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Review

Understanding the Pathogenesis of Trypanosoma brucei Infections: A Comparative Approach

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Almost more than any other disease affecting both people and livestock, trypanosomiasis straddles the ground between human health, livestock health, agricultural production and rural development. Consequently tackling trypanosomiasis has the potential to impact on all the development goals of many nations and international Organizations such as FAO and WHO which includes eradication of extereme poverty. Although the number of new cases of the human disease appears to be on the decline, the number of infections in tourists returning from tropical Africa has not abated. Due to limited active surveillance in endemic nations, sleeping sickness remains an important disease in Africa, while some of the old transmission foci have remained active with the likelihood of new ones arising from animal reservoir hosts, earlier incriminated in outbreaks of Sleeping Sickness. Limited number of autopsy reports on Sleeping Sickness has resulted in poor knowledge of the pathogenesis and pathology of human trypanosome infections, essential for clinical management of the disease. Knowledge of the pathology therefore rests on incorporation of findings in *T. brucei* subspecie infection of animal models. This subgroup includes *Trypanosoma brucei rhodesiense, T. b. gambiense,* causative agents of Human African Trypanosomiasis (HAT) also known as Sleeping Sickness., and *T. b. brucei*, causative agent of Animal African Trypanosomiasis (AAT) also described as Nagana. These do not only share similarities in stage dependent clinical diseases, epizootiology, pathogenesis and pathological features but also share many common hosts and are morphologically indistinguishable. This review is therefore a summation of the common findings in pathogenesis and pathology of *T. brucei* subspecie in humans and animal models with the view to enhancing knowledge and control of Afican trypanosomiasis.

Keywords: Pathology, *Trypanosoma brucei*, man, animals.

INTRODUCTION

Trypanosomiasis is a debilitating protozoan disease caused by parasites classified in the Phylum Sarcomastigophora, the Order Kinetoplastida, the Family Trypanosomatidae and of the Genus *Trypanosoma* (Stevens and Brisse, 2004). The trypanosome species of veterinary and medical importance had been described (Ormerod, 1970; Stevens and Brisse, 2004). The pathogenic trypanosomes are further divided into two sections; salivaria and stercoraria according to their site of development in the vector and mode of transmission either through the saliva or by fecal contamination of the wound caused by bite of the vector. *Trypanosoma brucei* belongs to the salivaria group in general and subgenus *Trypanozoon* in particular. The parasite was first

described from Zulu land in 1914 by Bruce and other scientists. Trypanosome species in this group are typically polymorphic with small subterminal kinetoplast, well developed undulating membrane and undergos development in the midgut and salivary glands of tsetse fly. The species belonging to this subgenus include, human infective *T. brucei* gambiense and T*. b. rhodesiense*, and *T. b. brucei* infective to animals which have been regarded as the three *T. brucei* subspecies of economic importance. The other, aberrant species, *T. evansi* and *T. equiperdum* are transmitted non-cyclically or by coitus. Despite decades of research, Trypanosomiasis of man and his domestic animals continues to pose important public health and economic problems in many parts of Africa and South America (Sachs, 2010). In Africa, tsetse transmitted trypanosomiasis is endemic in human and livestock populations distributed in an estimated 10 million km_2 of land space (Leach, 1973; Sachs, 2010), corresponding to the geographical distribution of the Glossina vector. This covers the tropical area extending from latitude 15_0N to 30_0S of the equator (Ukoli, 1984: Jordan, 1986). It is estimated that at least 50 million people as well as 30% of cattle (WHO, 1998; Sachs, 2010) are at risk to African trypanosomiasis. Tsetse fly population increases in the rainy season resulting to encroachment on livestock and human settlements resulting to increased fly to animal or fly to man contact and increases the risk of trypanosomiasis (Maikaje, 2002; Ahmed *et al.,* 2005). Animal trypanosomiasis constitutes a major threat to food security in several parts of sub-Saharan Africa including Nigeria (Onyiah, 1997; Budd, 1999; Swallow, 2000). FAO (2008) reported that almost more than any other disease affecting both people and livestock, trypanosomiasis straddles the ground between human health, livestock health, agricultural production and rural development; consequently tackling trypanosomiasis has the potential to impact on all eight millennium development goals of the Organization which includes eradication of extereme poverty. Although the number of new cases of the human disease appears to be on the decline, the number of infections in tourists returning from tropical Africal has not abated(Simarro *et al.,* 2012). Due to limited active surveillance, sleeping sickness remains an important diseases in Africa (WHO, 1998), while the old transmission foci have remained active with the likelihood of new ones arising from animal reservoir hosts, earlier incriminated in outbreaks of Sleeping Sickness (Abenga and Lawal, 2005).

