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The Mechanisms of Anaemia in Trypanosomosis: A Review

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1. Introduction

Trypanosomosis is an important disease of both humans and animals commonly found in most parts of Africa and South America (Swallow, 2000). The tsetse fly (*Glossina*) is responsible for biological (cyclical) transmission while haematophagus arthropod vectors of the family, *Tabanidae*, *Stomoxynae* and *Hippoboscidae* are responsible for its mechanical transmission (Soulsby, 1982). Transplacental transmission has also been recorded in cattle (Ogwu et al., 1992). *Trypanosoma congolense, T. vivax and T. brucei* have been reported to cause nagana in cattle while *T. evansi* caused surra in camels (*Camelus dromedarieus*) (Mbaya et al., 2010). In humans, *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodeseinse* are responsible for human sleeping sickness in West and East Africa respectively, while *T. cruzi,* transmitted by triatomid bugs (*Triatoma magista*) is responsible for transmitting chagas diseases to humans in South America (Solano et al., 2003). The *T. brucei* group of trypanosomes (*T. brucei, T. b. gambiense, T. b. rhodesianse* and *T. evansi*) mostly invade tissues (humoral) whereas, *T. congolense* and to a lesser extent *T. vivax* and *T. cruzi* predominantly restrict themselves to the blood circulation (haemic) (Igbokwe, 1994; Mbaya et al., 2011).

The mechanism or pathophysiology of anaemia in trypanosomosis is complex and multifactorial in origin (Naessens et al., 2005). It initiates a cascade of events leading to haemolytic anaemia and cardiovascular collapse (Anosa, 1988). In human trypanosomosis, disseminated intravascular coagulation has been reported (Barret-Connor et al., 1973). Among the complex and multifactorial etiologies associated with the anaemia is haemolysin, a sensory/excretory product of living trypanosomes. This product is known to lyse red blood cells in the absence of antibodies (*in-vitro*) and haemodilution (*in-vivo*). This mechanism has been adequately described in gold fish (*Carassius auratus*) infected with *Trypanosoma dahilewskyi* (Nazrul-Islam and Woo, 1991) and in murine models infected with *T. b. rhodesiense* (Naessens et al., 2005).

2. Haemolytic anaemia caused by animal and human trypanosomes

Haemolytic anaemia has been reported in *T. brucei* infection of red fronted gazelles (*Gazella rufifrons*) (Mbaya et al., 2009a), sheep and goats (Edward et al., 1956; Ikede & Losos, 1972), *T.*

congolense infection of sheep and goats (Edwards et al., 1956), *T. vivax* infection of sheep and goats (Anosa, 1977). Similarly, it was reported in vervet monkeys (*Cercopethicus aethiopes*) (Abenga & Anosa, 2006), and baboons (*Papio anubis*) (Mbaya et al., 2009c, b) infected with the West African human sleeping sickness trypanosome; *T.b. gambiense*.

2.1 Various stages of the anaemia in trypanosomosis

Three phases of anaemia have been reported to occur in trypanosomosis. They are, phase I (acute crises), phase II (chronic) and phase III (recovery) (Anosa, 1988).

2.1.1 Phase I: Acute crises

This phase begins with the initial appearance of trypanosomes in peripheral circulation. The parasitaemia in this case is usually high, fluctuating and evident in most days (Maxie & Losos, 1979; Anosa & Isoun, 1980; Anosa, 1988; Abenga & Anosa, 2006; Mbaya et al., 2009a, b, c; 2010; Mbaya & Ibrahim, 2011; Mbaya et al., 2011). During this phase the anaemia is morphologically classified as macrocytic and normochromic (Maxie & Losos, 1979; Anosa & Isoun, 1980). At this stage death commonly occurs due to severe pancytopoenia and other pathologies (Anosa, 1988). Sub-acute cases have been produced experimentally in rodents infected with *T. congolense* (Isoun & Esuroso, 1972) and with *T. brucei* (Mbaya et al., 2007, 2010, 2011).

2.1.2 Phase II: Chronic

This phase follows the acute crises phase and is characterized by low levels of parasitaemia. The low to moderate erythrocyte value at this point persists with minor fluctuations. This period ranges from several weeks to months. With the *T. brucei* group, which mostly invade tissues, this is the aparasitaemic phase when the parasites establish extravascularly and are less numerous in peripheral circulations (Rabo, 1995) or absent (Mbaya et al., 2007, 2009a, d). In this chronic phase, the morphological classification of the anaemia is normochromic and normocytic (Maxie & Losos, 1979).

2.1.3 Phase III: Recovery

This phase is characterized by the low, infrequent or absence of parasitaemia. At this point, declined erythrocyte values begin to return towards pre-infection values and other pathological changes undergo resolution (Anosa, 1988) leading to self-recovery as commonly encountered in trypanotolerant wildlife (Mbaya et al. 2009a).

3. The mechanism of anaemia in trypanosomosis

The interplay of several factors acting either individually or synergistically contributes to the development of haemolytic anaemia in human and animal trypanosomosis (Figure 1).
Most common among these factors are erythrocyte injury caused by lashing action of trypanosome flagella, undulating pyrexia, platelet aggregation, toxins and metabolites from trypanosomes, lipid peroxidation and malnutrition (Murray & Morrison, 1978; Morrison et al., 1981; Saror, 1982; Igbokwe, 1994). Meanwhile, idiopathic (unknown) serum and tumor necrosing factors are responsible for dyserythropoieses (Mabbot & Sternberg, 1995; Lieu & Turner, 1999; Maclean et al., 2001).

