Muslim) was the household "small boy" (the domestic of all work, age notwithstanding). He was a small, cheerful, but unbeautiful man; his name meant Son of the Frog, and West African "village" names are bestowed with deadly accuracy. The only maggot in Dan Quaddo's otherwise optimistic disposition was his unfathomable terror of "teef men" (pidgin for burglars, not dentists), and even during the hottest nights of the hot season he would barricade himself within his quarters. I once tried to reason with him: "Dan Quaddo, why do you do this? You are so poor and have so little, why would anyone want to teef you?" I vividly recall his reply, in which he explained with the patience of someone describing an immutable law to a small, rather dense child: "Suh, anyone who teef me be so bad he not need a reason."

A short time after this illuminating conversation he returned to his nearby village, on the slopes of the Bau-

chi Plateau, and spent several weeks there attending to "family affairs." A few weeks after returning he once again locked, bolted, and shuttered himself within his house, this time complaining not of "teef men," but of devils of fever and headache. The American reaction would be to exorcise these with aspirin, but in Africa, where malaria is commoner than the common cold, the first resort is routinely to the magic of antimalarial drugs. After a time the fever abated, but the headache persisted and Dan Quaddo became uncharacteristically eccentric and surly. He took to putting nonperishables in the refrigerator—theater tickets, tennis balls, my wife's brassière (the "small, small vest for chest"). There was no disputing that what ailed Dan Quaddo was not malaria and that he needed medical attention. In the tropics the microscopic examination of the blood takes pride of diagnostic precedence, and I remember peering into the microscope and seeing, for the first time outside a laboratory classroom, the trypanosomes of a human swimming in the microscopic field and the dancing movement of the red blood cells as they were disturbed by the thrashing parasites. We later found that Dan Quaddo's infection had progressed to the stage where his lymph glands had also been invaded by the Gambian trypanosomes, but fortunately the disease was caught before the central nervous system became involved. He was successfully treated and made an uneventful recovery. However, I was curious about how he had contracted the infection, since we were supposed to be outside the tsetse belt. Inquiry revealed that Dan Quaddo was actually one of the last victims of a cataclysmic sleeping-sickness epidemic, beginning some ten years earlier, that had brought his tribe to the verge of extinction.

In former times the outliers of the typical high forests

bordering streams and rivers had penetrated the dry savanna, and these outliers had provided a suitable ecological niche for the tsetse vector. The Rukubas had cut down most of the outliers, but each tribe preserved near its village a small area of forest that was sacred, the *tsafi* grove. The flies had retreated to these groves and were concentrated there in great numbers. Every seven years the elders and the young boys went to their sacred grove for a religious retreat, during which the youngsters were initiated into manhood. The secrets and mysteries of the Rukubas were passed from the old to the young, and the genealogy of the tribe was recounted. Circumcision rites were performed, and the elders harangued the initiates about morality. During these religious retreats man and fly were in close contact, but until the early 1940s the trypanosome was absent. The infection is believed to have originated with a farmer who, taking advantage of the relatively new state of intertribal tranquility imposed by the colonial government, traveled to the south of the plateau, an area of endemic trypanosomiasis. On his return, this farmer participated in a manhood initiation rite and was a source of infection to the fly and consequently to his coreligionists. The human infection slowly built in intensity, and by the mid-1940s one-fourth of some village populations had been stricken. When the first medical teams were sent to the area, the Rukubas either fled or hostilely ejected them from the villages. In 1944 they were finally convinced of their plight and accepted mass drug treatment and tsetse-eradication campaigns. By the early 1950s the epidemic, except for a trickle of infection, had been brought to a halt. My unfortunate friend Dan Quaddo, whose "family affairs" had really been a *tsafi*-grove ritual, was one of the last to become infected, and he had

almost been "teefed" of his life. The trypanosome was indeed, so bad it didn't need a reason to rob him.