The complex nature of the epidemiology of Human African Trypanosomiasis (HAT) had been described (Jordan, 1986; Sachs, 2010). Two forms of human trypanosomiasis are endemic in various parts of Africa. While Rhodesian sleeping sickness, the acute form caused by *T.b. rhodesiense* is endemic in East Africa, Gambian sleeping sickness, a chronic form of the disease caused by *T.b. gambiense*, occurs in West and Central Africa. The region around Lake Victoria has been identified as the meeting point of the two forms of the disease (Ukoli, 1984). *T brucei brucei* on the other hand has no regional epizootical limitations and causes virulent disease described as Nagana in animals side by side with Sleeping Sickness in several parts of Sub-Saharan Africa.

T.b. gambiense, *T.b. rhodesiense* and *T. b. brucei* have been identified as one of the major controversies associated with *Trypanozoon* subgenus (Anon, 1998) as they are morphologically identical, share common host susceptibility while *T. b. brucei* produces disease pattern that interphases between Sleeping Sickness and Nagana. The genomes of African trypanosomes is almost entirely based on the study of *T. brucei* (Melville *et al.,* 2004) probably because of the genetic diversity of the *T. brucei*-subspecies that has increased the chances of infectivity of these species to man which was confirmed about a dacade ago by report of sleeping sickness due to *T. evansi* infection to man in India (Anon, 2005).This underscores the relevance of advancing research on the pathology of *Trypanosoma brucei* infections.

The current research on aspects of the human disease remains inconclusive while the knowledge of the pathogenesis and pathology of trypanosomiasis in man is further hampered by the limited numbers of autopsy reports arising from Sleeping Sickness cases. The current knowledge of the pathology of the human disease is therefore premised on results of *Trypanosoma brucei*-subspecie experimental studies in animal models.

The aim of this review is to provide an assemblage of gross and histopathological findings as well as serum biochemical derangements associated with natural and experimental *Trypanosoma brucei* subspecies infections. This is with the view to filling the gaps in knowledge of pathology of HAT , providing basis for molecular based research on the lead events in the pathogenesis of trypanosomiasis in man and animals that would enable novel drug developments for control of the disease as well as, providing the needed basic knowledge on aspects of pathology of the disease to the teaming young researchers on African trypanosomiasis. Since research in all aspects of pathology, at gross and histopathology as well as molecular levels is dynamic, it suffices to state here that, the summations of the basic findings presented here are by no means conlusive.

CLINICAL FEATURES

Infections with *T. brucei* subspecies cause disease courses which are similar in nature whose severity depend on the specie of infecting organism and host factors (Losos, 1986). Common clinical features of African trypanosomiasis have been summarized by several authors (Ormerod, 1970; Losos and Ikede, 1972; WHO, 1998; Taylor and Authie, 2004). Animal infective *T.*

brucei brucei and human infective *T. brucei gambiense* and *T. brucei rhodesiense* cause stage dependent clinical diseases. Two stages or phases of the disease, the early stage and late stage have been described (Poltera, 1985; WHO, 1998). Both forms have been recognized as diseases of the central nervous systems (CNS) and other tissues with an initial period of infection of the blood which is followed later by invasion of the CNS. The time course of disease varies with the type of infecting trypanosome (Jordan, 1986).

The early or haematolymphatic stage is characterized by symptoms that occur before CNS invasion by trypanosomes. The first sign of infection is usually the development of a chancre at the site of tsetse bite within 5 to 15 days after fly bite, which is usually more frequently observed in *T.b. rhodesiense* infection than in the *T.b. gambiense* infections. The trypanosomes later invade blood stream and there is periodic fever which lasts one to seven days accompanied by headache. There may also be joint pains, muscle aches, pruritis and cachexia.