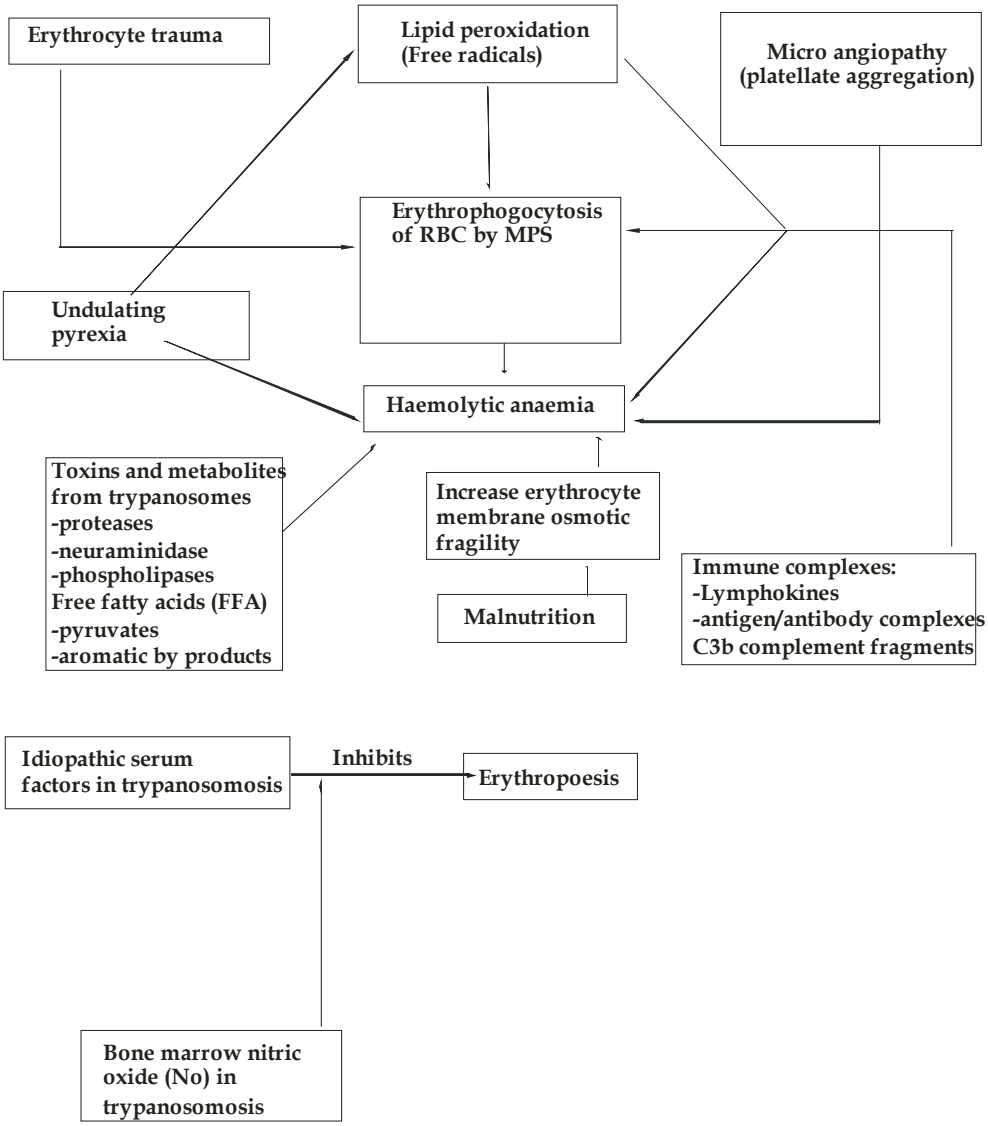


Fig. 1. Pathophysiology of anaemia in African trypanosomosis, Source by Dr. A.W. Mbaya.

4. Anaemia through mechanical injury to erythrocytes

Anaemia caused by mechanical injury to erythrocyte occurs by the lashing action of the powerful locomotory flagella and microtubule reinforced bodies of the millions of the organisms during parasitaemia (Vickerman & Tetley, 1978). Erythrocyte membrane damage has also been associated with adhesion of erythrocytes, platelets and reticulocytes to trypanosome surfaces via sialic acid receptors leading to damages to erythrocyte cell

membranes (Bungener & Muller, 1976; Banks, 1980; Anosa & Kaneko, 1983; Shehu et al., 2006). As such, several areas of discontinuity occur along the surface of erythrocyte membranes where they adhere to the trypanosomes. Mechanical damage to vascular endothelium has been reported when tissue-invading trypanosomes such as the *T. brucei* group penetrate tissues via the interstices (Anosa & Kaneko, 1983).

5. Anaemia through undulating pyrexia

In trypanosomosis, a direct relationship exists between undulating pyrexia and fluctuating parasitaemia (Nwosu & Ikeme, 1992; Igbokwe, 1994; Mbaya et al., 2009a, e). Under laboratory conditions, Karle (1974) exposed erythrocytes to temperatures above the normal body temperature and found out that the osmotic fragility and permeability of erythrocytes were greatly enhanced. It was also reported that increased body temperatures decreased erythrocyte plasticity and longevity *in-vivo* (Woodruff et al., 1972). Consequently, temperature elevation increased the rate of immunochemical reactions thereby initiating lipid peroxidation of erythrocytes (Igbokwe, 1994).

6. Anaemia through platelet aggregation (microangiopathy)

Intact trypanosomes or fragments of trypanosomes may cause platelet aggregation commonly called microangiopathy (Davies et al., 1974). This can lead to the release of platelet autoantibodies that in turn releases procoagulants and thereby causing fibrin deposits. Subsequently microthrombi formation or disseminated intravascular coagulation occurs (Igbokwe, 1994). During trypanosomosis, erythrocytes with weak cell membranes become fragmented and lyse as they squeeze through the fibrin deposits of the microthrombi (Anosa & Kaneko, 1983; Murray & Dexter, 1988). Disseminated intravascular coagulation has been reported in *T. b. gambiense* infection of the baboon (*Papio anubis*) (Mbaya et al., 2009b), *T. vivax* infection of cattle (Isoun and Esuroroso, 1972) and in goats (Vanden Inh et al., 1976; Anosa & Isoun, 1983).

7. Anaemia caused by trypanosome toxins and metabolites

Living and dead trypanosomes can produce various forms of active chemical substances, which can elicit erythrocyte injury (Tizzard & Holmes, 1976; 1977; Tizzard et al, 1977; 1978a, b, c; Zwart & Veenendal, 1978; Naessens et al., 2005). Common among these chemical substances are proteases, neuraminidase, phospholipase, free fatty acids, pyruvates and aromatic by-products. Neuraminidase has been generated *in-vitro* by *T. vivax* during periods of parasitaemia, making erythrocytes prone to phagocytosis (Esievo, 1979; 1983). One of the factors that make erythrocytes prone to phagocytosis by the expanded mononuclear phagocytic system (MPS) during trypanosomosis is associated with the activity of neuraminidase. This enzyme cleaves off sialic acids on the surface of erythrocytes and thereby disabling them (Verma & Gautam, 1978; Igbokwe, 1994; Adamu et al., 2009) and by damaging erythropoietin (Igbokwe et al., 1989).

