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The Pathogenesis of Anaemia in African Animal Trypanosomosis

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1. Introduction

The pathogenesis and pathology of animal trypanosomosis has been a subject of numerous investigations and anaemia has long been recognized as a significant pathological feature. It is the consensus that this anaemia is haemolytic in origin, occurring intravascularly in the acute phase and also extravascularly in the subacute and chronic stages of the disease. The cause of this anaemia is multifactorial and includes increase in erythrocyte destruction coupled with shortening of erythrocyte lifespan. The destruction of erythrocytes largely occurs in the liver by erythrophagocytosis. The other mechanism that has been suggested is that trypanosomes may exert a direct haemolytic action on erythrocytes by generating potentially haemolytic factors on autolysis, a phenomenon that was first described by Landsteiner & Raubitscheck (1901) who hypothesized that the haemolytic factor is lipid in nature. Other mechanisms that have been suggested are haemodilution, bone marrow dysfunction (dyshaemopoiesis) and immunologically-mediated destruction of erythrocytes. In this chapter, the roles of biochemical changes particularly the lipid sub-fraction, bone marrow dysfunction and haemodilution in Small East African goats experimentally infected with *Trypanosoma congolense* or *T. brucei brucei* shall be examined. The effect of *T. congolense* on the life span of erythrocytes in sheep, inferred from ^{51}Cr-labelled erythrocytes, will be presented and discussed.

An in-depth knowledge of development of anaemia during trypanosomosis in different animal species is pivotal in instituting appropriate treatment in clinically sick animals and during convalescence. Similarly, the same knowledge can be utilized by animal health workers to manage anaemia derived from causes other than trypanosomosis.

2. Free fatty acids and other blood biochemical changes

The subject of blood biochemical changes and the role of individual biochemicals mainly those derived from the protein and lipid sub-fractions have been investigated over decades with the aim of elucidating the mechanisms by which anaemia in trypanosome-infected animals is induced. Of particular significance in the pathogenesis of anaemia in trypanosome-infected animals are free fatty acids (FFAs). Free fatty acids generated from both *T. congolense* (Tizard & Holmes, 1976) and *T. brucei* (Huan et al., 1975) form potent hemolytic material when permitted to autolyse in saline at 20°C. This material contains a mixture of FFAs and to a lesser extent lysophospholipids (Tizard et al., 1977). Massive

trypanosome destruction as a result of the hosts' immune responses occurs especially during the acute phase of trypanosome infection. Therefore, the rapid decrease of the erythrocyte mass in this phase may among other factors be mediated by the generation of FFAs from autolysing trypanosomes (Biryomumaisho et al., 2003).

Free fatty acids may be saturated and unsaturated; both groups can significantly modify the host immune response (Berken & Benacerraf, 1968) by either blocking lymphocytic reactivity to mitogens (Mertin & Hughes, 1975) or antigens (Field et al., 1974) or through production of potent immunosuppressive prostaglandins (Quagliata et al., 1972). There is remarkable resemblance between the immunological lesions induced by administration of free fatty acids and those observed in trypanosomosis. The question is: what is the significance of variations of FFAs concentrations that are observed during trypanosomosis infections in different animal species? Observations have shown that relatively large quantities of FFA mostly stearic, linoleic, palmitic and oleic acids are generated by autolysing trypanosomes (Tizard et al., 1976; Assoku et al., 1977). These FFAs are potentially cytotoxic and haemolytic *in vitro*. In both *T. congolense* and *T. brucei* infected Small East African goats (Biryomumaisho et al., 2003), FFAs were significantly higher than those of control uninfected animals. However, the other biochemical parameters showed a different pattern: hypoproteinaemia, hypoalbuminaemia, hypocholestraemia, low and high density hypolipidaemia. These changes suggest that growing trypanosomes require some lipids and proteins to support their growth. At the same time, anaemia developed after goats were challenged with trypanosomes; the pattern of increase of FFAs corresponded to the decrease of packet cell volume (PCV), haemoglobin and erythrocyte counts. These observations re-affirm that FFAs generated from autolysing trypanosomes in goats contribute to anaemia development *in vivo.*

