Dyserythropoiesis in animal trypanosomosis

I. O. Igbokwe [1]

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L'hémolyse est la cause pathologique la plus évidente de l'anémie trypanosomienne. Les anémies hémolytiques s'accompagnent normalement d'une érythropoïèse accrue, d'une réponse réticulocytaire et d'une augmentation du volume moyen corpusculaire des érythrocytes circulants. Dans la trypanosomose, l'anémie s'accompagne d'une perturbation de l'érythropoïèse. Ce fait semble découler d'une réponse leucocytaire subnormale chez les rongeurs infectés, faible ou nulle chez les ruminants (infectés) et d'une capacité faible d'érythrogénèse du plasma de mouton infecté chez la souris. Le volume corpusculaire moyen augmente dans la phase aiguë pour atteindre un sommet 3 à 4 semaines après l'infection. Il chute jusqu'à la normale ou en-dessous de la normale pendant la phase chronique, ce qui indiquerait que l'érythropoïèse augmenterait modérément dans la phase aiguë, mais décroît progressivement, au point de devenir nulle, au cours de la phase chronique. Les raisons de la dysérythropoïèse ne sont cependant pas claires mais peuvent être associées à un trouble érythrocytaire, à une synthèse ralentie ou insuffisante de l'érythropoïétine, à une baisse de la synthèse de l'hémoglobine, ou à une combinaison interréactionnelle de ces facteurs. Dans ces différents domaines, il est évident que des études poussées sont nécessaires. *Mots clés* : Animal - Trypanosomose - Érythropoïèse - Anémie - Nigeria.

INTRODUCTION

Trypanosomosis is an important protozoan disease of domestic animals and man in most parts of Africa. It has been considered one of the major obstacles to livestock production in Africa. Some of the features of the disease which are responsible for great economic losses include stunting, wasting, drop in milk yield, infertility, stillbirths, abortion and deaths (7, 21, 30, 31).

The pathogenic trypanosomes of domestic animals include *Trypanosoma vivax, T. congolense, T. brucei, T. simiae, T. evansi* and *T. equiperdum*, each of which affects one or more species of animals. The human trypanosomes are *T. gambiense, T. rhodesiense* and *T. cruzi*. The trypanosomes are transmitted biologically by different species of tsetse flies (*Glossina* spp) except for *T. evansi, T. equiperdum* and *T. cruzi* which are transmitted mechanically. *Trypanosoma vivax*, apart from being biologically transmitted, can also be mechanically transmitted by biting flies (40).

Trypanosoma vivax and *T. congolense* are primarily parasites of the circulating blood while the other trypanosomes parasitize both the intravascular and extravascular milieu (14, 36, 37, 52). One consistent pathological feature of trypanosomosis is anaemia (3, 4). The anaemia is a good indicator of the severity of the disease. Haemolysis, haemodilution, haemorrhage and bone marrow dyserythropoiesis have been implicated in the pathogenesis of the anaemia. This paper presents evidences in support of inadequate erythropoiesis in trypanosomosis, reviews the possible causes of such inadequacy and highlights new areas of research on the causes of bone marrow dyserythropoiesis in trypanosome infections.

HAEMOLYSIS

Haemolysis is the most important pathogenic mechanism of the anaemia in trypanosomosis. This is supported by the existence of erythrophagocytosis and haemosiderosis in the spleen and the liver in *T. brucei* and *T. vivax* infections (10, 12, 13, 28, 49) and by the decreases in red cell mass and survival (5, 6, 10, 28). Indications for intravascular haemolysis include decreased plasma haptoglobin levels in *T. vivax* infection of cattle (20) as well as renal haemosiderosis in *T. congolense* infection of cattle (41, 43). Extravascular haemolysis is, however, more important than intravascular haemolysis (4).

HAEMODILUTION

While the erythrocyte mass decreased, the plasma volume increased and the blood volume remained normal in *T. brucei, T. congolense* and *T. vivax* infections (5, 17, 55). However, there are some reports of increased blood volume (1, 2). Although these findings suggest some measure of dilution of the cellular components of the blood, haemodilution cannot be considered consistently significant.

