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Trypanosomes

# Pathogenicity of Trypanosomes

Proceedings of a workshop held at Nairobi, Kenya, 20-23 November 1978



Editors: George Losos and Amy Chouinard



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Proceedings of a workshop held at Nairobi,  
Kenya, 20–23 November 1978

*Editors:* George Losos<sup>1</sup> and Amy Chouinard<sup>2</sup>

*Sponsored by*

Veterinary Research Department,  
Kenya Agricultural Research Institute,  
Muguga, Kenya

*in collaboration with*

International Development Research Centre,  
Ottawa, Canada,  
International Laboratory for Research on Animal Diseases,  
Nairobi, Kenya, and  
Canadian International Development Agency,  
Ottawa, Canada

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## **Anemia of bovine African trypanosomiasis: an overview**

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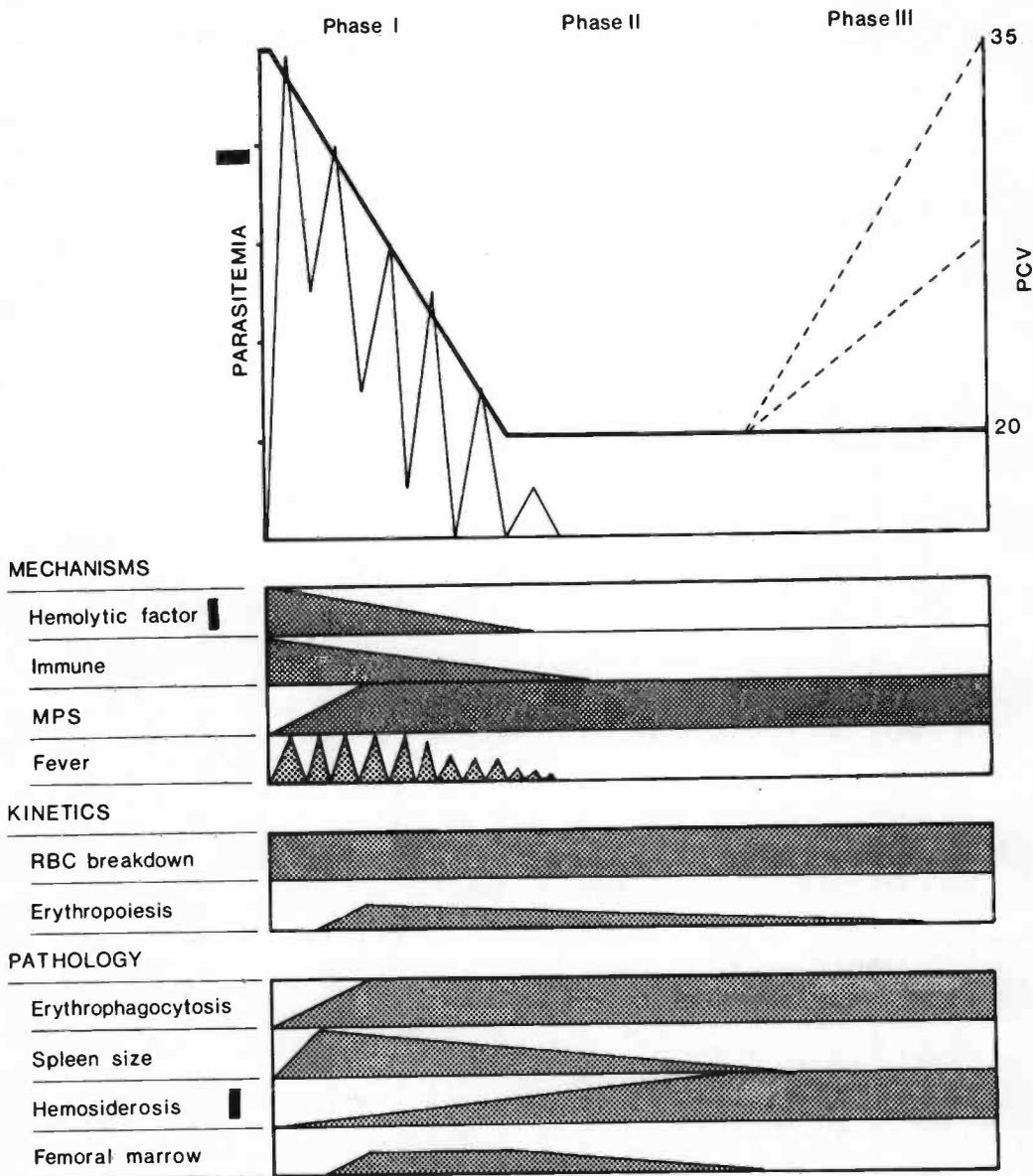
**Abstract.** The cardinal sign of African trypanosomiasis in the bovine is anemia. Based on the presence or absence of the parasite and on clinical and pathological findings, we have divided the disease into three phases. During phase one, the parasitemic phase, anemia is largely hemolytic, resulting from increased red blood cell destruction by phagocytosis; splenomegaly is a feature. Factors possibly involved in this process include hemolysis produced by the trypanosome, immunologic mechanisms, fever, disseminated intravascular coagulation, and an expanded and active mononuclear phagocytic system. Throughout phase two and three, in the apparent absence of trypanosomes, erythrocyte destruction continues, possibly due to the expanded mononuclear phagocytic system. During phase two, there is evidence of dyshemopoiesis and by phase three it is marked, possibly reflecting a defect in iron metabolism related to trapping in the mononuclear phagocytic system. The last phase is characterized by massive hemosiderosis, a yellow gelatinous inactive marrow, and a small spleen. The infection during any of the three phases may cause congestive heart failure and death due to a combination of anemia, circulatory disorder, and myocardial damage. Some animals survive with a persistent low grade anemia and are stunted or wasted, whereas others, particularly trypanotolerant breeds, may make a complete clinical recovery following the apparent elimination of the parasite.