The fatty acids of trypanosomes are mainly esterified as phosphoglycerides or as cholesterol esters though they also exist as FFAs (Dixon et al., 1972). Lipids constitute 15-20% of the dry weight of African trypanosomes with total lipid content of the stumpy forms being substantially higher than that of the slender forms (Vankatesan & Ormerod, 1976). On autolysis, *T. congolense* releases a number of haemolytic FFAs of which the most potent is linoleic acid. These fatty acids can lyse washed rat and bovine erythrocytes *in vitro* (Tizard et al., 1978); autolysis will cause increased erythrocyte fragility in whole rat blood but not in whole bovine blood. Observations in Small East African goats during the first 16 days post infection (Biryomumaisho et al., 2003) showed that total serum lipids decreased from 12.88 mg dl^{-1} three days before infection to 8.84 mg ml^{-1} on day 16 post infection in *T. brucei*-infected goats and to 9.46 mg ml^{-1} in *T. congolense*-infected goats respectively. These findings are in agreement with observations made in rats. Although this mechanism of red cell destruction may not be important in cattle, it may be important in small ruminants. In principal, mechanisms of red cell destruction may differ with different animal species; for instance, infections by *T. brucei* in mice (Igbokwe et al., 1994) and sheep (Taiwo et al., 2003) and *Babesia bigemina* in cattle (Saleh, 2009) render to the animals a reduced ability to peroxidation in the erythrocyte membrane. Furthermore, these oxidative changes in the erythrocytes can accelerate the destruction of these cells in the spleen (Morita et al., 1996). Lipid peroxidation studies in rats infected with *T. evansi* (Wolkmer et al., 2009) showed that these oxidative changes reduce the capacity of erythrocytes in rats to prevent oxidative damage in erythrocyte membrane *in vivo* as is the case *in vitro*.

The understanding of the lipid sub-fraction changes in different trypanosomes and animal species is an ongoing process; their effects could be associated with detrimental effects in

affected hosts (Adamu et al., 2009). Many studies have observed decline is serum lipids and cholesterol levels in trypanosomosis infections. These phenomena could aggravate the neurological disorders often associated with trypanosomosis since cholesterol is vital in cell signaling in neuronal synapses formation.

3. Dyshaemopoiesis as a mechanism of anaemia development

Studies on the role of dyshaemopoiesis in the pathogenesis of anaemia, done with *T. congolense* infection in cattle (Valli et al., 1978); *T. vivax* infection in calves (Logan et al., 1991); *T. congolense* infection in sheep (Katunguka-Rwakishaya et al., 1992); and in *T. congolense* infection in multimammate rats (Ojok et al., 2001), give conflicting results. In this chapter, the role of dyshaemopoiesis in anaemia development in Small East African goats is presented. Bone marrow biopsies were obtained with a 16-gauge Salah sternal puncture needle positioned at right angles to the bone. All biopsies were collected aseptically after a small sharp incision was made under local analgesia.

Bone marrow function was studied by aspirating bone marrow biopsies once a month lasting four months and determining the myeloid:erythroid ratio (M:E ratio) by making a differential count of a total of 500 cells of nucleated granulocytic precursors divided by the number of precursor cells of the erythrocytic series. Typical bone marrow cells are represented in Figure 1 and the results were recorded in a modified bone marrow tally sheet as described by Schalm et al., (1975). The lowest PCV and mean erythrocyte counts occurred between the 4th and 7th weeks after infection in both groups *T. congolense* and *T. brucei*-infected goats. Concurrently, the M:E ratio progressively decreased as the disease progressed (Table 1).

Days post infection	*T. congolense*	*T. brucei*	Uninfected controls
-5	0.48 ± 0.06	0.46 ± 0.07	0.41 ± 0.07
29	0.33 ± 0.06	0.29 ± 0.03	0.36 ± 0.22
59	0.21 ± 0.04*	0.32 ± 0.05	0.37 ± 0.03
85	0.22 ± 0.05*	0.27 ± 0.05	0.38 ± 0.04
121	0.28 ± 0.04	0.43 ± 0.10	0.44 ± 0.12

*$p < 0.05$.