Trypanosomes are capable of releasing proteolytic lysosomal enzymes (proteases) from pockets on their flagella and from damaged or dead trypanosomes (Vickermon & Tetley, 1978; Rautenberg et al., 1982; Londsdale-Eccles & Grab, 1986; Igbokwe, 1994). The enzyme, when released into the general circulation is capable of damaging erythrocytes and vascular

endothelium by cleaving sialic acid fractions from the cell membrane in the form of glycopeptides (Cook et al., 1966). It was also reported that aromatic amino acids could be metabolized by trypanosome to produce toxic by–products, which acts directly on the erythrocyte cell membrane to cause osmotic fragility and lyses (Igbokwe, 1994). Similarly, phenylalanine could be catabolized to phenylpyruvate, which is proteolytic in nature and inhibitory to mitochondrial gluconeogenesis (Igbokwe, 1994). Tryptophan can also be broken down during trypanosomosis to indole-ethanol, which damages erythrocyte cell membranes (Igbokwe, 1994).

8. Lipid peroxidation

The mechanism of aneamia in trypanosomosis is greatly associated with the generation of free radicals and super oxides following lipid peroxidation. These oxidative products generally attack the cellular integrity of erythrocytes during trypanosomosis (Anosa & Kaneko, 1983; Igbokwe, 1994; Umar et al., 2007). They also particularly attack erythrocyte membrane polyunsaturated fatty acids and proteins (Slater, 1984) or red blood cells directly leading to oxidative haemolysis (Ameh, 1984; Igbokwe, et al., 1989; Umar et al., 2007). Sialic acids consist of about four derivatives of nine-carbon sugar neuraminic acids (Varki, 1992; Schauer & Kamerling, 1997). It was therefore concluded that anaemia in trypanosomosis might occur due to erythrophagocytosis (Holmes & Jennings, 1976) and may be associated with the formation of antigen-antibody complexes with sialic acids (Audu et al., 1999).

Esievo et al. (1982) pointed out that trypanosomosis may cause a deficit in the systematic antioxidant capacity of the infected host. This has been demonstrated in acute *T. b. gambiense* infection in rats (Ameh, 1984), *T. evansi* (Wolkmer et al., 2009) and in *T. brucei* infected mice (Igbokwe et al., 1989), where erythrocytes were susceptible to free radical-damage following hydrogen peroxidation. This process in mice led to enhanced oxidative haemolysis. Peroxidation caused the erythrocytes to produce large quantities of lipid peroxidation by-products. This is suggestive therefore that erythrocytes of the infected animals possessed decreased antioxidant ability, leading to its inability to withstand oxidative stress (Igbokwe, 1994). *Trypanosoma vivax* produced neuraminidase enzyme, which had a direct relationship with parasitaemia. It was therefore concluded that neuraminidase produced by trypanosomes *in-vivo,* cleaved off erythrocyte surface sialic acid, making the red cells prone to phagocytosis. Similarly, Nok and Balogun (2003) showed a progressive increase in the level of serum sialic acid corresponding with anaemia and parasitaemia in *T. congolense* infected mice. *Trypanosoma vivax* was observed to be highly erythrogenic in mice, which was probably associated with depressed erythropoietin activity following the cleaving of sialic acid fragments (Igbokwe et al., 1989). It has also been reported that glycolysis in trypanosomosis leads to the accumulation of pyruvate *in-vivo* as parasitaemia increases (Grant & Fulton, 1957; Coleman et al., 1957).

A ten-fold increase of pyruvate has been observed in *T. brucei* infected rabbits (Goodwin & Guy, 1973). In as much as the influence of pyruvate is debatable, it may not reach toxic levels in the blood during trypanosomosis (Igbokwe, 1994) however, Newton (1978) suggested that pyruvate might lead to acidosis and a lowered affinity of haemoglobulin for oxygen. It also inhibited the tricarboxylic acid cycle (TCA) in human mitochondria during *T. b. gambiense* infection (Seed & Hall, 1985). After death and autolysis, trypanosomosis releases large quantities of phospholipase A1 and lysophospholipase A1 (Tizard et al., 1978c). These chemical substances can cause erythrocyte degradation, damage to vascular

endothelial cells and haemolysis (Colley et al., 1973). Phospholipase A1 was demonstrated in extreme proportions *in-vitro* in tissue fluids and less in plasma of rabbits infected with *T. brucei* (Hambrey et al., 1980). Tizard et al. (1978a, c) observed that phospholipase released free fatty acids (FFA) from phosphatidylcholine *in-vivo*. Most common of them were palmitic, stearic and linoleic acids (Tizard & Holmes, 1977).
Tizard et al. (1978b) reported that linoleic acid possessed a detergent - like activity, which produced severe haemolysis and cytotoxicity *in-vitro*. It was however believed that free fatty acids are easily bound by albumin and may not cause haemolysis *in-vivo*. The author however pointed out that during high parasitaemia in *T. congolense* infection, the FFA released exceeded the binding capacity of albumin and thereby leading to cytotoxicity and haemolysis. Similarly, it was reported that even the albumin bound FFA may cause haemolysis due to the activities of its oxidized products. Nok et al. (1992a, b) reported that trypanosomes could cause certain alterations that invariably affected erythrocyte membrane fluidity hence a decrease in erythrocyte membrane-bound enzymes (NoK-ATpase and CaMg-ATpase). Lipid peroxidation of membranes has been associated with decrease in membranes fluidity and in the activities of membrane-bound enzyme (McCay & King, 1980; Slater, 1984; Igbokwe, 1994). It was however suggested that a comprehensive study in ruminants is needed to highlight the extent of anti-oxidant deficiency and the degree of susceptibility of red cells to oxidative damage during trypanosomosis (Igbokwe, 1994).

9. Idiopathic serum factors

In trypanosomosis, an unknown (idiopathic) serum factor, not of a trypanosome origin but a heat stable-protein has been demonstrated to inhibit activities of erythropoiesis (Kaaya et al., 1979; 1980). It was however reported that serum from cattle infected with *T. congolense* and *T. vivax* did not depress colonies of erythrocytes *in-vitro*. However, an unknown serum factor entirely different from those reported by Kaaya et al. (1979; 1980) had effect on an erythroid colony (Igbokwe et al., 1989).

