ASPECTS OF COMPARATIVE PATHOLOGY AND PATHOGENESIS OF TRYPANOSOMAL INFECTIONS IN AFRICA

by

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Introduction

There have been several studies to explain the pathogenesis of trypanosomiasis in man and animals. These studies have often been done in abnormal hosts (rats, mice, etc.), with old trypanosome laboratory strains, no longer transmittable by tsetse flies and with massive, but single doses of trypanosomes. Stephen (54) warns against this approach and strongly favours studies of the pathology and pathogenesis with wild, tsetse transmitted trypanosomes in indigenous animals.

True as this may be, this article follows a slightly different approach, guided by the principle: «The host can respond to insult in only a limited number of ways» (29). The emphasis will therefore be on the pathways by which the trypanosomes act upon the host and not so much on the variation of trypanosomes and hosts which lead to a whole scale of pathological conditions. With a right choice of experimental animals and Trypanosoma species, various pathways can then be studied. Great care must always be exerted to extrapolate these findings to man, farm- and game animals living in a tsetse environment. In this article, the similarities in trypanosomiasis of man (18) and animals (28) have been stressed.

First events — The chancre and lymphnode swelling

Following the successful feed of an infected tsetsefly, metacyclic trypanosomes become established in the skin. Several days after the tsetse transmitted infection a local skin reaction can develop in man as well as in domestic animals (1, 15, 18).

Local skin reactions are considerable smaller or even absent in African buffaloes when compared with cattle and may thus give an indication on the degree of trypanotolerance. Chancres can also be used to distinguish different serodomes (15).

The trypanosomes leave the skin via the draining lymphatics before a chancre is detectable (16). There is a widespread proliferation in the lymphnode cortices which ensues in a swelling of the draining lymphnode e.g. in the neck of human patients with trypanosomiasis (18). In long standing
infections lymphoid depletion occurs, but this is much more pronounced in mice than in cattle (33).

Changes in the vascular bed

During the acute phase of trypanosomiasis, the changes in the vascular bed are the most striking. Thrombi formation may develop as a result of fibrin deposits in the bloodvessels (61), sometimes mixed with thrombocytes, parasites and monocyteid cells (57).

Thrombocytopения is a constant feature of trypanosomiasis in animals and men (13); platelet aggregation was shown to be associated with serotonin release (53).

A consumption coagulopathy, sometimes combined with severe bleedings, has been reported (60, 41). The importance of coagulation in the pathology may reflect the differences in the relative dynamics of coagulation between different host species (24).

Vasculitis in varying degrees, has been described (61, 34).

Adhesion of T. congoense (4) and T. simiae (61) in the smaller blood vessels, may damage the host after an immune response to the parasites, through the release of biological active compounds (55).

The trypanosomes or immune complexes consisting of trypanosomal antigen, may activate the Hageman factor. This factor stands at the top of a cascade and may further activate the kinin, coagulation, fibrinolytic and complement system (7).

Vasoactive substances thus formed like e.g. bradykinine and serotonin, may lead to leakage of the bloodvessels (66) and hypotension (8).

Boreham (7) puts all the amines, peptides and lipids with pharmacological activity together under the name «autocoids». The species of the host may determine the relative amounts of the different autocoids released, but their release under influence of immune complexes, constitutes an important key to the development of pathology in various organs of man and animals.

Inflammatory processes in various organs

Sequential studies of central nervous systems lesions in African trypanosomiasis have used either acute T. brucei brucei or T. brucei rhodesiense models (44, 35, 49) or a more chronic T. brucei gambiense model (10, 11).

The first lesion in the central nervous system is a meningitis, which gradually spreads via the leptomeninges of vessels entering the brain resulting in a meningo-encephalitis (10, 49). Very early in the infection, trypanosomes and inflammatory infiltrates are found in the pituitary gland. The choroid plexus is only involved in the terminal stage but this can be different in more acute infections (11). It is most likely that the amastigotes described in the choroid plexus (42) are degenerating forms as a result of immunological aggression (44, 62). In order to gain access to the brain the trypanosomes must use one of two ways: either by rupturing the blood brain
barrier e.g. at the pituitary gland or by entering the brain through one of the areas where the blood brain barrier does not exist e.g. the choroid plexus. The former is the most likely in *T. brucei gambiense*. These extravascular forms are held responsible for relapses (25, 62, 63). It is most likely that the blood brain barrier can also be damaged to some extent by a superimposed infection or a drug, before the trypanosomes can enter the brain (50, 11).