Table 1. Mean myeloid: erythroid ratios (± standard error of the mean) of goats infected with either *T. congolense* or *T. brucei* and of uninfected controls.

The results from the experiment with goats agree with the findings of Valli et al., (1978) in experimental *T. congolense* TREU 112 infection in Holstein calves: the anaemia was of moderate severity and normochromic and macrocytic in the acute phase changing to normochromic, normocytic with chronicity. At the same time, the anaemia was haemolytic and regenerative as was shown by sharply decreased myeloid: erythroid ratio. In the East African goats, however, the anaemia was severe as shown by a sharp decline of haemoglobin concentration by the 7th week from 9.2 ± 0.2 g dl^{-1} pre-infection to 5.4 ± g dl^{-1} in *T. congolense*-infected group and from 9.5 ± 0.2 g dl^{-1} to 5.9 ± 0.1 g dl^{-1} in goats challenged with *T. brucei* (Biryomumaisho et al., 2007). At the same time, the anaemia was regenerative, a parameter that was inferred from decreased M:E ratios. For the parameters observed, *T. congolense* produced more severe effects than *T. brucei*.

Panel 1   **Panel 2**
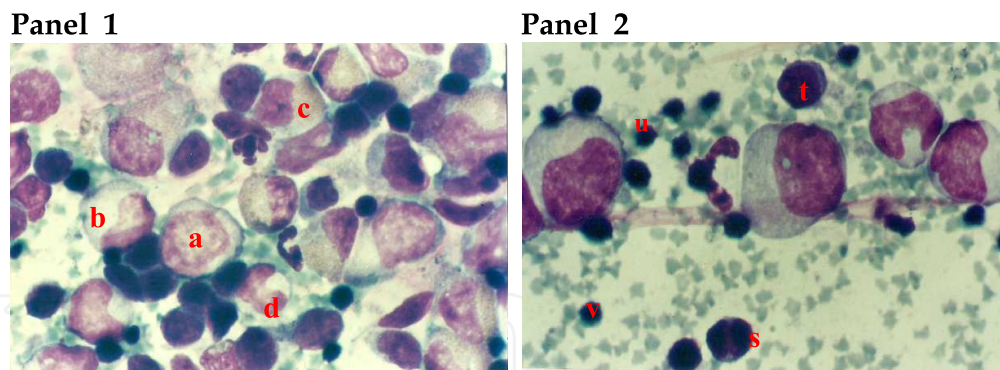
[Micrographs adopted from Biryomumaisho, 2001].

Fig. 1. Giemsa-stained sternal bone marrow biopsies from Small East African goats (x 1,000).
Panel 1. A highly cellular bone marrow micrograph showing precursors of both myelocytic and erythrocytic series at different development stages collected 5 days before infection with trypanosomes in Small East African goats. Cell (a) is progranulocyte; (b) neutrophilic myelocyte; (c) eosinophilic myelocyte and (d) band neutrophil
Panel 2: One month after infection, when animals reached the lowest PCV value, it was more difficult to collect marrow smears without contamination with peripheral blood. (s) dividing metarubricyte; (t) rubricyte and (u) late rubricyte; (v) more late rubricytes can be seen in the micrograph. The large nucleated cells are myelocytic cell line precursors.

Ojok et al., (2001) made similar observations in multimammate rats; but in chronic stages, erythropoietic activity reduced while intra and extra-vascular erythrophagocytic activity increased. Also in agreement is *T. vivax* infection in calves where erythroid hyperplasia, evidenced by decrease in the M:E ratio, was observed (Logan et al., 1991).