Lymphadenopathy is common. There is gross palpable firm, mobile and painless enlargement of lymph glands especially in the neck region. There may also be marked generalized oedema especially of the face described as "moon face" in man (Jordan, 1986). Generalized oedema may also extend to appendages (Wellde *et al.,*1989a). There is also moderate anaemia as well as endocrinological disorders which result in disturbances in reproduction such as reduced libido, impotence, abortion, and infertility (WHO. 1998). Abnormalities in electro-cardiogram in patients is also commonly reported (WHO, 1998). This was resently coloberated by Ajibola and Oyewale (2014) in dogs experimentally infected by *T. b. brucei*. These also include, prominent jugular pulse, and weight loss. Splenomegaly occurs in both man and animals(Losos, 1988). Wellde *et al.,* (1989a) observed splenomegaly in twenty six patients infected with *T.b. rhodesiense* and five of the patients had hepatomegaly

The late or meningoencephalic stage occurs following CNS involvement and is established by examination of the cerebrospinal fluid (CSF) for the presence of trypanosomes (Poltera, 1985). This stage is characterized by disturbances of the nervous system and may manifest as deep hyperaesthesia, paraesthesia, convulsions, mental disorders, insomnia, somnolence, ataxia, paresis and paralysis (Jordan, 1986: WHO, 1998). In the typical *T.b. gambiense* disease, invasion of the CNS is delayed and death of untreated victim may not occur for several years. In our observations in experimental *T b. gambiense* infection of vervet monkeys, the late stage occurred eight weeks after infection which was followed by CNS disturbances(Abenga and Anosa, 2006).The patient emaciates over many months and also displays typical sleeping syndromes (Jordan, 1986).

Infection with *T.brucei rhodesiense* results in an acute course and the patient may die within few weeks or months of infection without CNS involvements.

PATHOGENESIS OF *TRYPANOSOMA BRUCEI* INFECTIONS

Considerable similarities exist in lesions and pathogenesis of the disease caused by members of the *T.brucei* subgroup of parasites, namely, *T.b. brucei. T.b. gambiense* and *T.b. rhodesiense.* Ormerod (1970), Poltera (1985) and Losos(1986), had described various aspects of the pathogenesis of trypanosomiasis of man and animals.

In natural circumstances, infection with the trypanosome occurs following subcutaneous inoculation of the host with metacyclic forms of trypanosomes by an infected fly. Ormerod (1970) reported that the minimum infective dose of 300 to 450 metacyclics are required to cause infection in man. The parasites multiply in the skin leading to the development of a chancre which is more prominent in *T.b. brucei* and *T.b. rhodesiense* than in *T.b. gambiense* infection (Poltera, 1985). Trypanosomes from the chancre enter the blood either directly or through the lymphatics, and are disseminated throughout the body by circulating blood thereby causing parasitaemia and lodgement into various organs and tissues. Parasitaemia, which is usually accompanied by hyperthermia, is generally marked in *T.b. rhodesiense* but lowest in *T.b. gambiense* infections. The incubation period in man varies form one to three weeks (Ormerod, 1970; Olowe, 1975).

The *T.brucei* group of trypanosomes generally became localized in solid tissues particularly the connective tissue stroma of various organs causing extensive degenerative changes and anaemia (Ormerod, 1970; Morrison *et al.,* 1981. Poltera, 1985).

Fiennes *et al.* (1946). Losos and Ikede (1972) and Morrison *et al.* (1979; 1981) described the major processes associated with pathogenesis of *T. brucei* infection. These include:

a) Extravasation of parasite into body tissue leading to severe lesions,

b) Vasculitis, increased vascular permeability and thrombosis,

c) Increased erythrophagocytosis resulting to excessive destruction of red blood cells.

d) Direct toxic damage caused by biologically active substances produced by either dead (dying) or living trypanosomes.

T. brucei is tissue invasive (Losos and Ikede, 1972) with blood changes being of secondary importance (Griffin, 1978). Characteristic lesions arise from extensive inflammation of primary tissues affected mediated by increase in the levels of cytokines such as Tissue

Necrotic Factor (TNF-a) and Interleukines 6(IL-6) (Reincke *et al.,* 1998) with cellular infiltrations predominantly by lymphocytes followed by plasma cells, macrophages and neutrophils (Morrison *et al.,* 1981). The role of free radicals-induced oxidative stress in pathogenesis of trypanosome infections had been described (Igbokwe,1994; Ogunsanmi and Taiwo, 2007; Akanji *et al.,* 2009). *T. b.brucei* had been found to not only produce large amounts of reactive Oxygen species and Hydrogen peroxide (Meshnick *et al.,* 2007) but may also alter the host's antioxidant defence against free radicals(Igbokwe 1992, Omer *et al.,*2007). Yusuf *et al* (2012) demonstrated that admistration of methanol extracts of *Vernonia amygdalina* leaf improved oxidative status of *T. brucei* infected animals resulting to limiting of parasitaemia, anaemia and protecting against liver damage. Microvascular injury (Edeghere, 1980) and vasculitis (Morrison *et al*., 1981) are important factors leading to increased vascular permeability and widespread embolism and thrombosis in small arteries and veins. This leads to tissue, hypoxia further tissue damage, necrosis and inflammatory reaction (Fiennes *et al.,* 1946; Losos and Ikede, 1972; Tizard. 1985). The paminiform plexus, venous plexus of the ovary and renal veins appear to be most affected. Vasculopathy readily recognized and manifested by petechiae and leakage of fluid and protein into extravascular spaces is particularly noticeable in infections with *T. brucei* sub group of trypanosomes as a result of their predilection of connective tissue (Goodwin, 1970; Tizard, 1985). Goodwin (1970) and Edeghere (1980) observed endothelial gaps and swollen endothelial cells in experimental *T.b. brucei* infections of rabbits. Their tissue activities leading to generation of brain Nitric Oxide had been associated with crossing of the blood brain barrier(Jannin and Cattand, 2004).