The cardinal sign and major disease-promoting factor of bovine African trypanosomiasis is anemia (Hornby 1921; Murray, M. 1974). Despite its importance, it has many unexplained aspects about which reports frequently appear to conflict. Too often, in discussing the kinetics and mechanisms of the anemia, authors consider only the static situation rather than the progression of the disease. My overview of the development of anemia is meant to reconcile the different views. It includes cumulative experience of ILRAD studies on cattle infected by needle challenge with bloodstream forms of trypanosomes and on cattle exposed to natural tsetse fly challenge (Fig. 1). In Fig. 1, no specific values have been included, only estimates, as the major parameters of anemia, parasitemia, and time vary with breed, challenge, previous exposure, nutritional status, age, parturition, etc. The disease may also be affected by the virulence and species of trypanosome involved, although in our experience mixed infections of *T. congolense*, *T. vivax*, and *T. brucei* are more common than single infections in natural field conditions. Based on the presence or absence of trypanosomes and on clinical and pathological findings, we have divided the disease into three distinct, but overlapping, phases.

### **Phase One**

The first phase may last from 3 to 12 weeks, during which death may occur. The onset and severity of the anemia is directly related to the appearance of the parasite in the blood and to the level of parasitemia (Murray, P.K., Murray, Wallace, et al. in press a, in press b). There is now considerable evidence that the anemia during this phase, is hemolytic (Mamo and Holmes 1975; Holmes 1976; Preston and Welde 1978; Dargie et al. in press) and that red-cell destruction is mainly phagocytosis by the expanded and active mononuclear phagocytic system (MPS) (Murray, M. 1974; Murray, M., McIntyre, Murray et al. in press b). Splenomegaly is marked, partially as a result of massive red-cell sequestration and erythrophagocytosis as well as striking lymphoid hyperplasia. Erythrophagocytosis is not confined to the spleen and is widespread throughout the liver, lungs, hemal nodes, bone marrow, and circulation.