10. Immune complexes

Immunological mechanisms in trypanosomosis have been advanced as a major reason for the removal of erythro autolologous immunoglobulin (IgM and IgG) antibodies and complement (C3) on the surface of red cells (Kobayashi et al., 1976; Facer et al., 1982; Assoku & Gardiner, 1992; Naessens et al., 2005). The mechanism suggested that autoantibodies appeared after the first peak of parasitaemia that correlated with the decline in packed cell volume (PCV). Red cell surfaces may bind auto or poly reactive antibodies, or may be sensitized by absorption of immune complexes (Naessens et al., 2005). Alternatively, erythrocytes may passively absorb trypanosome molecules followed by binding of antitrypanosome antibodies with subsequent removal from the system (Rifkin & Lansberger, 1990; Naessens et al., 2005). Although Naessen et al. (2005) reported that immunological competence is not essential for the development of anaemia, irradiated rats still became anaemic after *T. brucei* infection (Murray & Dexter, 1988) and when cattle were depleted of T-cells. The authors also reported that specific, non-specific antibody production was drastically reduced, delayed, and at the same time, anaemia was consistent. Several authors (Ikede & Losos, 1972; Mackenzie & Cruickshank, 1973; Mackenzie et al., 1978; Anosa & Isoun, 1983; Igbokwe, 1994) reported an overwhelming proliferation of tissue macrophages during trypanosomosis.

The activation of macrophages was through lymphokines, antigen-antibody complexes and C3b complement fragments (Woo & Kobayashi, 1975; Allison, 1978). It was suggested therefore, that cytokines mediated loss of erythrocytes in trypanosomosis (Naessens et al., 2005). Similarly, strong evidence suggested that anaemia in trypanosomosis was mediated by TNF-a, IFN gamma and other inflammatory cytokines (Jelkmann, 1998). However, in more recent studies (Nemeth et al., 2004) suggested that anaemia in trypanosomosis involving hypofferaemia was caused by IL-6 and hepeidin. Although Naessens et al. (2005) concluded that this is unlikely to cause anaemia in trypanosomosis, some weak evidence of the role of THF-a-in the severity of anaemia in trypanosome-infected cattle (Silegham et al., 1994), mice infected with *T. brucei* (Magez et al., 1999) and in *T. brucei gambiense* infected mice (Naesens et al., 2005) was documented.

11. Malnutrition

Trypanosomosis may cause a drop in feed intake hence there is energy deficit and loss of tissue associated with catabolism of body fat, deficiencies of vitamin C, B and essential amino acids (Igbokwe, 1994). Inadequate energy supply to erythrocytes may alter the erythrocyte membrane surface therefore leading to weakening of the cell membrane, increased osmotic fragility and haemolysis (Jennings, 1976).

12. Tumor necrosis factor/Bone marrow nitric oxide (NO)

It has been reported that tumor necrosis factor (TNF) production by monocytes from cattle infected with *Trypanosoma* (*Duttonella*) *vivax* and *T*. (*Nannomonas*) *congolense*, was found to play in concert in the severity of anaemia associated with trypanosomosis (Sileghem et al., 1994). Bone marrow cell population from *T. brucei* infected mice exhibited levels of bone marrow nitric oxide production. This was found to coincide with suppressed bone marrow T-cell proliferation in response to stimulation with mitogen concanavalin *in-vivo* and *in-vitro*. It was therefore concluded that nitric oxide might inhibit proliferation of haemopoitic precursors leading to anaemia in trypanosomosis (Mabbot & Sternberg, 1995; Liew & Turner, 1999). A similar synthesis of nitric oxide and cytokines leading to anaemia in human trypanosomosis has been reported (MacLean et al., 2001).

13. Conclusion

The mechanism of anaemia in trypanosomosis was caused mainly by extra vascular haemolysis in the expanded active mononuclear phagocytic system of the host. This was followed by a drastic reduction of all red blood cell indices during successive waves of parasitaemia. The pattern of anaemia varied, depending on whether the specie of trypanosome was “humoral” or “haemic”. Although the mechanism of anaemia is complex and multifactorial, it primarily compromised the cellular integrity of erythrocytes leading to either haemolytic anaemia or enhanced erythrophagocytosis. Injuries sustained by red blood cell (RBC) membranes caused by the flagella and microtubule reinforced body of the organisms greatly enhanced erythrophagocyosis of damaged RBC by the MPS. Similarly, erythrocytes, reticulocytes and platelets that adhered to trypanosomes via sialic acid receptors, caused injuries to erythrocyte membrane at the point of contact. Other factors that promoted haemolytic anaemia in trypanosomosis were trypanosome autolysates,

immunochemical reactions, platelet aggregation, undulating pyrexia, oxidative stress, lipid peroxidation, nutritional and hormonal imbalances, disseminated intravascular coagulation, idiopathic and tumor necrosis factors (TNF) and bone marrow nitric oxide (NO) activity.

14. Acknowledgement

The authors highly appreciate the efforts of Professor I.O. Igbokwe in providing some of the literature used in this chapter.

15. References

Abenga. J.N. & Anosa, V.O. (2006). Clinical studies on experimental Gambian trypanosomosis in vervet monkeys, *Veternarski Arhiv* 76(1): (February 2008), 11-18, ISSN 0372-5480

Adamu, S., Maashin Useh, N., Ibrahim, D.N., Nok, A.J. & Esievo, K.A.N. (2009). Erythrocyte surface sialic acid depletion as predisposing factor to erythrocyte destruction in sheep experimental model of African trypanosomosis: A preliminary Report, *Slovenian Veterinary Research* 46(1): (March 2009), 19-28, ISSN 1580-4003

Allison, A.C. (1978). Mechanisms by which activated macrophages inhibit lymphocyte responses, *Immunology Review* 40: (June 1979), 23-27, ISSN 1550-6606

Ameh, D.A. (1984). Depletion of reduced glutathione and the susceptibility of erythrocytes to oxidative haemolysis in rats infected with *Trypanosoma brucei gambiense*, *Parasitology and Infectious Disease* 12: (March 2008), 130-139, ISSN 1996-0778

Anosa, V.O. (1977). *Studies on the Mechanism of Anaemia and the Pathology of Experimental Trypanosoma vivax (Zieman, 1905) Infection in Sheep and Goats.* PhD Thesis, University of Ibadan, Ibadan, Nigeria

Anosa, V.O. (1988). Haematological and biochemical changes in human and animal trypanosomosis, Parts I & II, *Revue d' Elevage et de Medicine Ve'te'rinaire des pays Tropicaux* 41(2): (June 1988), 65-78, ISSN 151-164

Anosa, V.O. & Isoun, T.T. (1980). Haematological studies on *Trypanosoma vivax* infection of goats and splenectomized sheep, *Journal of Comparative Pathology* 90 (4): (November 1980), 153-168, ISSN 1695-7504