Thrombosis, tissue necrosis, microangiopathic anaemia has thus been attributed to disseminated intravascular coagulation (Tizard, 1985). The occurrence of microthrombi in the capillary loops of glomeruli, vessels within the brain, liver, lungs, heart and plexus paminiform plexus of the testis were also reported by Isoun and Anosa (1977) and Isoun (1980). The localised trypanosomes in endocrine tissues cause severe inflammation leading to their destruction, especially the pituitary gland and gonalds thereby resulting to a cascade of infertility problems in man and animals. This is believed to result to inefficiency of the gonalds as a result of impairment in the hypothalamic-pituitary-gonadal axis(Petzke *et al.,*1996) or hypothalamo-pituitary-adrenal axis(Reincke *et al.,*1998); a special portal that links the hypothalamus, pituitary and the gonalds(Noakes *et al.,* 2009). The pathogenesis of trypanosome-induced reproductive dysfunction was covered in the reviews by Ikede *et al*(1988) and Raheem(2014). The end result is reduction in circulating Leuteinizing Hormone, testosterone in males and Follicle Stimulating Homone in females. These together with direct testicular lesions affect spermatogenesis resulting to poor semen quality and infertility in males while ovarian lesions along with endometritis cause irregular estrous cycle, infertility, feotal deaths and abortion in females. This had been collaborated in the findings of Emeh and Nduka (1983) in women with advanced cases of Gambian trypanosomiasis and Obi *et al (*2013) in *T. brucei* infected dogs.

Main factors associated with pathogenesis of anaemia in *T. brucei* infections would be covered in a subsequent review. However Anosa, (1988a) described factors in pathogenesis of anaemia in African trypanosomiasis. These include hemolysis, haemorrhages and dyshaemopoiesis while the roles of hemodilution remain douptful.

Several workers described the existence of biologically active substances produced by dead and living trypanosomes. Seed (1969) demonstrated that extracts of *T.b. gambiense* were capable of increasing vascular permeability in the rabbit. Haemolytic factors were also shown to be produced by *T.b. brucei* (Huan *et al*., 1975). Similar factors were observed in *T. congolense. T. vivax, T.b. gambiense* and *T.b. rhodesiense* (Morrison *et al*,, 1978). Tizard (1985) reported that trypanosomes contain macromolecules that are potentially toxic to the host. Davies *et al.* (1974) on their part demonstrated a heat labile non-complement dependent platelet agglutination factor produced by *T.b. rhodesiense* while Tizard *et al.* (1979) stated that dying trypanosomes release, enzyme phospholipase A_1 and lysophospholipase A_1 which hydrolyse phospholipids with the eventual formation of fatty acids which have toxic biological properties. These acids are known to be hypoglycemic, mitogenic and cytotoxic which could ultimately lead to anaemia, disseminated intravascular coagulation (DIG) and immunosuppression (Tizard, 1985). Tizard (1985) also reviewed the roles played by several autocoids such as kinins, histamine and catecholamine in the pathogenesis of African trypanosomiasis.

Henson and Noel (1979) and WHO (1998) reported that trypanosome induced immunosuppression lowers hosts resistance to other antigens resulting in intercurrent infections. Observations of Tizard(1985) reveal that macrophages play a central roles resulting to immunosuppression in African trypanosomiasis.

PATHOLOGY OF TRYPANOSOMA *BRUCEI INFECTIONS*

Only few postmortem reports on cases of sleeping sickness had been documented (WHO, 1998), one of the latest being the report of Ayub *et al* (2011) on result of necropsy carried out on a young Army officer on United Nations peace mission in Liberia, who died of HAT. Current understanding of the pathology of human

trypanosomiasis rests largely on observations on experimental animal models (Fiennes, 1970; Losos and Ikede, 1972; Murray *et al*., 1974; ISCTRC. 1985; Wellde *et al..* 1989b) and the severity of lesions is generally dependent on the number of parasites in the tissues (Morrison *et.al*.,1983, Kaggwa *et al*., 1983).