Evidence that hemodilution is involved in the development of anemia (Fiennes 1954; Naylor 1971; Holmes 1976; Valli, Forsberg, and McSherry 1978) has now been refuted by Dargie et al. (in



**Fig. 1.** Anemia of bovine African trypanosomiasis in relation to parasitemia, time, underlying mechanisms, erythrokinetics, and postmortem findings. Hatched areas represent an estimation of the importance of a reaction at any one time. Total time approximates 1 year and is based on a single needle challenge with bloodstream forms of trypanosomes or a tsetse fly challenge limited to a few months of the year such as occurs in the Gambia.

press) whose findings have important clinical implications and establish that measurement of packed red cell volume (PCV) provides a reliable index of the degree of anemia. That the bone marrow is responsive has been confirmed by ferrokinetic studies (Mamo and Holmes 1975). Furthermore, although the anemia is usually nor-

mocytic normochromic, we have observed, in individuals, a macrocytic response, a change also seen by Valli, Forsberg, and McSherry (1978), and, frequently, we have found an increase in red marrow in longitudinal sections of the femur. Occasional petechial and ecchymotic hemorrhages may be found scattered throughout the carcass, but

widespread hemorrhage is not a feature, apart from a distinct syndrome involving *T. vivax* in which massive hemorrhage predominates.

## Phase Two

If cattle survive phase one, they pass into a second phase that lasts for several months and is characterized by transient and scanty parasitemias (often parasites cannot be detected) and by a persistent low grade anemia.

Erythrocyte destruction by the expanded and active MPS continues, although splenomegaly is no longer a consistent feature (Dargie et al. in press; Murray, M., McIntyre, Murray et al. in press b). Ferrokinetic studies have confirmed that there is increased erythropoiesis but not to the extent expected in relation to the degree of anemia (Dargie et al. in press). The femoral marrow response varies from animal to animal and frequently shows little obvious change. A significant new feature is increased hemosiderin deposition throughout the body. Animals with a PCV of 20% or less may die during this phase.

## Phase Three

Provided cattle do not die or become reinfected during phase two, they pass into another stage of the syndrome that may be ongoing or may end in the animals' death or recovery. This phase is characterized by the absence (admittedly difficult to confirm) of parasites in blood and tissues. Because of the implication of this finding, namely that the disease continues in the absence of trypanosomes, we intensively examined cattle in this phase for the presence of parasites. One study involved 47 cattle (37 Ndama and 10 Zebu) that had previously been infected with *T. congolense* and *T. brucei* and had then been subjected to challenge by *Glossina palpalis*. We took both jugular and peripheral blood samples and checked them for parasites using the highly sensitive blood buffy coat darkground phase contrast technique (Murray, Murray, and McIntyre 1977); we also subinoculated cattle blood into laboratory rodents. Necropsy was conducted on 10 cattle and tissues were inoculated into laboratory rodents. For 90 days, and in many cases longer before the termination of this study, no trypanosomes were detected in any animals. A significant proportion of cattle made a slow but complete clinical recovery as judged by hematological values and clinical condition; more Ndama than Zebu behaved in this way. Other cattle made a partial

recovery with PCVs remaining between 25 and 30%. However, despite the absence of detectable parasites for several months, one group made no clinical improvement and had persistently low PCV levels (20–25%).

These experimental studies have been confirmed by longitudinal epidemiological investigations of some 2000 cattle over 5 years, which indicate that this chronic trypanosomiasis syndrome, i.e., a persistent low grade anemia in the absence of trypanosomes, is common. Animals may die, but many remain alive in poor health characterized by wasting or stunting.

Although the erythrokinetics and ferrokinetics of the chronic trypanosomiasis syndrome remain to be investigated, our postmortem findings give some indication of what is going on, namely, continued red cell destruction, iron trapping, and dyshemopoiesis. Thus, although splenomegaly is not a feature, erythrophagocytosis is still found throughout the body. Hemosiderosis is widespread in the spleen, lungs, liver, and bone marrow, and the femoral marrow is often yellow, gelatinous, and inactive.

We believe that the underlying mechanisms of the anemia can be divided into two categories. In the first are mechanisms that operate when the parasite is present, and in the second are those involved in the apparent absence of the trypanosome. In the earlier parasitemic phases of the disease, trypanocidal drug treatment causes a dramatic return to normal hematological values (Holmes and Jennings 1979; Murray unpublished data), whereas in the last phase of the disease, i.e., phase three, there is usually a poor response to chemotherapy (Murray unpublished data).