Anosa, V.O. & Isoun, T.T. (1983). Pathology of experimental *Trypanosoma vivax* infection in sheep and goats, *Zentraiblatt fur veterinarmedizin* 30 (1): (November 1983), 685-700, ISSN 0721-1856

Anosa, V.O. & Kaneko, J.J. (1983). Pathogenesis of *Trypanosoma brucei* infection in deer mice (*Peromyscus maniculatus*), Light and electron microscopic studies on erythrocyte pathologic changes and phagocytosis, *American Journal of Veterinary Research* 44 (4): (August 1983) 645-651, ISSN 0002- 9645

Assoku, R.K.G. & Gardiner, P.R. (1992). Detection of antibodies to platelets and erythrocytes during haemorrhagic *Trypanosoma vivax* infection of Ayrshire cattle, *Veterinary Parasitology* 31(2): (April 2009) 199-216, ISSN 1932-6203

Audu, P.A., Esievo, K.A.N., Mohammed, G. & Ajanusi, O.J. (1999). Studies of infectivity and pathogenicity of an isolate of *Trypanosoma evansi* in Yankasa sheep, *Veterinary Parasitology* 86 (4): (October 1999) 185-190, ISSN 0304-4017

Banks, K.L. (1980). Injury induced by *Trypanosoma congolense* adhesions to cell membranes, *Journal of Parasitology* 6(1): (October 1980) 34-37, ISSN 0002-9645

Barret-Connor, E., Ugoretz, J.R. & Braude, A.I. (1973). Disseminated intravascular coagulation in trypanosomiasis, *Archives of Internal Medicine* 131(4): (April 1973) 574-577, ISSN 0003-9926

Bungener, W. & Muller, G. (1976). Adharenz phanomene bei *Trypanosoma congolense* [Adgerence phenomena in *Trypanosoma congolense*], *Tropenmedizin und parasitologie* 27 (2): (September 1976) 370-371, ISSN 0303-4208

Coleman, R.M., Brand, T. & von (1957). Blood pyruvate levels of rats during haematophagus infections, *Journal of Parasitology* 43 (1): (June 1957) 263-270, ISSN 0022-3395

Colley, C.M., Zwaal, R.F.A., Roeofsen, B. & Decssen, L.L.M. van (1973). Lytic and non-lytic degradation of phospholipids in mammalian erythrocytes by pure phospholipase, *Biochimica et Biophsica Acta* 307(1): (April 1973) 74-82, ISSN 0006-3002

Cook, G.M.W., Heard, D.H. & Seaman, G.V.F. (1966). A sialomuscopeptide liberated by trypsin from the human erythrocyte, Nature (*London*) 188 (1): (August 1967) 1011-1012, ISSN 1523-1747

Davies, C.E., Robins, R.S., Weller, R.D. & Broude, A.I. (1974). Thrombocytopenia in experimental trypanosomiasis, *Journal of Clinical Investigation* 53(1): (June 1974) 1359-1367, ISSN 1558-8238

Edwards, E.E., Judd, J.M. & Squire, F.A. (1956). Observations on trypanosomiasis in domestic animals in West Africa II, The effect on erythrocyte sedimentation rate, plasma protein, bilirubin, blood sugar, osmotic fragility, body weight and temperature in goats and sheep infected with *Trypanosoma vivax, T. congolense* and *T. brucei*, *Annals of Tropical Medicine and Parasitology* 50(2): (December 1957) 242-251, ISSN 0003-4983

Esievo, K.A.N. (1979). *In-vitro* production of neuraminidase (sialidase) by *Trypanosoma vivax*, *Proceedings of the 16th meeting of the International Scientific Council for Trypanosomiasis. Nairobi, Kenya: Organization of African Unity, Scientific, Technical and Research and Control*, pp. 205-210, ISSN 0372-5480, Yaoundé, Cameroon, August 24-29, 1978

Esievo, K.A.N. (1983). *Trypanosoma vivax*, stock V 953: inhibitory effect of type A influenza virus anti HAV8 serum on *in-vitro* neuraminidase (sialidase) activity, *Journal of Parasitology* 69(1): (December 1983) 491-495, ISSN 0022-3395

Esievo, K.A.N., Saror, D.I., Ilemobade, A.A. & Hallaway, M.H. (1982). Variation in erythrocyte surface and free serum sialic acid concentrations during experimental *Trypanosoma vivax* infection in cattle, *Research in Veterinary Science* 32 (2): (January 1982) 1-5, ISSN 0034-5288

Facer, C.A., Crosskey, J.M., Clarkson, M.J. & Jenkins, G.C. (1982). Immune haemolytic anaemia in bovine trypanosomiasis, *Journal of Comparative Pathology* 92(1): (October 1973) 293-401, ISSN 0721-1856

Goodwin, L.G. & Guy, M.W. (1973). Tissue fluids in rabbits infected with *Trypanosoma* (*Trypanozoon*) *brucei*, *Parasitology* 66 (1): (September, 1973) 499-513, ISSN 0031-1820

Grant, P.T. & Fulton, J.D. (1957). The catabolism of glucose by strains of *Trypanosoma rhodesiense*, *Biochemical Journal* 66 (2): (October 1957) 242-243, ISSN 0264-6021

Hambry, P.N., Tizard, I.R. & Mellors, A. (1980). Accumulation of phospholipase A1 in tissue fluid of rabbits infected with *Trypanosoma brucei*, *Tropen medizin und parasitologie* 31(1): (December 1980) 439-443, ISSN 0303-4208

Holmes, P.H. & Jennings, F.W. (1976). *Pathogenicity of parasitic infections*, Academic Press New York, ISBN 0372-5480, New York, USA

Igbokwe, I.O., Obagaiye, I.K., Esievo, K.A.N. & Saror, D.I. (1989). Dyserythropoesis in animal trypanosomiasis, *Revue d'Elavage et de Medicine veterinaire des pays Tropicaux* 42(4): (November 1990) 423-429, ISSN 0035-1865

Igbokwe, I.O. (1994). Mechanisms of cellular injury in African trypanosomiasis, *Veterinary Bulletin* 64(7): (March 1994), 611-620, ISSN 1684-5315

Ikede, B.O. & Losos, G.K. (1972). Pathology of the disease in sheep produced experimentally by *Trypanosoma brucei*, *Veterinary Pathology* 9(2): (July 1972) 278-289, ISSN 0300-9858