The interpretation of results of M:E ratio should be viewed within the framework of the ratio of erythrocytic to granulocytic cell precursors: if the ratio is equal to one, the implication is the rate of manufacture of granulocytic precursors equals that of erythrocytic precursors. A decrease in the ratio means erythrogenesis exceeds granulopoiesis, a phenomenon that was observed in the Small East African goats (Biryomumaisho et al., 2007). The expectation, however, is that if erythrogenesis was increased, anaemia development would be halted. Progressive development of anaemia insinuates that the rate of destruction of erythrocytes exceeds the rate of their replenishment by the bone marrow which results in decrease of all parameters indicative of anaemia *viz.* lowered PCV, hypohaemoglobinaemia and decreased erythrocyte counts in peripheral blood. In the goats in this experiment, increased erythrogenesis did not sufficiently compensate for red cell loss. Similar observations in sheep (Katunguka-Rwakishaya et al., 1992) were made and in both instances erythrogenesis was enhanced but did not sufficiently compensate for the accelerated destruction of erythrocytes. The conclusion here is that anaemia state at those stages of trypanosomosis could be attributed to increased destruction of erythrocytes since there was no evidence of dyshaemopoiesis (as observations in sheep and goats suggest).

4. Reduced red cell lifespan: Erythrokinetic studies

Knowledge of the normal life span of red cells in different animal species is helpful in understanding the dynamics of red cell production and destruction. Life-span studies in

animals indicate that erythrocytes of each animal species have a characteristic mean survival time that is the result of both the potential life span and loss of cells from random destruction irrespective of the age of the animal. Early reports of red blood cells (RBC) survival studies were done in canines using a serological technique as reported by Schalm et al., (1975). Serological techniques involve treating the recipient's blood with specific immune serum to cause RBC autoagglutination leaving the donor or transfused cells unagglutinated. For instance, this method estimated RBC life-span to be 90-100 days in the canine; however, a longer (112-133 days) erythrocyte survival period was estimated by Hawkins & Whipple (1938), using bilirubin production as a measure of the length of red cell life. Tagging or labeling erythrocytes with isotopes is considered to be more accurate. Using isotopes, the mean RBC life span in man with ^{15}N is 127 days; 70-133 days in adult sheep by ^{14}C; 125 days in an adult domestic goat by ^{14}C and 150 days in a mature cow by ^{14}C (Schalm et al., 1975).

4.1 Factors influencing erythrocyte lifespan

Erythrocyte survival may be related to age of the animal; for instance, rapid destruction of erythrocytes has been observed in newborn puppies between birth and 2 weeks of age (Lee et al., 1971). However, erythrocyte survival in new born babies is similar to that of adults (Berlin, 1964) although fetal red cells have a shorter life span of 70 days. Differences in life span (days) with ^{14}C-labeled erythrocytes for sheep at different ages has been shown to be 75 ± 14.8 days for newborn lambs, 46 days for three-month old lambs; 52 days in lambs one year old while adult sheep have an average of 130 days (Schalm et al., 1975).

Diet has been shown to be a factor in erythrocyte survival: *T. congolense*-infected N'Dama 2-5 year old cattle supplemented with 4 kg hay day^{-1} of a mixture of rice bran, groundnut cake, milled *Andropogon* hay and common salt developed similar degrees of anaemia as animals which were not supplemented but recovered from the anaemia more rapidly. Ferrokinetic measurement in *T. congolense*-infected Blackface Scottish sheep (Katunguka-Rwakishaya et al., 1997) indicated that plasma iron turnover rates and ^{59}Fe-incorporated rates were higher in the high protein infected group than the low protein infected group. Comparatively, nutritional deficiencies (Vitamin B$_{12}$, folic acid and iron) in man are reported to result in defective red cells having shortened survival time (Harris & Kellermeyer, 1970). However, in pyridoxine (Vitamin B$_6$) deficiency, the erythrocyte survival time has been shown to be normal but in folic acid and copper deficiencies, it was decreased in swine (Bush et al., 1956).

4.2 Erythrokinetics during animal trypanosomosis

Studies of animal trypanosomosis have consistently indicated reduced life span of erythrocytes: erythrokinetic studies in N'dama and Zebu cattle experimentally infected with *T. brucei* (Dargie et al., 1979); *T. congolense*-infected calves (Valli et al., 1978; Preston et a., 1979) all showed reduced life span. Erythrokinetic and ferrokinetic studies (Katunguka-Rwakishaya et al., 1992) of sheep after infection with *T. congolense* had lower ^{51}Cr-red cell half lives and lower red cell life spans than control sheep. Similar observations were made by Mamo & Holmes (1975) in *T. congolense*-infected bovines and Ikede et al., (1977) in *T. congolense*-infected mice that was accompanied by progressive increase in osmotic fragility.