During phase one of the disease, when the anemia is due largely to increased red cell destruction by the expanded and active MPS, several mechanisms are possible:

- *Hemolytic factors*: Because a significant drop in PCV occurs within a few days of infection, coinciding with the first parasitemia, and subsequent progress of the anemia parallels waves of parasitemia, several workers have speculated that the trypanosome produces a factor capable of damaging red blood cells. Huan et al. (1975) showed that *T. brucei* produces a protein (molecular weight 10 000 daltons) that is capable of lysing red blood cells, and other investigators demonstrated that *T. congolense* during autolysis generates phospholipase A activity and free fatty acids that can destroy red blood cells (Tizard and Holmes 1976; Tizard, Holmes, and Nielsen 1978a; Tizard et al. 1978). So far, we have found that the major African trypanosomes including *T. congolense*, *T.*

*vivax*, *T. brucei*, *T. rhodesiense*, and *T. gambiense* are all capable of producing a hemolytic factor or factors (Murray, M., Huan, Lambert et al. in press). We have detected hemolytic activity in fresh freeze-thawed trypanosomes and in material prepared from dying trypanosomes. The hemolytic factor described by Murray et al. (Murray, M., Huan, Lambert et al. in press) is a heat-stable, trypsin-sensitive substance with a molecular weight just less than 12 000 daltons and isoelectric points in different preparations ranging from pH 5.0 to 5.5. In other words, the trypanosomes seem to produce more than one factor capable of causing red blood cell damage — a possibility that requires further investigation.

The most relevant question is whether or not the factors operate in vivo or just in vitro. Our evidence, at least from studies in *T. brucei*-infected rats, suggests that they are operative in vivo, but that the activity is generated mainly by dying trypanosomes. The onset and course of anemia and the development of parasitemia correlate strikingly with the generation of hemolytic activity in the plasma (Fig. 2). Our figures came from plasma samples prepared immediately after collection: these were heated at 56 °C for 1 hour before use. Blood samples that were left on the bench for a few hours or were collected as serum had significantly greater hemolytic activity, a finding that suggests trypanosomes generate hemolytic activity as they die.

• *Immunologic mechanisms*: Even before the turn of the century, there was evidence that immunologic mechanisms were involved in the anemia of African trypanosomiasis; in 1898 Kanthack, Durham, and Blandford reported autoagglutination and increased sedimentation rates in cattle and humans with trypanosomiasis (reviewed by Gall, Hutchinson, and Yates 1957). More recently, Woodruff et al. (1973) have demonstrated immunoglobulin and complement on erythrocytes of a small number of patients using indirect hemagglutination. Zoutendyk and Gear (1951) and Barrett-Connor, Ugoretz, and Braude (1973) had similar results using direct hemagglutination, and Woo and Kobayashi (1975) found some evidence that immunologic mechanisms operate in the development of anemia in rabbits infected with *T. brucei*. Erythrocytes from infected rabbits lyse in the presence of fresh complement, suggesting the presence of antigen-antibody complexes, and antibodies directed against the trypanosomes can be eluted from erythrocytes of infected rabbits. Also, trypanosome antigen is readily absorbed on to normal rabbit erythrocytes, which then lyse in the

presence of complement and homologous antisera (Woo and Kobayashi 1975).

Immunoglobulins and C3 have been demonstrated on erythrocytes of calves that have been experimentally infected with *T. congolense* (Kobayashi, Tizard, and Woo 1976), and IgM and IgG with antibody activity against *T. congolense* have been eluted from the erythrocytes. The presence of complement-dependent trypanosome antigen-antibody complexes on erythrocytes of infected animals likely facilitates phagocytosis by the expanded and active MPS via Fc or complement receptors on the macrophage. If elevated immunoconglutinin levels, which are known to occur in African trypanosomiasis (Ingram and Soltys 1960; Woodruff 1973) reflect fixation of complement to erythrocytes, immunoconglutinin may facilitate increased erythrocyte clearance from the circulation by causing agglutination.