Isoun, T.T. & Esuruoso, G.O. (1972). Pathology of natural infection of *Trypanosoma vivax* in cattle, *Nigerian Veterinary Journal* 1(2): (September 1972), 42-45, ISSN 0721-1856

Jelkmann, W. (1998). Proinflamatory cytokines lowering erythropoietin production, *Journal of Interferon Cytokine Research* 18(2): (March 1998), 555-559, ISSN 0022-3751

Jennings, F.W. (1976). The anaemia of parasitic infections, *Proceedings of the 7th International Conference of the World Association for the Advancement of Veterinary Parasitology*, pp. 41-67, ISBN 0-12655 365- 3, Thessalonica, Greece, October 15-19, 1975

Kaaya, G.P., Valli, V.F., Maxie, M.G. & Losos, G.J. (1979). Inhibition of bovine granulocyte/macrophage colony formation *in-vitro* by serum collected from cattle infected with *Trypanosoma vivax* or *T. congolense*, *Tropen medizin und parasitologie* 30(2): (June 1979), 230- 235, ISSN 0303-4208

Kaaya, G.P., Tizard, I.R., Maxie, M.G. & Vall, V.O. (1980). Inhibition of leucopoiesis by sera from *Trypanosoma congolense* infected calves, partial characterization of the inhibitory factor, *Tropen medizin und parasitologie* 30(1): (June 1980), 230-235, ISSN 0303-4208

Karle, H. (1974). The pathogenesis of the anaemia of chronic disorders and the role of fever in erythrogenesis, *Scandinavian Journal of Haematology*, 13 (1): (October 1974), 81-86, ISSN 0036- 5534

Kobayashi, A., Tizard, I.R. & Woo, P.T.K. (1976). Studies on the anaemia in experimental African trypanosomiasis II. The pathogenesis of the anaemia in calves infected with *Trypanosoma congolense*, *American Journal of Tropical Medicine and Hygiene* 25(1): (May 1976), 401-406, ISSN 0002-9637

Liew, F.Y. & Turner, C.M.R. (1999). T. cell responses during *Trypanosoma brucei* infections in mice deficient in inducible nitric oxide synthase, Infection *and Immunology* 67(1): (May 1999), 3334- 3338, ISSN 0022-1767

Lonsdale-Eccles, J.D. & Grab, D.J. (1986). Proteases in African trypanosomes. In: Cytokine proteinases and their inhibitors, V.J. Turk, (Ed.), 189-197, Walter de Grayter, Berlin, Germany

MacLean, L., Odiit, M., & Sternberg, J.M. (2001). Nitric oxide and cytokine synthesis in human African trypanosomiasis, *The Journal of Infectious Disease* 184(4): (July 2001), 1086-1090, ISSN 0022-1899

Mackenzie, P.K.I. & Cruickshank, J.G. (1973). Phagocytosis of erythrocytes and leucocytes in sheep infected with *Trypanosoma congolense* (Broden, 1904), *Research in Veterinary Sciences* 15(1): (February 1973), 256-262, ISSN 0034-5288

Mackenzie, P.K.I., Boyt, W.P., Nesham, V.W. & Pirie, E. (1978). The etiology and significance of the phagocytosis of erythrocytes in sheep infected with *Trypanosoma congolense* (Broden, 1904), *Research in Veterinary Sciences* 24 (1): (April 1978), 4-7, ISSN 0034-5288

Mabbot, N. & Sternberg, J. (1995). Bone marrow nitric oxide production and development of anaemia in *Trypanosoma brucei* infected mice, *Infection and Immunology* 63(4): (June 1995), 1563-1566, ISSN 1098-5522

Magez, S., Radwanaska, M., Beschin, A., Sekikawa, K. & Debaetselier, P. (1999). Tumor necrosis factor alpha is a key mediator in the regulation of experimental *Trypanosoma brucei* infections, *Infection and Immunology* 67(5): (June 1999), 3128-3132, ISSN 1098-5522

Maxie, M.G. & Losos, G.J. (1979). Release of *Trypanosoma vivax* from the microcirculation of cattle by Berenil®, *Veterinary Parasitology* 3: (June 1979), 277-281, ISSN 0019-9867

McCay, P.B. & King, M.M. (1980). Endogenous sources of free radicals, In: Basic and Clinical Nutrition and development of anaemia in *Trypanosoma brucei* infected mice, L.J. Machlin, (Ed.), 269-303, Marcel Decker Inc, New York, USA

Mbaya, A.W., Nwosu, C.O. & Onyeyili, P.A. (2007). Toxicity and anti-trypanosomal effects of ethanolic extract of *Butyrospermum paradoxum* (*Sapotacea*) stem bark in rats infected with *Trypanosoma brucei* and *T. congolence*, *Journal of Ethnopharmacology* 111: (May 2007), 536-530, ISSN 0378-8741

Mbaya, A.W., Aliyu, M.M., Nwosu, C.O., Taiwo, V.O. & Ibrahim, U.I. (2009a). Effects of melarsamine hydrochloride (Cymelarsan®) and diaminazene aceturate (Berenil®) on the pathology of experimental *Trypanosoma brucei* infection in red fronted gazelles (*Gazella rufifrons*), *Veterinary Parasitology*, 163 (1-2): (July 2009), 140-143, ISSN 0304-4071

Mbaya, A.W., Aliyu, M.M., Nwosu, C.O. & Taiwo, V.O. (2009b). An assessment of the efficacy of DFMO in baboons (*Papio anubis*) infected with *Trypanosoma brucei gambiense*, *Global Journal of Pure and Applied Sciences*, 15 (1): (September 2009), 69-78, ISSN 1118-0579

Mbaya, A.W., Aliyu, M.M., Nwosu, C.O. & Ibrahim, U.I. (2009c). Effect of DL-α-difluoromethylornithine on biochemical changes in baboons (*Papio anubis*) experimentally infected with *Trypanosoma brucei gambiense*, *Nigerian Veterinary Journal*, 30(1): (September 2009), 35-44, ISSN 0331-3026

Mbaya, A.W., Aliyu, M.M. & Ibrahim, U.I. (2009d). Clinico-pathology and mechanisms of trypanosomosis in captive and free-living wild animals: A review, *Veterinary Research Communications,* 33: (April 2009), 793 – 809, ISSN 1573-7446

Mbaya, A.W., Aliyu, M.M., Nwosu, C.O. & Egbe-Nwiyi, T.N.C. (2009e). The relationship between parasitaemia and anaemia in a concurrent *Trypanosoma brucei* and *Haemonchus contortus* infection in red fronted gazelles (*Gazella rufifrons*), *Veterenarski Arhiv*, 79 (5): (September 2009), 451-460, ISSN 03720-5480