5. Blood volume changes and anaemia development

The total volume of circulating blood is a function of lean body weight: in most animals, blood volume occupies approximately 7-8% of the body weight except in the cat (4%) (Radostatis et al., 2000). The blood volume is very important to dynamics of circulation that it is kept relatively constant despite periodic water intake, production of water by metabolism and continuous loss of water through various body organs like the skin, lungs, alimentary tract and kidneys.

5.1 Methods of obtaining blood volume

The earliest methods for estimating blood volume consisted of bleeding animals to death followed by washing out the blood vessels and adding the blood contained in the washings to that collected during bleeding (Schalm et al., 1975). Another early method was by injection of known quantity of isotonic solution (NaCl) into the vascular system and shortly noting the extent of dilution of blood as determined by the change in specific gravity, red cell number or haemoglobin concentration.

At present, the most accurate and reliable method for the determination of plasma volume is by measurement of the intravenous dilution of macromolecules labeled with radioisotopes (Mackie, 1976). However, such animals become unfit for human consumption; coupled with the difficulty of maintaining animals treated with radioactive material and disposal of waste from such animals. Basing on these reasons, Evan's blue dye (T-1824) that binds to albumin component of plasma and can rapidly be removed from the body can be used. Plasma and total blood volume in Small East African goats infected with either *T. congolense* or *T. brucei* (Biryomumaisho, 2001) were determined by injecting a 0.03% solution of T-1824 at a dose rate of 0.4 mg kg^{-1} of the goat in the right jugular vein and after 10 minutes, blood was collected from the left jugular and centrifuged to obtain plasma-tagged dye. By using absorbance of the dye in plasma of the standard against a blank (prepared from plasma of individual goats) in a U-1,000 Hitachi spectrophotometer at a wavelength of 620 nm, the concentration of the dye in plasma was calculated as follows:

$$\frac{\textbf{[T-1824] in Plasma} \text{ (mg)}}{\text{[T-1824] in Standard}} = \frac{\textbf{Optical density of diluted Plasma}}{\text{Optical density of the Standard}} \quad (1)$$

$$\text{Plasma volume (mls)} = \frac{\textbf{mg of dye injected}}{\text{mg/ml of dye in Plasma}} \quad (2)$$

$$\text{Blood volume (mls)} = \frac{\textbf{Plasma volume} \text{ x 100}}{\text{100-PCV x 0.98*}} \quad (3)$$

Trapped plasma after centrifugation was corrected for by including a 2% (0.98) factor.

Plasma volume and total blood volume of individual goats in ml kg^{-1} were determined by dividing the values obtained in (2) and (3) by the body weight of individual goats. Mean values of all 5 measurements taken at 30-day intervals are shown in Table 2 while measurements taken in *T. congolense*-infected Scottish Black Face sheep with ^{125}I-albumin and ^{51}Cr-red cells respectively are shown in Table 3 (Katunguka et al., 1992).

5.1.1 Blood volume changes in trypanosomosis

In trypanosomosis infections, anaemia development has been shown to be mainly haemolytic during the acute phase of the disease. In the sub acute and chronic stages of the

disease, however, extravascular mechanisms are thought to play a major role. One such mechanism is thought to involve an abnormal retention of large quantities of fluid within the plasma compartment. Results from *T. congolense*-infected N'Dama and Zebu cattle (Dargie et al., 1979) showed that both groups developed significant anaemia. Measurement of plasma and red cell volumes showed that the low PCV of infected cattle was due to reductions in red cell volume and not haemodilution.

The implication of increased plasma here can be explained by a normal homeostatic response for maintenance of blood volume and pressure. Studies using ^{51}Cr-red cells, ^{125}I-albumin and ^{59}Fe as ferric citrate 11 weeks after infection revealed that infected sheep had significantly lower mean circulating red cell volumes but higher plasma and blood volumes than control sheep (Katunguka-Rwakishaya et al., (1992). In *T. congolense* and *T. brucei*-infected goats (Biryomumaisho, 2001), the mean plasma volume and total blood volume values were higher than those of the controls although the differences were not significant (Table 2).