1. Department of Veterinary Pathology, University of Maiduguri, Maiduguri, Nigeria.

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HAEMORRHAGE

In acute *T. vivax* infections of cattle, sheep and goats, petechial and ecchymotic haemorrhages have been described in various organs (3). Haemorrhages produced by haemorrhagic *T. vivax* may be significant in contributing slightly to the pathogenesis of the anaemia.

DYSERYTHROPOIESIS

Evidences

Anaemia in trypanosomosis is predominantly haemolytic. Haemolytic anaemias are expected to stimulate considerable reticulocyte response (45, 50). The reticulocytes are larger in size than the mature erythrocytes and an increase in the number of circulating reticulocytes will increase the mean corpuscular volume (MCV) of erythrocytes. Reticulocytosis and increased MCV are therefore measures of erythropoietic response in anaemias (Fig. 1).

Reticulocytosis was very mild in *T. congolense* infection of sheep (38) and absent in *T. vivax* infection of sheep and goats (6, 26) and *T. congolense* infection of cattle (56). The MCV of erythrocytes was elevated during the early acute phase of *T. vivax* infection of sheep (6, 26) and cattle (48) and *T. congolense* infection of cattle (55). As the disease progressed into the chronic phase, the MCV fell to normal or even below normal despite the persistence of the anaemia (6, 42, 55, 56).

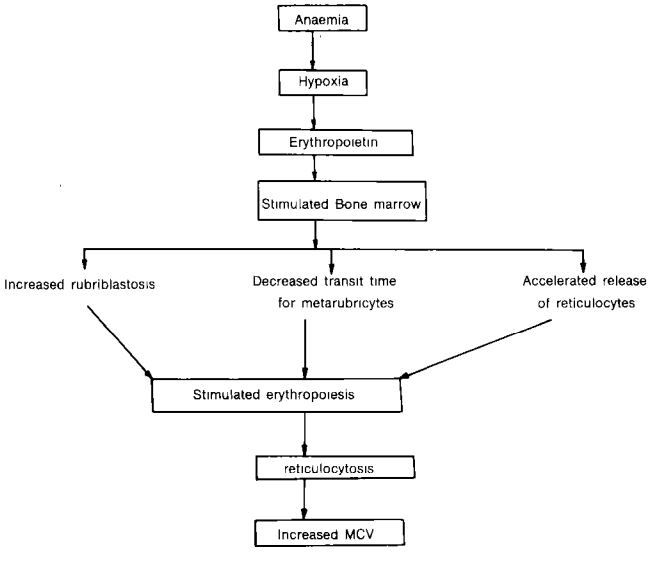

Fig. 1 : A schematic illustration of erythropoietic response to anaemia.

In the acute phase, there was expansion of the bone marrow in the long bones with an erythroid hyperplasia, a drop in myeloid : erythroid ratio and an increase in iron uptake (6, 55, 56). During the chronic phase, however, the bone marrow was hypoblastic (22) or normoblastic (42) and some reports indicated gelatinous changes in the bone marrow (16, 17, 56).

The little or no reticulocytosis in acute ruminant trypanosomosis in association with macrocytosis and erythroid hyperplasia, suggests that although erythropoiesis is increased, it is inadequate. This is true when it is considered that haemolytic anaemia in ruminants elicit considerable reticulocyte response (9, 50). Reticulocytosis of 1.5 ± 1.0 per cent accompanied an acute anaemia induced by *in vitro* erythrocyte heat treatment in sheep (26). The anaemia was comparable in degree and classification to the anaemia produced by acute *T. vivax* infection of sheep which had not elicited any reticulocytosis. Furthermore, the plasma from the sheep with artificially induced anaemia caused more reticulocyte response in mice when subcutaneously administered than plasma from sheep with *T. vivax* induced anaemia ; which suggested that the infected sheep plasma was weakly erythrogenic (26). These observations pointed to the inadequate erythropoietic response in the *T. vivax* infected sheep and further supported bone marrow dyserythropoiesis. It is noteworthy that BOYCOTT *et al.* (15) had earlier suggested bone marrow dyserythropoiesis in *T. brucei* infection of rodents judging from the inadequate erythropoietic response to phenylhydrazine and aniline induced haemolysis in rabbits infected with *T. brucei*.

