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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 haematophagous 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 dromedarius*) (Mbaya et al., 2010). In humans, *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* 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. rhodesiense* 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 haemolysis, 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 pancytopenia 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).

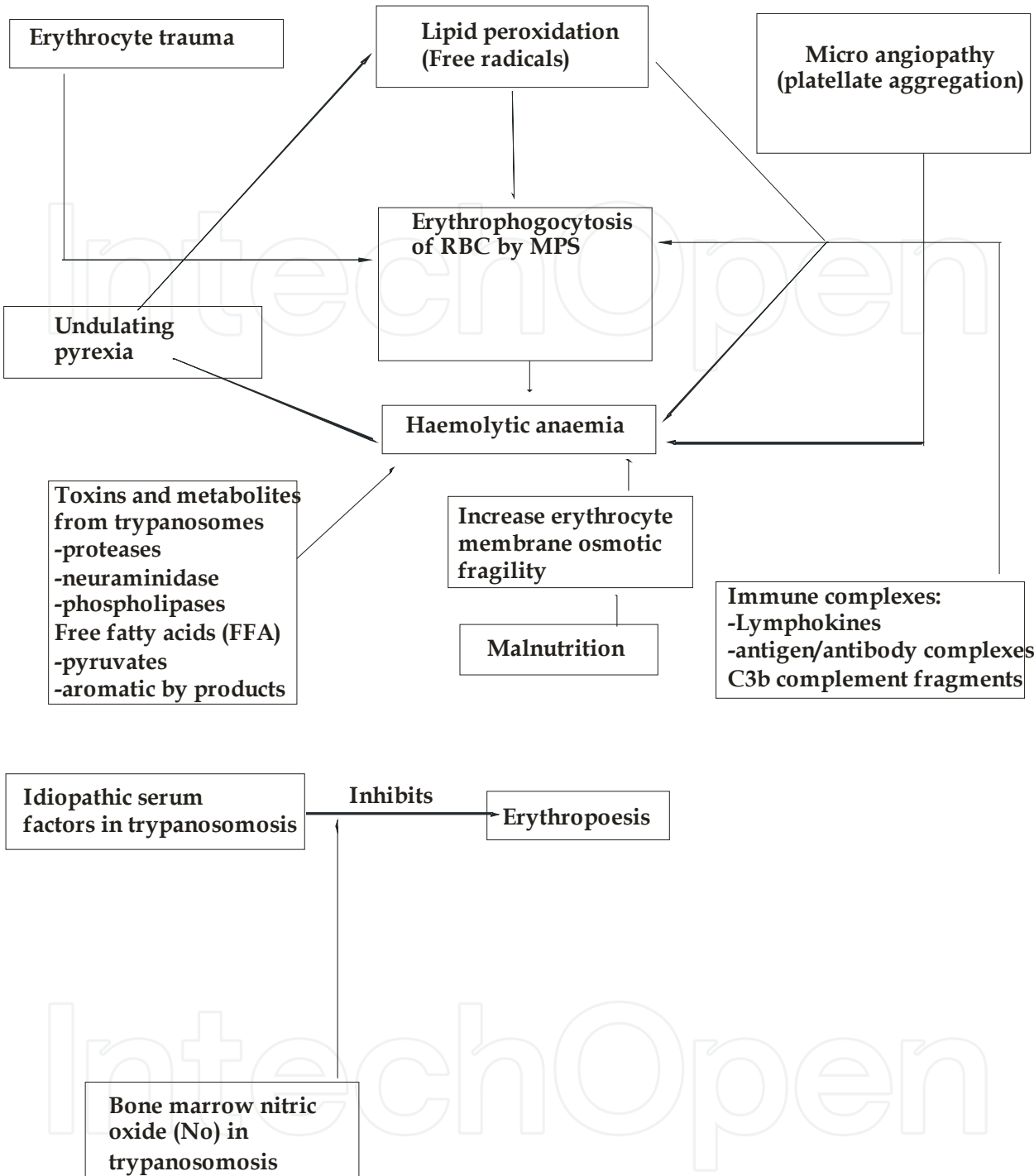


Fig. 1. Pathophysiology of anaemia in African trypanosomosis, Source by Dr. A.W. Mbaya.

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 (Vickerman & Tetley, 1978; Rautenberg et al., 1982; Lonsdale-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 anaemia 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 haemoglobin 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 autologous 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- $\alpha$ , IFN gamma and other inflammatory cytokines (Jelkmann, 1998). However, in more recent studies (Nemeth et al., 2004) suggested that anaemia in trypanosomosis involving hypoferraemia was caused by IL-6 and hepcidin. Although Naessens et al. (2005) concluded that this is unlikely to cause anaemia in trypanosomosis, some weak evidence of the role of TNF- $\alpha$  in the severity of anaemia in trypanosome-infected cattle (Sileghem et al., 1994), mice infected with *T. brucei* (Magez et al., 1999) and in *T. brucei gambiense* infected mice (Naessens 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 haemopoietic 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 species 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 erythrophagocytosis 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.

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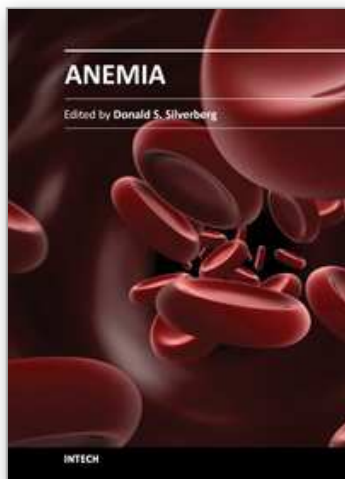


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## **Anemia**

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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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