Gross pathology

In both rhodesian and gambian human trypanosomiasis emaciation, oedema of the face and appendages, ascites and palpable enlargement of cervical lymph nodes are common findings (Apted, 1970; Scott, 1970; Jordan. 1986). The chancre is a erythematous skin reaction at the site of tsetse bit (Poltera, 1985). Anaemia though less prominent in the human disease is characterized by pallor of mucous membranes and is less pronounced in the gambian trypanosomiasis (Poltera, 1985 Jordan. 1986). Other changes include myocarditis and pericardial effusion in advanced stages accompanied by dilatation of the heart (WHO, 1998). Peritoneal and pleura effusions containing trypanosomes have been reported in autopsies on victims of rhodesian disease (Hawking an Greenfield, 1941) while visceral complications had been described for the gambian trypanosomiasis (Francis, 1972).

Morrison *et al.* (1981) observed wide spread haemorrhages affecting the diaphragm, other viscera, and the central nervous system in *T. brucei* infected dogs. Although Poltera (1985) reported no involvement of the gastro intestinal tract in man, Olowe (1975) observed gross haemorrhages into the intestines, mesentery, mediastinum as well as the myocardium in an autopsy of a three week old baby with congenital gambian trypanosomiasis. This has been coloberated by the necropsy findings of Ayub *et al* (2011) on a *T.b. gambiense* infected soldier on peace mission. Wellde *et al.* (1989a) observed enlargement of spleen and the liver in patients with *T. rhodesiense* disease. These changes were similar to those earlier observed in *T.brucei* infected dogs (Morriso *et. al.*, 1981; Kaggwa *et*. *al.,* 1983) and rabbits (Vanden Ingh 1976). The heart may be pale and rounded with marked oedema and necrosis of the pericardial fat, petechiations and ecchymoses of the myocardium, giving the heart a mottled pale haemorrhagic appearance (Morrison *et al,* 1981; 1983, Ayub *et al.*, 2011) and pericarditis. These haemorrhagic syndromes mimic those observed in *T. vivax*; infected cattle (Wellde *et al.,* 1989). There may also be massive pulmonary edema(Ayub *et al.,*2011) as well as foci of consolidation(Ikede and Losos, 1988)

In experimental infection, *T. b.brucei* caused corneal opacity 21 days post infection in the dog (Morrison et al 1981). Similar observation was made in a dog (Omotainse, 1989). Wellde *et al*., (1989b) reported apparent blindness in cattle infected with *T.b. rhodesiense* without corneal opacity, suggesting this is not a regular finding in natural Sleeping Sickness. Additional ocular lesions such as unilateral or bilateral conjunctivitis and keratitis have also been reported (Losos and Ikede, 1972).

In early stages of the infection, the heart is generaly considered to be most at risk in rhodesian sleeping sickness with death arising mainly from pancarditis (Ormerod, 1970 Poltera, 1985). Similar observations were made in monkeys suffering from acute trypanosomiasis (Poltera, 1985). In *T.b. gambiense* infection however, cardiac lesions were complicated by bacteria infection (Poltera, 1985).

The involvement of the CNS is associated with chronicity (Losos and Ikede, 1972; WHO. 1998) and may manifest grossly as oedema of the brain and meninges. Morrison et al.(1981) observed swollen choroid plexus 21 to 25 days post infection as a result of oedema and presence of massive numbers of trypanosomes mixed with cellular infiltrates of the plexus in the *T. brucei* infection. Other parts of the brain commonly involved include the thalamus, hypothalamus, hippocampus and basal ganglia (Ikede and Losos, 1972).

Although emaciation and muscular wastage occur commonly in man, skeletal muscles are only irregularly involve (Poltera, 1985). Atrophy of the skeletal muscles had been reported by Losos and Ikede (1972) and Kaggwa et al. (1983). Van den Ingh (1976) observed pale kidneys, severe degeneration of the kidneys in most of the rabbits with chronic *T.b. brucei* infection. Although hepato-splenomegaly occurs commonly in African trypanosomiasis (Losos and Ikede, 1972; Anosa and Kaneko 1984a, and Poltera, 1985) and the liver may also show atrophy in *T. brucei* infections (Van den Ingh 1976), the spleen may be dark-red and firm (Losos and Ikede. 1972).