In the chronic phase of trypanosomosis, bone marrow dyserythropoiesis becomes more severe. The moderate increase in erythropoiesis observed in the acute phase of trypanosomosis begins to wane after 3 to 4 weeks post-infection, despite the increase in the severity of the anaemia, in *T. vivax* infection of sheep (26), *T. congolense* infection of cattle (55) and *T. brucei* infection of mice (10). The mean corpuscular volume of erythrocytes peaked at 3 weeks after infection in *T. vivax* infection of sheep and *T. brucei* infection of mice and at 4 weeks after infection in *T. congolense* infection of cattle. As trypanosomosis progresses into the chronic phase, erythropoiesis is completely depressed as shown by the absence of both reticulocytosis and macrocytosis in association with normal or low erythroid cell population in the bone marrow (16, 17, 56).

Causes

The causes of the bone marrow dyserythropoiesis in trypanosomosis have not been clearly understood. Attention is drawn to the following target sites in erythropoiesis : erythroid cells, erythropoietin production and bioactivity and haemoglobin synthesis (Table I). The factors that may be associated with dyserythropoiesis in the erythropoietic pathway are outlined in figure 2.

TABLEAU I Some factors considered in the aetiology of bone marrow dyserythropoiesis in trypanosomosis.

1. Bone marrow erythroid cells : Cell injury Phagocytosis Depression or suppression
2. Erythropoietin : Depressed production : • Lesions in the liver and kidney • Hormonal deficiencies Interference in bioactivity : • Neuraminidase activity
3. Haemoglobin synthesis : Iron sequestration Amino acid deficiency Depletion of vitamin B series

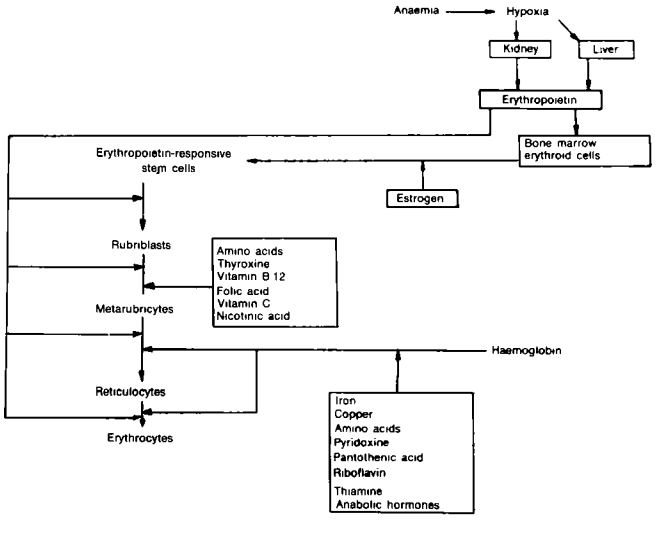

Fig. 2 : A schematic illustration of erythropoiesis and the factors (in blocks) that influence it.

KAAYA *et al.* (34) suggested that erythroid depression in trypanosomosis could be due to competition among stem cells for space and nutrition. LAWSON *et al.* (35) did not find any significant difference in the number of erythroid colonies produced by marrow cultures from control calves and calves infected with *T. congolense* but however noted that erythroid colonies from infected calves were less haemoglobinized than those from the controls. Phagocytosis of erythroid cells was demonstrated in the spleen of mice infected with *T. brucei* (12, 13) and it was thought to have been due to erythroid cell abnormalities or due to immunologic mechanism similar to that which predisposed red cells to erythrophagocytosis. *In vitro* studies have shown that sera from cattle infected with *T. vivax* or *T. congolense* did not depress erythroid colonies (34). It is possible that the inhibitor of erythropoiesis in the sera of the infected cattle did not affect the erythroid colonies (CFU-E) because they had matured beyond the sensitive stage but would affect the colony of less differentiated erythroid progenitors.