Mbaya, A.W., Ibrahim, U.I. & Apagu, S. T. (2010). Trypanosomosis of the dromedary camel (*Camelus dromedarius)* and its vectors in the tsetse-free arid zone of northeastern, Nigeria, *Nigerian Veterinary Journal*, 31(3): (September 2010), 195-200, ISSN 0331-3026

Mbaya, A.W. & U.I. Ibrahim (2011). *In-vivo* and *in-vitro* activities of medicinal plants on haemic and humoral trypanosomes: A review, *International Journal of Pharmacology*, 7(1): (January 2011), 1- 11, ISSN 1812-5700

Mbaya, A. W. Nwosu, C. O. & Kumshe, H. A. (2011). Genital lesions in male red fronted gazelles (*Gazella rufifrons*) experimentally infected with *Trypanosoma brucei* and the effect of melarsamine hydrochloride (Cymelarsan®) and diminazene aceturate

(Berenil®) in their treatment. *Theriogenology,* 16: (May 2011) 721-728, ISSN 1879-3231

Morrison, W.I., Max Murray, Sayer, P.D. & Preston, J.M. (1981). The pathogenesis of experimentally induced *Trypanosoma brucei* infection in the dog, Tissue and organ damage, *American Journal of Pathology* 102: (September 1981), 168-181, ISSN 0001-5598

Murray, M. & Dexter, T.M. (1988). Anaemia in bovine African trypanosomiasis: A review, *Acta Tropica* 45: (December 1988), 389-432, ISSN 0001-706X

Murray, M. & Morrison, W.I. (1978). Parasitaemia and host susceptibility in African trypanosomiasis, *Proceedings of a workshop,* pp.*71*`-81, ISBN 0-088936-214—9, *Nairobi, Kenya*, Nov. 20-23, 1978

Naessens, J., Kitani, H., Yagi, Y., Sekikawa, K., Iraqqi, F. (2005). TNF-a mediates the development of anaemia in a murine *Trypanosoma brucei rhodesiense* infection, but not the anaemia associated with a murine *T. congolense* infection, Clinical and Experimental Immunology 139(3): (March 2005), 403-410, PMID: PMC 180 9320

Nazrul-Islam, A.K.M. & Woo, P.T.K. (1991). Anaemia and its mechanism in goldfish (*Carassius auratus*) infected with *Trypanosoma danilewsky*, *Disease of Aquatic Organisms* (11): (November 1991), 37- 43, ISSN 0177-5103

Nemeth, E., Rivera, S., Gabayan, V., Keller, C., Taudorf, S., Pedersen, B.K. & Ganz, T. (2004). IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin, *Journal of Clinical Investigation* 113: (May 2005), 1271-1276, ISSN 0021- 9738

Newton, B.A. (1978). The metabolism of African trypanosomiasis in relation to pathogenic mechanisms, In: *Pathogenicity of trypanosomes*, G. Losos, A. Chouinard, (Eds.), pp. 17-22, ISBN 0-88936-214-9 Proceedings of a workshop, Nairobi Kenya, November 20-23, 1977

Nwosu, C.O. & Ikeme, M.M. (1992). Parasitaemia and clinical manifestations in *Trypanosoma brucei* infected dogs, *Revue d'Elavage et de Medicine veterinaire des pays Tropicaux* 45(3-4): (September 1992), 273-277, ISSN 0035-1865

Nok, A.J. & Balogun, E.O. (2003). A blood stream *Trypanosoma congolense* sialidase could be involved in anaemia during experimental trypanosomiasis, *The Journal of Biochemistry* 133(6): (June 2003), 725-730, ISSN 1756-2651

Nok, A.J., Esievo, K.A.N., Ukoha, A.I., Ikediobi, C.O., Baba, J., Tekdek, B. & Ndams, I.S. (1992a). Kidney NaK-ATPase: kinetic study of rats during chronic infection with *Trypanosoma congolense*, *Journal of Clinical Biochemistry and Nutrition* 13: (September 1992), 73-79, ISSN 0912- 0009

Nok, A.J., Esievo, K.A.N., Ajibike, M.O., Achoba, I.I., Tekdek, K., Gimba, C.E., Kagbu, J.A. & Ndams, I.S. (1992b). Modulation of the calcium pump of the kidney and testes of rats infected with *Trypanosoma congolense*, *Journal of Comparative Pathology*, 107: (July 1992), 119-123, ISSN 0021- 9975

Ogwu, D., Njoku, C.O. & Ogbogu, V.C. (1992). Adrenal and thyroid dysfunction in experimental *Trypanosoma congolense* infection in cattle, *Veterinary Parasitology* 42: (April 1992), 15-26, ISSN 0304-4017

Rabo, J.S. (1995). Toxicity studies and trypanosuppressive effects of stem bark extract of *Butyrospermum paradoxum* in laboratory animals, PhD Thesis, University of Maiduguri, Maiduguri, Nigeria

Rautenberg, P., Schedler, R., Reinwalde, E. & Risse, H.J. (1982). Study on a proteolytic enzyme from *Trypanosoma congolense*, Purification and some biochemical properties, Molecular and some biochemical properties, *Molecular and Cellular Biochemistry* 47: (September 1982), 151-159, ISSN 0300-8177

Rifkin, M.R. & Landsberger, F.R. (1990). Trypanosome variant surface glycoprotein transfer to target membranes: A model for the pathogenesis of trypanosomiasis, *Proceedings of the National Academy of Science,* pp. 801-806, ISSN 0027-8424, May 23-27 USA, 1990

Saror, D.I. (1982). Aspects of the anaemia of acute bovine trypanosomiasis, *Proceedings of the first National Conference on Tsetse and Trypanosomiasis Research*, pp. 12-14, ISSN 0049-4747, August 10-12, Kaduna, Nigeria, 1981

Schauer, R. & Kamerling, J.P. (1997). Chemistry, biochemistry and biology of sialic acid. In: *Glycoptroteins*, J. Montrevil, J. .F. G. Vigenther & H. Shachter (Eds.) 241-400, Elsevier, ISBN 0- 444-80303-3, Amsterdam, The Netherlands

Seed, J.R. and Hall, J.E. (1985). Pathophysiology of African trypanosomiasis. In: *Immunology and pathogenesis of trypanosomiasis,* I.J. Tizard (Ed.), CRC Press, ISBN 0-8493-5640-7, Boca Raton, Florida, USA