The trypanosomes that infect domestic animals are not restricted to any particular forest ecosystem; animal trypanosomiasis exists wherever there are tsetse flies of any species. The presence of wild-game reservoirs—along with the fact that the flies, in all probability, carry the trypanosomes (*T. brucei*, *T. congolense*, and *T. vivax*)—contributes to a level of transmission so intense and ubiquitous as to effectively preclude stock production in one-fourth of Africa. Nomadic and semisettled cattle-owning tribes have been forced to pasture their animals in the fly-free zones in and near the arid Sahel. As the dry season approaches, the Sahel is no longer able to sustain the herds and the annual trek into the fly-infested Guinea savanna begins. Losses to trypanosomiasis always occur, but where nutrition is adequate and the density of flies not too great, the stock may manage to survive, if not flourish.

The breed of cattle favored by the African pastoralist is the zebu, a large, humpbacked longhorn, well adapted to semiarid conditions. Although it produces relatively high yields of milk and meat, the zebu has the unfortunate disadvantage of being susceptible to trypanosomiasis. There are smaller, even dwarf, breeds of cattle, such as the N'dama and Muturu, that possess remarkably high resistance to or tolerance of the trypanosome. Studies carried out at the Nigerian Institute for Trypanosomiasis Research have proved that the resistance of these breeds is due to a highly efficient immune response. Two conditions are necessary for the attainment of this level of protective immunity. First, the animals must be born of a hyperimmune dam, and second, they must receive an early and continuous

infection of trypanosomes, so that they produce a protective antibody.

These tolerant breeds have not as yet been economically exploited, probably because of their small size, although the N'dama is large enough to be used for meat. Crossbreeding with zebu or European breeds does not result in offspring capable of developing hyperimmunity.

Combating trypanosomiasis calls for heroic measures, but because of the severity of the side effects, the remedies may not be practicable. The battle against the disease has included massive alteration of the environment, social dislocation, wholesale slaughter of wild fauna, and the mass administration of toxic drugs. A commonly employed means of control has been to deny the tsetse its required habitat by selective or large-scale deforestation. Fly-free zones can only be maintained by intensive land use, brought about by the collectivization of the population into large agricultural villages and townships. This forced dislocation from the traditional, stable life in small, scattered tribal groups has resulted in a disturbing upheaval of the social order.

Perhaps the most controversial control measure was the game-destruction program carried out in East Africa during the 1950s. Designed to open up land to human settlement, this scheme was faultless in its logic. Game animals harbor *T. rhodesiense* and are the main source of blood for the tsetse; therefore, destroying the large fauna means good riddance to both trypanosome and fly. After the campaign, however, small mammals survived in sufficient numbers to support the fly population. Also, as the game was decimated, herdsman moved their cattle into the cleared areas, the fly began to feed on the livestock and the pastoralists, and the

result was continued and intensified transmission of both animal and human trypanosomes. Finally, revulsion against the studied slaughter brought the program to a halt.

Another possibility is to control the spread of the disease by means of insecticides. Ironically, one researcher, Dr. Walter Ormerod, has proposed that the use of insecticides was a major, if not prime, contributor to the great drought that recently ravaged sub-Saharan Africa. The reasoning of this hypothesis is as follows: Increasing urbanization and prosperity in West Africa precipitated a demand for meat. Traditional cattle-owning tribes increased the size of their herds to match the market. Widespread, government-sponsored aerial spraying of insecticides, in conjunction with mass chemoprophylactic injections of cattle, followed, permitting growth of herds not only in the Sahel but also in the adjacent Guinea savanna. The large numbers of cattle overgrazed the meager stands of grass and other plant life in this fragile ecosystem, resulting in a higher reflectance of sunlight from the denuded land. There is good evidence that such a situation causes a decrease in rainfall, and in this region matters did indeed proceed to a point where the result was climatic havoc.

Despite more than seventy years of research and effort, the freeing of Africa from trypanosomiasis has not been realized. The effective, practicable means of control now available are too harsh. Except for limited areas, insecticide spraying is too costly. Governments of the new African nations are often too poor in economic and technical resources to maintain the anti-trypanosome and anti-tsetse programs begun during the colonial era.