Although anaemia of trypanosomosis is largely haemolytic and elevated erythropoietin production is expected, plasma erythropoietin levels and bioactivity may actually be depressed (26). The organs involved in erythropoietin production such as the liver and the kidney (57) are damaged to some extent in *T. vivax* infection of sheep and goats (8, 57) and cattle (32, 40). Changes in the liver include fatty degeneration of hepatocytes, dilatation of the sinusoids, proliferation of haemosiderotic kupffer cells, infiltration of the portal triads by lymphocytes, plasma cells and macrophages (8) and centrilobular degeneration of the liver (57). Lesions in the kidney consist of fibrin microthrombi (8, 57), hypercellular glomeruli and dilatation of proximal tubules (57), hypertrophy and hyperplasia of the cells lining the Bowman's capsule, swelling of the proximal and distal tubular epithelial cells, accumulation of proteinaceous exudate in the Bowman's capsule and in the tubules, haemorrhages and focal infiltration by lymphocytes and macrophages (32, 40). The pathologic changes in the liver and kidney may be associated with decreased cellular secretion of erythropoietin.

Erythropoietin is a highly glycosylated protein containing terminal sialic acid residues (51). Neuraminidase destroys the *in vivo* biologic activity of erythropoietin by cleaving the sialic acid residues to produce asialoerythropoietin (23). *Trypanosoma vivax* has been shown to produce neuraminidase *in vitro* (18, 19). *In vivo* production of neuraminidase has not been investigated but it is surmised that in trypanosomosis, as the trypanosomes increase in the blood at peak parasitaemias, neuraminidase may be produced in significant amount to destroy the biologic activity of plasma erythropoietin.

Deficiencies of endocrine hormones of the pituitary, adrenal thyroid and gonads depress erythropoietin production and erythropoiesis (50). Deficiencies or depressed secretion of androgens, estrogens, thyroid stimulating hormone, adrenocorticotropic hormone, growth hormone, cortisone, thyroxine, epinerphrine and norepinerphrine and excessive secretion of estrogens decrease erythropoietin production (50). GOODWIN (24) suggested that catecholamine metabolism was defective in trypanosomosis because tryrosine, an important precursor of catecholamines was depressed (50 per cent of control levels) in the sera of rabbits infected with *T. brucei*. The depression of serum tryrosine levels may also affect thyroxine biosynthesis which requires tryrosine residues. Lesions are produced in the pituitary of goats and cattle infected with *T. vivax* (39). The lesions include diffuse congestion, impaction of blood vessels with leucocytes and lymphocytic infiltration of the pars nervosa. In sheep, *T. brucei* infection causes gliosis and perivascular mononuclear infiltration of the neurohypophysis, oedema, acute coagulative necrosis and fibrosis of the adenohypophysis, adrenocortical hypertrophy and thyroid atrophy (27). In *T. vivax* infection of sheep, goats and cattle, there is testicular and cystic ovarian degeneration (7, 30, 31). These findings suggest endocrine imbalance associated with the diseased organs. The role of endocrine imbalance in dyserythropoiesis of trypanosomosis is still not clear.

The depression of the serum levels of certain free amino acids which occurs in trypanosomosis (25, 33) may be responsible for the reduction in the rate of synthesis of the globin moiety of haemoglobin. Globin synthesis precedes haeme synthesis and is nearly complete by the time haemoglobin synthesis begins (54). It is possible that reduced globin synthesis slows erythropoiesis.

Vitamins B-complex are required in erythropoiesis. ISOUN (29) demonstrated that thiamine was required to maintain a high parasitaemia in *T. brucei* infection of rats.

This suggests that trypanosomes metabolize thiamine and could deplete the host's supplies in very high parasitaemias. STIBBS and SEED (53) suggested there was decreased niacin (nicotinic acids) synthesis in *T. gambiense* infection. Possible interference by trypanosomes in the metabolism of the vitamins involved in erythropoiesis has not been investigated. It is probable that a few vitamins in the B series are depleted in trypanosomiais.

During chronic crisis, normocytic or even microcytic normochromic anaemia exists along with adequate supply of storage iron. The inhibition of iron utilization at cellular levels as seen in anaemia of chronic disorders (44) is considered a possibility. Erythropoiesis is interfered with when iron is sequestered in the macrophage phagocytic system of the spleen, liver and bone marrow leading to a depression in serum iron, total iron-binding capacity and unbound iron-binding capacity (46).