Lesions leading to disturbances in reproduction such as the development of cysts in the ovary (Zwart, 1989) and placental pathology associated with abortion and oophoritis (Losos and Ikede, 1972; Poltera, 1985) have also been reported. These have been supported by observations of Akpavie *et al.* (1987), Anosa and Isoun (1980), Ikede *et al.* (1988) and Sekoni *et al.* (1980) in animals. Further more, in males, orchitis is accompanied by testicular enlargement and scrotal dermatitis" histopathology (Ikede *et al*., 1988).

Histopathology

The interstitial activities of trypanosomes in tissues attract severe inflammatory reaction in various organs (Ormerod, 1970; Losos and Ikede, 1972; Anosa and Kaneko, 1983a,b; Poltera 1985) which are characterized by mononuclear cellular infiltration composed largely of lymphocytes and plasma cells. The organs most affected include the heart and brain, the characteristic

lesions being vasculitis with perivascular mononuclear cell infiltration (WHO, 1998; Zwart 1989). However lesions observed in the *T. brucei* infected rabbits were those of severe granulomatous inflammation consisting of many macrophages or epithelioid polynuclear giant cells and polynuclear leucocytes in chronic infections (Van den Ingh, 1976).

There is pancarditis in the human disease which involves all the cardiac layers, valves and the conducting system (Poltera *et al.*, 1976; Poltera, 1985). This is accompanied by focal or diffuse mononuclear cell infiltration of the interstitium and the perivascular spaces (Poltera *et al*, 1976). Myocytolysis, focal endomyocardial fibrosis, have also been reported (Poltera and Cox 1977). Similar observations were made on victims of rhodesian sleeping sickness at necropsy (Hawking and Greenfield. 1941: Cohen. 1973). WHO (1998) report also included endocardial granuloma formation around degenerated muscle fibers. These changes occure also in *T. brucei* infected dogs (Morrison *et. al*, 1983).

Changes in the lymph nodes include follicular hyperplasia sinus histiocytosis, and perivascular mononuclear infiltration of plasma and morula cells (Peruzzi, 1928). Capsular and tubular fibrosis were also observed in advanced cases by Peruzzi (1928) in some infected vervet monkeys.

Poltera (1980) observed oedema and dilation of lymphatic sinuses in trypanosome infected rats and exhaustion of the local cellular response. The spleen and lymph nodes showed diffuse inflammatory reaction with haemorrhages, necrosis and polymorphonuclear cell, lymphocyte and plasma cell infiltration in canine *T. brucei* infection (Kaggwa *et al.* , 1983).

These changes were consistent with earlier findings of Van den Ingh (1976) in rabbits infected with *T.b. brucei*. The red pulp of the spleen was hypercellular due to mononuclear and polymorphonuclear cell infiltration and general hyperplasia of follicles. Van den Ingh (1976) reported that changes in the liver included centrilobular degeneration, hypercellular sinuses with accumulation of plasma cells, lymphocytes and activated Kupffer cells, and some granulomatous reaction in the chronic *T.b. brucei* infected rabbits. In donkeys infected with *T.b. brucei*, the liver showed marked haemosiderosis, centrilobular congestion and fatty change (Ikede, *e t a l* . , 1977). In one of the donkeys, there was extreme erythrophagocytosis by the Kupffer cells.

The hepatic sinusoids get distended with inflammatory cells and oedema fluid in *T. brucei*-infected dogs (Kaggwa *e t a l* . , 1983). Morrison *e t a l* . , (1983) reported disorganization of hepatic cords as well as diffuse vacuolation of hepatocytes with fatty degeneration around central veins, and necrosis of hepatocytes. Van den Ingh (1976) and Ikede *e t a l* ., (1977) described pathological changes in the kidneys in *T . b . b r u c e i* infection of rabbits and donkeys respectively. The glomeruli of the kidney were hypercellular suggesting proliferative glomerulonephritis and dilatation of proximal tubules with low, cuboidal pale-staining epithelial cells. Ikede *e t a l .* (1977) also observed foci of mononuclear perivascular cuffing in a donkey as well as presence of proteinaceous and crystalline casts in tubules of the infected animal.

The brain is involved in late stage of human African trypanosomiasis. The lesions reported include meningo-encephalitis characterized by vasculitis, perivascular cuffing with mononuclear cells including lymphocytes, plasma ceils and macrophages (Poltera, 1985; Zwart, 1989). These changes involve mainly veins and capillaries. Topographically, the di- and mesencephalon as well as cortical areas of the brain and cerebellum are most severely affected (Poltera. 1985). There is destruction of neurons, microglial reaction. diffuse scattering of the inflammatory cells in the neurophil and demyelinisation which also occurs to a varying degree. Ikede *et al.* (1977) described similar brain lesions in donkeys infected with *T.b. brucei* with lesions extending to the spinal cord. The gasserian ganglia and optic nerves were also involved.