	T. congolense n = 10	*T. brucei* n = 10	Controls n = 5	Significance
Plasma volume (mls /kg) ± SEM	58.3 ± 3.0	53.1 ± 6.1	44.7 ± 7.0	P > 0.05
Total blood volume (mls / kg) ± SEM	72.8 ± 3.9	67.9 ± 7.5	58.6 ± 7.4	P > 0.05

[Table adopted from S. Biryomumaisho, 2001].

Table 2. Mean T-1824-plasma and blood volume in trypanosome-infected goats.

	Plasma volume mls kg $^{-1}$ ± SEM	Blood volume mls kg $^{-1}$ ± SEM
Infected, n=5	45.1 ± 1.5	57.9 ± 1.1
Control, n = 5	36.2 ± 1.0	52.9 ± 2.2
Significance	P < 0.01	P < 0.01

Table 3. Blood volumes of sheep infected with *T. congolense* (mls kg $^{-1}$ ± SEM).

6. Conclusion

Knowledge about the pathogenesis of anaemia can be utilized to manage cases of anaemia caused by trypanosomosis as well as cases of anaemia derived from other causes other than trypanosomosis provided the primary cause is dealt with. The aspects of cross matching the blood of donor and recipient animals and whether to replace whole blood or its components are beyond the scope of this chapter. However, a veterinarian can utilize some aspects of the knowledge of dyshaemopoiesis and blood volume to manage anaemia in routine practice.

Blood volume changes can be estimated at clinical examination: basically, most animals with exception of the cat have blood volumes approximately 7-8% of their body weight. An animal health care worker can estimate the total blood volume of a donor animal that way. However, the amount of blood lost (in the anaemic / recipient animal) can be estimated from measurement of PCV as follows:

$$\text{Blood lost (litres)} = \frac{\textbf{Normal PCV of animal species – patient PCV}}{\text{Normal PCV x 0.08 of patient weight in kg}} \qquad (4)$$

In our opinion and experience, for blood transfusion to be effective, at least 25% of the deficit should be corrected.

Haemodilution is a state when the fluid content of blood is increased and this results into lowered concentration of the formed elements. For the case of the red cell component, this can result in apparent anaemia. The converse is haemoconcentration, a state in which there is increased concentration of formed elements of blood mainly as a result of loss of water from the body. The clinical importance of both scenarios dictates that the veterinarian should first evaluate the animal as to whether haemoconcentration or haemodilution is pathological or not. In both cases, the primary cause should be dealt with.

The more commonly encountered of the two scenarios is haemoconcentration and subsequent hypovolaemia resulting from loss of fluid such as in diarrhaea / dysentery, vomiting (especially in monogastric animals), skin burns, starvation and thirst, among other causes. In all cases, hypovolaemia leads to reduction in blood plasma and, in severe instances, leads to hypovolaemic shock. A low blood volume leads to multiple organ failure, kidney and brain damage and death. An appropriate fluid for replacement containing electrolytes, metabolic enhancers or plasma expanders should be chosen (selection of suitable fluids for therapy is outside the scope of this chapter).

Basing on presenting clinical signs, the degree of dehydration and hence amount of water lost can be estimated from the percentage of dehydration basing on skin elasticity, demeanor of the animal and sinking of the eyes in the orbit.

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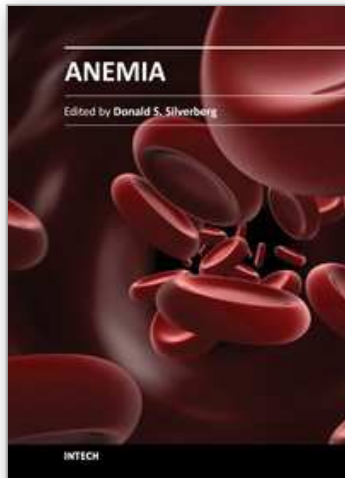
Anemia

Edited by Dr. Donald Silverberg

This book provides an up- to- date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.

How to reference

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