Drug treatment of infected people has brought about

a decline in human trypanosomiasis, but the trypanosomes can develop resistance. Confronted with this impasse, scientists have long sought the biological "magic bullet"—immunization—as a solution of the problem. Vaccination has brought many of the great scourges of mankind, such as smallpox and yellow fever, under control without necessitating changes in the environment or turmoil in the socioeconomic order. But unlike the immunologically amenable bacterial and viral pathogens, the trypanosome has confounded all attempts to induce protective immunity. The reason for this failure stems from the parasite's ability to elude the host's immune defense by a process known as antigenic variation.

There is currently great concern over the antigenic shift of the influenza virus, a phenomenon that seems to occur about every ten years. A trypanosome undergoes the same process, but a new antigenic variant arises every five to ten days. This is tantamount to the host's being assaulted by a new, personal epidemic each and every week.

During the course of a trypanosomal infection the host may develop an antibody that eliminates most, but not all, of the trypanosomes. The survivors are of a different antigenic character from the others, so the antibody fails to recognize them. The variant trypanosomes then begin to proliferate in the blood stream. The host responds by producing a new specific antibody. The process is repeated over and over, for the trypanosome possesses the remarkable ability of producing a large, probably infinite, number of antigenic variants.

The underlying mechanism responsible for antigenic variation has been the subject of a long controversy between those who hold it to be a selective process,

which presupposes a starting parasite population of one predominant and many minor variants, and those who believe that antigenic variants arise by mutation. There are difficulties in supporting either of these explanations by experimental evidence. Electron microscopy and immunochemical analysis suggest that the trypanosome antigen—the face the parasite presents to its world—is a glycoprotein coat, or pellicle, situated outside the trypanosome's limiting plasma membrane. Apparently this coat is periodically shed, and the parasite, acting as its own couturier, designs and makes a new antigenic garment.

T. vivax, the important pathogen of livestock, seems to have developed still another maneuver to survive in the immunized host—antigenic mimicry. This trypanosome may be able to absorb a coat of host serum protein that disguises its alien status and also acts as a protective shield against any antibody that the host may produce. A similar phenomenon, the absorption of host substances to the external parasite surface, occurs in the schistosome blood flukes of man. Antigenic disguise may thus be another important adaptive evolutionary strategy that permits some parasites to exist in the immunized host.

New methods for dealing with human and animal trypanosomiasis are urgently needed. However, the extent of research and the amount of resources invested are minuscule compared to the magnitude of the problem. A new trypanocidal drug has not been added to the chemotherapeutic armamentarium for twenty years. Pharmaceutical companies candidly admit that the high cost of development and the potentially poor profits from selling to the generally impoverished underdeveloped nations have virtually taken them out of tropical-

disease research. I feel confident, however, that improved means of combating the infections will eventually be forthcoming. A quality of biomedical science is its incurable optimism that all things are possible, given time and support.

But it may well be that Africa's real problems will commence with the effective control of trypanosomiasis. Scientists and the administrators carrying out the practical applications of research often fail to recognize that they are engaged in a gigantic chess game. As one enemy piece is captured, other pieces move to threaten. As trypanosomiasis is conquered, overgrazing, soil erosion, social disruption, and faunal extinction may result. Until the time comes when scientists and their technical-administrative partners appreciate the grand strategy of acting sanely and effectively to protect the well-being of all Africa's citizens, both two-legged and four-legged, we may applaud the cosmic wisdom that has made the tsetse, rather than man, Africa's custodian.

7

RIVER BLINDNESS

Information has reached me that the village of St. Pierre has disappeared; all that is known of it is that the houses are completely deserted and broken down.

—A. Rolland, 1972

In 1963 a small band of settlers, driven by hunger, left their overpopulated and infertile land in the savanna of West Africa and migrated to the banks of the Keralie River, a tributary of the Black Volta. There, they built the village of Saint Pierre and began to farm the rich valley land.

Five years later, 75 percent of these pioneers had developed ocular lesions. Some were already functionally blind. Finally, life and sight became too precarious and they fled. By the time epidemiologist A. Rolland made his report, Saint Pierre had become one more ghost town of the West African savanna—another community crumbled by the parasitic filarial worm *Onchocerca volvulus* and its vector, the blackfly *Simulium damnosum*.

The disease onchocerciasis, familiarly known in Africa as river blindness, has a quality of gothic horror