Shehu, S.A., Ibrahim, N.D.G., Esievo, K.A.N. & Mohammed, G. (2006). Role of erythrocyte surface sialic acid inducing anaemia in Savannah Brown bucks experimentally infected with *Trypanosoma evansi, Veterenarski Arhiv* 26(6): (October 2006), 521-530, ISSN 0372-5480

Sileghem, M., Flynn, J.N., Logan-Henfrey, L. & Ellis, J. (1994). Tumour necrosis factor production by monocytes from cattle infected with *Trypanosoma* (*Dutonella*) *vivax* and *T.* (*nannomonas*) *congolense*, Possible association with severity of anaemia associated with the disease, *Parasite Immunoassay*, 16(1): (January, 1994), 51-54, ISSN 0141-9838

Slater, T.F. (1984). Free radical mechanism in tissue injury, *Biochemistry Journal* 222: (August 1984), 1-15, ISSN 0264-6021

Solano, P., Dela Roqoes, S. & Duvalet, G. (2003). Biodiversity of trypanosomes pathogenic for cattle and their epidemiological importance, *Annals of Society* 68: 169 – 171.

Soulsby, E.J.L. (1982). *Helminthes, Arthropods and Protozoa parasites of domesticated Animals*, Bailere Tindal, ISBN 0702008206 9780702008207, London

Swallow, B.M. (2000): Impacts of trypanosomosis in African agriculture, Programme against African Trypanosomosis Technical and Scientific series, Food Agriculture Organization (F. A. O.) 2: (April 2000), 45 – 46, ISSN 1020-7163

Tizard, I.R. & Holmes, W.L. (1976). The generation of toxic activity from *Trypanosoma congolense*, *Experentia* 32: (May 1977), 1533-1534, 0014-4754

Tizard, I.R. & Holmes, W.L. (1977). The release of suitable vasoactive material from *Trypanosoma congolense* intraperitoneal diffusion chambers, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 71: (June 1977), 52-55, ISSN 0035-9203

Tizard, I.R., Holmes, W.L., Yorke, D.A. & Mellors, A. (1977). The generation and identification of haemolysin of *Trypanosoma congolense*, *Experintia* 33: (July, 1977), 901-902, ISSN 0014-4754

Tizard, I.R., Holmes, W.L. & Nielsen, K. H. (1978a). Mechanisms of anaemia in trypanosomiasis: Studies on the role of haemolytic fatty acids derived from

Trypanosoma congolense, *Tropen medizin und parasitologie* 29: (March, 1978), 108-114, ISSN 0303-4208

Tizard, I.R., Nielsen, K. H., Mellors, A. & Assoku, R.K.G. (1978b). Biologically active lipids generated by autolysis of *Trypanosoma congolense*. In: *Pathogenecity of Trypanosomes. Proceedings of a workshop*, pp. 103-110, ISBN 0-88936-214-9, Nairobi, Kenya, November 20-23, 1978

Tizard, I.R., Sheppard, J. & Nielsen, K. (1978c). The characterization of a second class of haemolysin from *Trypanosoma brucei*, *Transactions of the Royal Society of Tropical Mediciene and Hygiene* 72: (July 1978), 198-2000, ISSSN 0035-9203

Umar, I.A., Ogenyi, E., Okodaso, D., Kimeng, E., Stanecheva, G.I., Omage, J.J., Isah, S. & Ibrahim, M.A. (2007). Amelioration of anaemia and organ damage by combined intraperitoneal administration of vitamin A and C to *Trypanosoma brucei brucei* infected rats, *African Journal of Biotechnology* 6(18): (July 2007), 2083-2086, ISSN 0035-9203

Van den Ingh. T.S.G.A.M., Zwart, D., Schotman, A.J.H., Van miert, A.S.J.P.A.M. & Veenaidal, G.H. (1976). The pathology and pathogenesis of *Trypanosoma vivax* infection in the goat, *Research in Veterinary Science* 21: (June 1977), 264-270, ISSN 0034-5288

Varki, A. (1992). Diversity in the sialic acids, *Glycobiology* 2: (February 1992), 25-40, ISSN 0959-6658

Verma, B.B. & Gautam, O.P. (1978). Studies on experimental surra (*T. evansi* infection) in Buffalo and cow calves, *Indian Veterinary Journal* 55: (August 1978), 648-653, ISSN 0019-6479

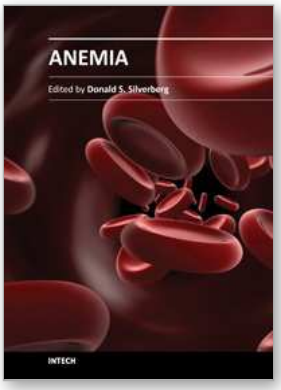
Vickerman, K. & Tetley, L. (1978). Biology and ultra structure of trypanosomes in relation to pathogenesis. In: *Pathogenecity of trypanosomes*, Proceedings of a workshop, pp. 231-31, ISBN 0- 88936-214-9, Nairobi, Kenya, November 20-23, 1978

Woodruff, A.W., Topley, E., Knight, R. & Downie, C.G.B. (1972). The anaemias of Kalaazar. *British Journal of Haematology* 22: (March 1973), 319-329, ISSN 0007-1048

Wolkmer, P., Shafer da Silva, A., Treasel, C.K., Paim, F.C., Cargncutti., J.F., Pagononcelli, M., Picada, M.E., Monterro, S.G. & Anjus Lopes, S.T. (2009). Lipid peroxidation associated with anaemia in rats experimentally infected with *Trypanosoma evansi*, *Veterinary Parasitology* 165: (1-2): (October 2009), 41-46, ISSN 1873-2550

Woo P.T.K. & Kobayashi, A. (1975). Studies on the anaemia in experimental African trypanosomiasis, Preliminary communication on the mechanism of the anaemia. *Annals Society Belge Medicine Tropicale* 53(1): (October 1973), 37-45, ISSN 0772-4128

Zwart, D. & Veenendal, G.H. (1978). Pharmacologically active substances in *Trypanosoma vivax* infections. In: *Pathogenecity of trypanosomes*. Proceedings of a workshop, pp. 111-113, ISBN 0-88936-214-9, Nairobi, Kenya, November 20-23, 1978



Anemia

Edited by Dr. Donald Silverberg

ISBN 978-953-51-0138-3
Hard cover, 440 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

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.

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