Demyelinisation was not reported in the rats infected with *T.b. gambiense* (Chirmwami *et al.,* 1988; Zwart, 1989). In the *T.b. rhodesiense*-infected cattle, lesions were first evident in the dorsal meninges of both cerebrum and cerebellum, followed by perivascular cuffing of the parenchyma (Wellde *et al*., 1989). As the disease progressed, there was severe involvement of the basal ganglia, the thalamus, hypothalamus and cerebellar peduncles as well as areas of mixed grey and white matter, and myelinated tracts. Only minimal involvement of the spinal and peripheral nerves was observed (Wellde *et al*., 1989). The CNS lesions observed by Losos and Ikede (1972) and Morrison *et al*, (1981) were most severe in the choroid plexus and pituitary gland. Focal haemorrhages and infiltrations by neutrophil and macrophages in the pituitary gland were reported (Ikede and Losos. 1972). These lesions could be confused with those induced by arsenical drugs on human patients (Ormerod, 1970).

Changes in the lungs such as bronchopneumonia in man (Cohen 1973; Poltera *et al.,* 1977), hypercellularity of alveolar space, perivascular cuffing by macrophages, lymphocytes and plasma cells, and microthrombi in pulmonary vessels (Van den Ingh, 1976) have been reported. In cattle infected with T. rhodesiense, there were large numbers of hemosiderin-laden macrophages in the alveolar walls (Wellde *et al*., 1989b). There is no detailed information on the involvement of the digestive system in man (Poltera, 1985). However, the lamina propria of the entire gastrointestinal tract of *T. brucei*-infected dogs was severely thickened due to the presence of trypanosomes, lymphocytes and plasma cells in the subepithelial area (Morrison *et al.,* 1981).

Testicular lesions are those of orchitis, testicular

degeneration, severe seminiferous tubular granulomatous inflammation leading to necrosis of spermatids, spermatocytes and spermatogonia, depopulation of seminifeous tubules, deplation of spermatogenic cells while the sertoli cells may show marked vacoulation (Anosa and Kaneko, 1983; Obi *et al*., 2013) and in some cases complete aspermatogenesis (Ikede and Losos, 1972). In females degenerative and inflammatory lesions include endometritis and placentalitis (Leigh *et al*., 2014)

Biochemical Changes

Tissue activities of *T. brucei* subspecies evoke marked serum biochemical derangements. Anosa (1988b) reviewed serum biochemical changes in African trypanosomiasis. Serum total proteins had been found to be generally increased accompanied by increase in serum globulins and decrease in albumin levels with resultant fall in the albumin: globulin ratio. However, normal or decreased total proteins had also been reported (Anosa 1988b) in infections due to other trypanosome species. increases in total proteins in African trypanosomiasis is believed to arise from hyperglobulinaemia and especially hypergamma-globulinaemia and has been associated with increase in immunoglobulin M (1gM) as well as dehydration which are consistent finding in trypanosomiases of man and animals (Anosa, 1988b). Albumin is produced entirely in the liver and plays important roles in the regulation of flow of water between the plasma and tissue fluids by its effect on colloid osmotic pressure. Hypoalbuminaemia on the other hand is therefore the result of decreased protein synthesis due to hepatic dysfunction (Anosa, 1988b) in trypanosomiasis