CONCLUSION

There are clear indications that trypanosomosis is featured by dyserythropoiesis. The causes of the dyserythropoiesis are not clear. Erythroid cell abnormalities are suspected from the observation of erythroid phagocytosis in *T. brucei* infection of mice (12, 13). That plasma from sheep infected with *T. vivax* was weakly erythrogenic in mice suggested that erythropoietin production in the infected sheep was depressed (26). Moreover, trypanosome neuraminidase produced *in vivo* may desialylate circulating plasma erythropoietin to render it biologically inactive.

Although iron and copper are not limiting factors in erythropoiesis in trypanosome infected animals (47) it is believed that iron utilization is interfered with by iron sequestration in the macrophage phagocytic system. Iron utilization and haemoglobin biosynthesis may further be depressed by depletion of plasma free amino acids (25, 33) and some important vitamins (29, 53).

Since erythropoietic response is moderate in the acute phase of trypanosomosis and absent in the chronic phase, it is thought that the factors responsible for dyserythropoiesis during the different phases may not be the same and may not be acting in similar intensities. The disparity could be responsible for the different rates and speeds of recovery when specific treatment with trypanocidal drug is administered at different stages of the disease. It is known that when acutely infected animals are treated, recovery of the erythrocyte parameters is rapid, but when treatment is carried out during the chronic phase, recovery is slow and in some cases, reversal of the erythrocyte picture is not possible. When the causes of erythropoietic depression in trypanosomosis are fully elucidated, the nature of supportive treatment in chronic and terminal cases will be better understood to enhance recovery of such clinical patients.

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Haemolysis is the most prominent pathogenic cause of the anaemia in trypanosomosis. Haemolytic anaemias are normally accompanied by increased erythropoiesis, reticulocyte response and increase in the mean corpuscular volume of circulating erythrocytes. In trypanosomosis, the anaemia is accompanied by inadequate erythropoiesis. This is suggested by suboptimal reticulocyte response in infected rodents, little or no reticulocyte response in infected ruminants and weak erythrogenic capacity of infected sheep plasma in mice. The mean corpuscular volume increases in the acute phase reaching a peak at 3 to 4 weeks after infection and drops to normal or below normal in the chronic phase ; suggesting that erythropoiesis moderately increases in the acute phase but Wanes and becomes completely depressed as the disease progresses into the chronic phase. The causes of the dyserythropoiesis are meanwhile not clear but may be found to be associated with erythroid injury, depressed erythropoietin synthesis and bioactivity or depressed haemoglobin synthesis or their interplay. Extensive studies in these areas are still necessary. *Key words* : Animal - Trypanosomosis - Dyserythropoiesis - Anaemia - Nigeria.

IGBOKWE (I. O.). Diseritropoiesis en la tripanosomosis animal. *Revue Élev. Méd. vét. Pays trop.*, 1989, **42** (3) : 423-429.

La hemolisis es la causa patológica más patente de la anemia en la tripanosomosis. Con las anemias hemoliticas, se observan normalmente una eritropoeisis aumentada, una respuesta reticulocitaria y un acrecimiento del volumen medio corpuscular de los eritrocitos circulantes. En la tripanosomosis, la anemia se acompaña con una pertubación de la eritropoeisis ; lo que parece resultar de una respuesta leucocitaria subnormal en los roedores infectados, reducida o nula en los rumiantes (infectados) y de una capacidad baja de eritrogenesis del plasma de oveja infectada en el ratón. El volumen medio corpuscular aumenta durante la fase aguda hasta llegar a un máximo 3 a 4 semanas después de la infección. Cae hasta el valor normal o debajo durante la fase crónica, lo que indicaría que la eritropoeisis aumentaría moderadamente durante la fase aguda, pero disminuye progresivamente hasta volverse nula durante la fase crónica. No son evidentes los motivos de la diseritropoeisis sino pueden proceder de un desorden eritrocitario, de una síntesis de la hemoglobina o de una combinación interreaccional de estos factores. Se necesitarían estudios más profundizados sobre estos asuntos. *Palabras calves* : Animal - Tripanosomosis - Eritropoeisis - Anemia - Nigeria.

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