• *Fever*: The occurrence of fever, often coinciding with a trypanolytic crisis, is a well recognized feature of African trypanosomiasis, and in vitro studies have demonstrated that red blood cells exposed to temperatures of a few degrees above normal body temperature for a few hours have increased osmotic fragility, undergo accelerated hemolysis, and have a shortened life span in vivo (Karle 1969). It is possible, therefore, that fever plays a role in red cell damage and destruction.

• *Disseminated intravascular coagulation (DIC)*: Disseminated intravascular coagulation can lead to hemolytic anemia, termed microangiopathic hemolytic anemia, in which the red blood cells are damaged by widespread fibrin deposition in the microvasculature; the erythrocytes then appear as distorted cells or schisocytes, which are liable to lysis or phagocytosis (Wintrobe 1975). DIC has been described in humans infected with *T. rhodesiense* (Barrett-Connor et al. 1973; Robins-Browne, Schneider, and Metz 1975), and it may occur in *T. brucei*-infected rabbits (Boreham and Facer 1974). It has also been suggested as a mechanism of anemia in African trypanosomiasis by Jenkins et al. (1974) who describe marked alterations in red cell morphology, including red cell fragments, in *T. brucei*-infected rabbits. Valli, Forsberg, and McSherry (1978) observed some fragmented red cells in cattle infected with *T. congolense*; however, we have found little histopathological evidence that DIC is important in cattle except, perhaps, in the hemorrhagic syndrome caused by *T. vivax*.

• *Role of the mononuclear phagocytic system*:

One of the most striking features of bovine African trypanosomiasis is the expanded and active MPS that develops soon after infection and continues throughout the disease (reviewed by Murray, M. 1974; Murray, M., McIntyre, Murray et al. in press b). It is likely that the condition of the MPS results from the massive intravascular presence of living, dying, and dead trypanosomes as well as antigen-antibody complexes, as the size and activity of the MPS is a direct function of its particulate work load (Jandl et al. 1965). That splenomegaly and an expanded MPS are capable of causing anemia has been shown by studies in which methyl cellulose (Palmer et al. 1953; Zuckerman, Abzug, and Burg 1969), zymosan (Gorstein and Benacerraf 1960), and *Corynebacterium parvum* (Nussenzweig 1967) produced hemolytic anemia. Investigators have suggested that splenomegaly leads to red cell stasis within the spleen, prolonged contact with expanded and active MPS, and hence increased erythrophagocytosis. Morphological and kinetic studies indicate that this mechanism is also operative in bovine trypanosomiasis with an increased rate of removal of normal as well as "damaged" erythrocytes.

It appears that the hemolytic anemia of phase one of bovine African trypanosomiasis depends on the presence of the trypanosome and has a multifactorial etiology that may include hemolytic factors produced by the trypanosome, immunologic mechanisms, fever, DIC, and an active MPS. Although each factor may function independently, it is much more likely that they interact, e.g., the hemolytic factors, fever, and/or DIC damage the erythrocyte membrane, which then more readily binds antigen-antibody complexes or complement, predisposing it to erythrophagocytosis.

During phases two and three, increased rates of hemolysis persist, and a progressive dyshemopoiesis develops. A possible explanation for the continuing erythrocyte destruction by the MPS in the absence of trypanosomes comes from the work of Jandl et al. (1965) who found that after prolonged and repeated stimulation the MPS in rats remains active long after the stimulant has been withdrawn. An analogous situation may exist in cattle in phases two to three and the MPS, no doubt stimulated initially by the massive trypanosome challenge, may continue to be active long after the disappearance of the parasite, thereby causing hypersequestration and increased red cell hemolysis.