Elevated fibrinogen levels occured in *T .b. g a m b i e n s e* (G r e en w o o d an d W h it t l e , 1975) and *T . b . r h o d e s i e n s e* (Robins-Browne *e t a l . ,* 1975) infection of man. French (1938) reported normal fibrinogen levels in *T . b r u c e i* and *T. c o n g o l e n s e* - i nf ected cattle. Serum bilirubin levels also change in African trypanosomiasis. However, normal bilirubin levels were reported in *T.b.brucei* infected rabbits (Jenkins *et al.,* 1980) and in *T.b.rhodesiense* infection of monkeys (Sadun *et al.,* 1973) and man (Barret-Connor *et al.,* 1973) and had been associated with glomerulonephritis and fever which are common features of trypanosomiasis, and could act together to elevate blood urea nitrogen (BUN) level. (Anosa, 1988b). These increases were consistent with the previous observations in *T.b. brucei* infected rabbits (Arowolo *et al.,* 1988) and goats (Adejinmi and Akinboade, 2000) and *T.b. gambiense* – infected vervet monkeys (Abenga and Anosa, 2007). Elevated serum urea levels had been associated with kidney diseases such as glomerulonephritis, urinary tract obstruction and excessive protein catabolism associated with severe toxic and febrile conditions (Anosa, 1988b). Fever and glomerulonephritis are consistent features of African trypanosomiasis (Poltera, 1985). Serum elevations in urea level along with creatinine serve as markers of onset of renal pathology in the infected hosts. Although serum creatinine concentrations only increased slightly in the first week of infection as observation by Sadun *et al.* (1973) in rhesus monkeys infected with *T.b. rhodesiense, T.b. gambiense* infected vervet monkeys (Abenga and Anosa, 2005), Awobode (2006) reported high plasma creatinine levels in *T.b. gambiense* infected human population than their uninfected control group. Creatinine is formed during normal muscle metabolism and is believed to be excreted at a relatively constant rate regardless of diet, age or other factors while its increase in serum levels is associated with conditions that impair glomerular filtration (Sirois, 1995). Like the liver, the kidneys play roles in erythropoietin biosynthesis and regulation of erythropoiesis and ability to respond to aneamia. Increase in the serum creatinine levels therefore signals the setting in of renal pathology and eventual compromise of the role of the kidney in responding to anaemia in trypanosomiasis. Serum cholesterol levels are also elevated as demonstrated in rabbits infected with *T.b. gambiense* (Diehl and Risby, 1974) and in rats infected with *T.b. rhodesiense*.

African trypanosomiasis, also causes changes in serum enzyme levels of infected hosts. Aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) levels increased in *T.b. rhodesiense* infection of mice (Moon *et al,* 1968), monkeys (Sadun *et al.,* 1973) and man (Wellde *et al.,* 1989a). Normal serum ASAT and ALAT however may also be normal as demonstrated in *T.b. gambiense* infection of man (Olowe, 1972; Diehl and Risby, 1974). These increases are believed to arise from liver and kidney damage at different stages of the disease (Poltera, 1985). Decreases in levels of alkaline phosphatase have been reported in *T.b. rhodesiense* – infected mice (Moon *et al.,* 1968).

Increases in serum sodium levels occured in rabbit infected with *T. brucei* (Goodwin and Guy, 1973). Hyponatremia was however reported in human *T.b. rhodesiense* infection (Barret- Connor *et al.,* 1973), Serum potassium levels increased in *T. equiperdum* and *T.b. brucei* infection of rats (Ikejiani, 1946) and had been attributed to release of potassium from red blood cell d tissue damage (Anosa. 1988b). Normal serum potassium levels were reported in *T.b. rhodesiense*-infected mice (Moon *et al.,* 1968). Depressed calcium levels occurred in *T.b. evansi* infected camels (Raisinghani *et al.,* 1981) and were associated with damage of the thyroid gland. Serum phosphate levels remained normal in *T.b. rhodesiense*-infected mice (Moon *et al.,* 1968). There may be decline in plasma Leutinizing hormone, testosterone and Follicle Stimulating Hormone levels (Ikede *et al;* 1988, Raheem, 2014), as well as concentrations of lipids and cholesterol (Adamu *et al.,* 2009). However, increase in serum sialic acid levels

due to sialidase activities of infecting trypanosomes as a result of their cleavage from erythrocyte surfaces there by leading to anaemia (Esievo, 1979; Nok and Balogun, 2003).

CONCLUSION

African trypanosomiasis has become a global meeting point of biomedical scientists and intergrated approach to the control of human and animal trypanosomiasis rests on the application of all inclusve findings in natural hosts and laboratory animal models. *Trypanosoma brucei* infections of economic importance are *T.brucei brucei,* infective to animals and *T.b. rhodesiense* and *T.b.gambiense*, infective to man. For effective diagnosis and clinical management of HAT, findings from animal models are essential. Although contemporary findings on the pathology and pathogenesis of the disease have not deviated much from those made many decades ago, advent of molecular research tools and techniques has opened a new horizon in identification of the lead molecules in the pathogenesis of African trypanosomes. Research into the genes controlling sialidases produced by infecting trypanosomes and their roles in pathogenesis of disease, as well as those of; free radicals, cytokines and other molecules should be advanced in order to enhance understanding of mechanisms associsted with crossing of blood brain barrier and tissue damage by *T. brucei* organisms. This would be required for strategic reaserch towards drug development in the control of trypanosomiasis in man and animals.

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