In ferrokinetic studies carried out during phase two, there was no overt evidence of dyshemopoiesis, although the level of erythropoietic activity was surprisingly moderate in relation to the degree of anemia (Dargie et al. in press). Whereas

there was accelerated utilization of transferrin-bound iron indicative of hyperactive marrow, the proportion of iron carried to the marrow and subsequently incorporated into erythrocytes was lower in infected cattle than in controls. Moreover, a substantial amount of the total iron incorporated into red cells was either reutilized extremely slowly or became unavailable for further hemoglobin synthesis following erythrophagocytosis. Either iron was being excreted or its release into plasma and subsequent transport to the bone marrow was being blocked by the MPS. The former seems unlikely because hemorrhage is not a major feature of the disease. Dargie et al. (in press) estimated that *T. congolense*-infected cattle lose between 40 and 55% of their circulatory iron. Their findings combined with the build up of hemosiderin deposits suggest defective iron reutilization and raise the possibility that, in long-standing infections, the marrow is effectively starved of iron and the anemia is complicated by dyshemopoiesis.

It seems the underlying mechanisms of anemia in phases two and three are similar to those in anemia associated with chronic disorders in humans (Karle 1974). The latter have been resolved by administration of testosterone, cobalt, or purified erythropoietin (Haurani and Green 1967; Zucker, Friedman, and Lysik 1974; Karle 1974), all of which may directly or indirectly release iron from the mononuclear phagocytic system, as well as acting directly on stem-cell proliferation. This offers the interesting possibility that their administration may be of therapeutic value in bovine trypanosomiasis.

Despite apparent elimination of the parasite from the blood and tissues during phase three, some cattle remain anemic although others do make a clinical recovery with a return of normal hematological values. In our studies, the trypanotolerant Ndama were most often able to recover. One possible explanation is that their MPS, following the disappearance of the parasite, returns to normal function more readily than does that of the Zebu because they sustain consistently lower parasitemias (Murray and Morrison in press) and, therefore, less MPS stimulation.

## Death

Death in cattle due to African trypanosomiasis may occur at any time, depending on such factors as the animals' breed, previous exposure, and nutritional status as well as the level of challenge and the virulence of the organism. Our experience has been with cattle in natural conditions where

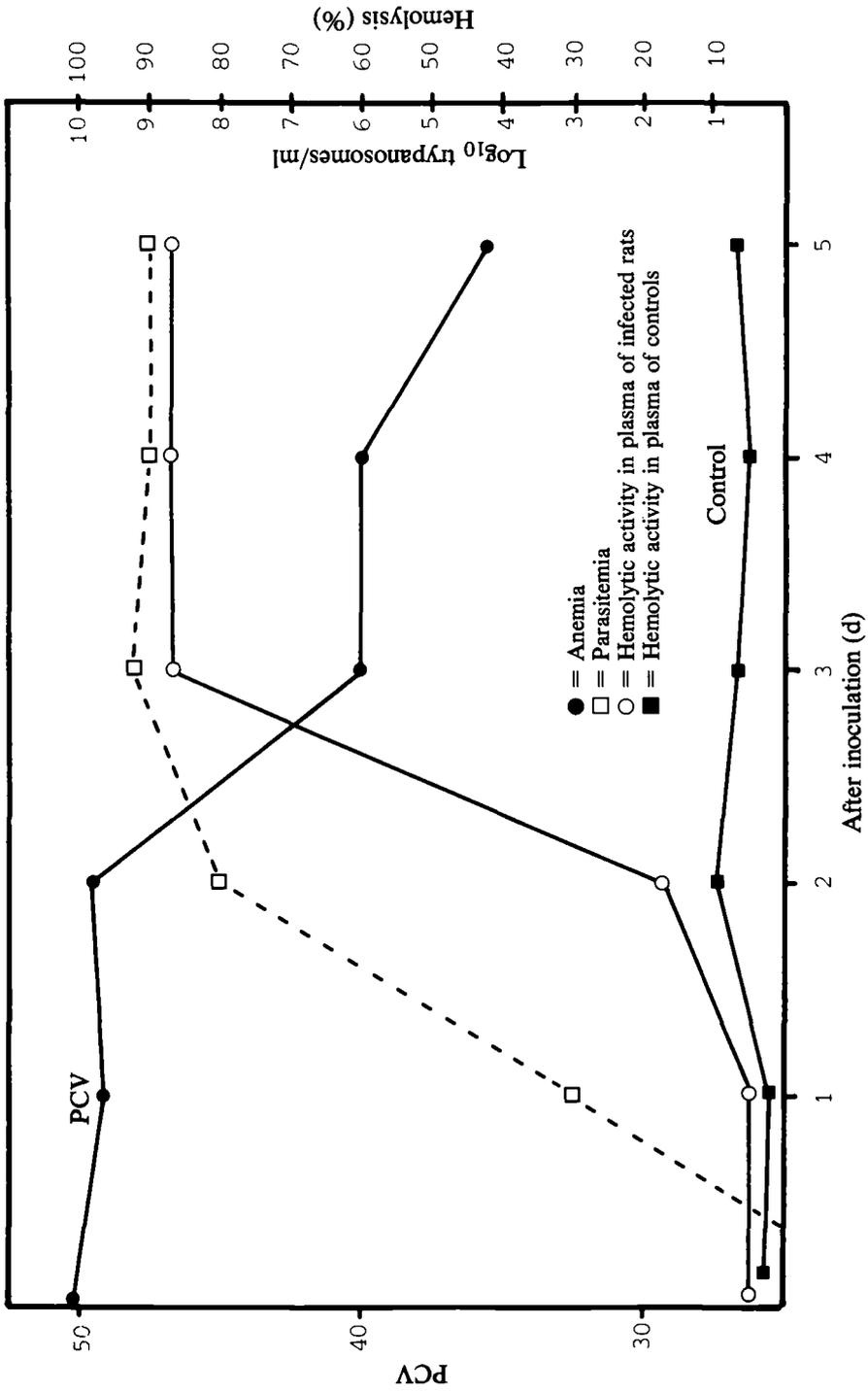


Fig. 2. The development of anemia in rats infected with *T. brucei*.

they sometimes forage up to 27 km in a day. In such circumstances, they often die of acute congestive heart failure from a combination of anemia, circulatory disturbance associated with increased vascular permeability, and myocardial damage (Murray, M. 1974; Murray, M. McIntyre, Murray et al. in press a, in press b). We have found severe myocardial damage in *T. congolense*-, *T. vivax*-, and *T. brucei*-infected cattle. We based our diagnosis on clinical signs correlated with postmortem findings. Terminally, cattle became extremely weak and lethargic, often refusing to rise. A jugular pulse was usually obvious and hemic murmurs were occasionally heard. Following tachycardia, often of a paroxysmal nature, bradycardia with a barely detectable pulse developed. Some animals, particularly those that survived for several days, developed subcutaneous edema in the submaxillary area, in the brisket, and in the lower abdomen. At necropsy, the heart was pale, dilated, and decompensated, and edema was a prominent feature in subcutaneous tissues and between skeletal muscle bundles. Often fluid was increased in the serosal cavities, especially in the pericardium and in the joints. Occasionally, there was edema of the folds of the abomasum and in the coils of the mesentery. The liver was swollen and sometimes mottled due to early chronic venous congestion. Considered together, these clinical and postmortem findings are characteristic of congestive heart failure.

Although a PCV of between 15 and 20% is unlikely to kill inactive cattle, similar PCV values

in ranging animals may lead to death. An animal with a major red blood cell deficit is not able to forage over the wide distances required in the savanna, and its efforts to do so may cause cardiac decompensation. In this respect, we have frequently noted that animals in serious condition often improve dramatically if moved from the range and into a situation where they are fed and are not required to forage.

## Conclusion

Throughout the course of trypanosomiasis, anemia persists as the cardinal sign, but its mechanisms and kinetics appear to vary, depending on the presence or absence of trypanosomes. Most research has concentrated on the early parasitemic phase when the anemia is hemolytic and red cell destruction is mainly by phagocytosis. We have directed special attention to the later phases when anemia persists even in the apparent absence of trypanosomes. The kinetics and mechanisms of this aspect of the disease are poorly understood, although there is evidence that dyshemopoiesis develops and hemolysis continues. The outcome of African trypanosomiasis in the bovine may be death, complete or partial recovery, or more commonly a syndrome characterized by stunting, wasting, and persistent low grade anemia, which we have termed chronic trypanosomiasis syndrome.