Demyelisation could not be found in *T. simiae* infections of pigs (V. Dijk, pers. com.) or *T. brucei gambiense* infection in rats (10). Immune complexes and auto-antibodies may play an aetiological role, but Greenwood and Whittle (18) failed to detect immune complexes in the central nervous system in man with Gambian sleeping sickness and de Raadt (14) failed to detect antineural antibodies in patients with Rhodesian sleeping sickness.

A *myocardiitis* is often found during trypanosomiasis in man (18, 27) and animals (35). In the lesions, trypanosomes can be found, even when the blood is negative (60).

Lesions in the Purkinje fibres are less frequently seen in African trypanosomiasis as in South American trypanosomiasis caused by *T. cruzi*.

No auto-antibodies against heart muscular fibres or immune complexes were observed in *T. vivax* infected cattle with a myocarditis (v.d. Ingh., pers. comm.).

Inflammatory processes in the testes in man and animals will lead to a severe *orchitis* (21). The severity of testicular and epididymal lesions is reflected in poor quality of semen and a high percentage of abnormal spermatozoa.

Successful treatment with trypanocides will lead gradually to normal spermatogenesis if the original lesions are not too severe or complicated by secondary infection (2).

Other organs which can be involved during trypanosomiasis are the eye (54) and the endocrine organs (22). Inflammatory processes in the pituitary gland, will lead to severe consequences of the overall hormonal balance in man and animals of both sexes (21). Abortions occur, but a parasitaemic foetus is rare (21). Greenwood and Whittle (18) consider sleeping sickness an immunoproliferative disorder of B lymphocytes and plasma cells. These cells are either directly or indirectly responsible for the impaired function of various organs.

**Anaemia**

Anaemia in man and animals is of major clinical importance in trypanosomiasis, but the etiology is multifactorial with hemolysis, hemodilution and disordered erythropoiesis all playing a part and the contribution of each varying throughout the infection and the host involved (24). Initially the anaemia is hemolytic with a shortened half life time of the red blood cells (12, 30, 45).

The bone marrow remains active during the first period of infection (58) reflected by the presence of enzymes, characteristic of young erythrocytes.

Later during the chronic stage of disease, the anaemia may not be related to the presence of the parasites, but due to a defect in iron metabolism, resulting in iron trapped in the liver (37).
The mechanism of the red cell destruction is not quite clear and several processes may be acting at the same time.

An haemolytic factor, derived from trypanosomes (19) may be involved. Another immunological mechanism, whereby trypanosomal antigen alone or in the form of immune complexes adheres to the erythrocytes, can facilitate phagocytosis by macrophages (37).

**Glomerulonephritis**

In experimental trypanosomiasis the development of glomerulonephritis associated with deposits of immunoglobulins and complement along the glomerular capillary wall resulting in proteinuria, is a constant finding (9).

**Immunosuppression**

Immunosuppression has been well documented in laboratory animals and a number of mechanisms are involved. The suppression can be mediated by thymus-derived lymphocytes (67), by macrophages (31) or induced by polyclonal stimulation and subsequent clonal exhaustion of bone marrow derived lymphocytes (20). Antigenic competition (38), low complement levels and the inability to change from IgM to IgG production (40) can also play a role. The suppression may be mediated by trypanosome-derived antigens or products (3, 56).

Living trypanosomes are probably essential, because the immune competence is quickly restored after therapy (48).

Great care must be exercised to extrapolate the findings from laboratory animals, to domestic animals and man. Greenwood and Whittle (18) are of the opinion that impairment of immunity may play some part in the predisposing patients with sleeping sickness to secondary infection. They found a reduced response to typhoid vaccine, but the general debility and poor nutritional state of many patients with advanced sleeping sickness are likely to be equally important. Although significant suppression of antibody responses to various antigens was found in *T. congolense* infected cattle, challenge experiments are few. Ilemobade et al. (32) reported the development of chronic carriers, when *T. congolense* infected cattle were vaccinated against bovine pleuro-pneumonia and subsequently challenged. Scott et al. (51) found that the antibody titres after vaccination against foot-and-mouth disease in *T. congolense* infected cattle offered sufficient protection.

**Anorexia and metabolic changes**

Anorexia, accompanied by fever, is found in most infectious diseases. Despite high fever and elevated bradykinin levels during acute *T. vivax* infection in goats, Veenendaal et al. (66) did not find a decreased rumen motility. Zwart (unpublished results) also observed that 25% of his *T. vivax* infected dwarf goats remained eating, despite high fever and parasitaemia.
Anorexia, fever and muscular wastages are interlinked and probably all under influence of pharmacological active substances, like interleukin I (32,65), interferon (17), prostoglandin E2 (5) and cachectin (6). The fever during an infection will further augment the breakdown of muscular protein (5). Very little is known about the role of these substances during trypanosomiasis. They may also play a role, however, in the cachectic condition during trypanosomiasis, rather than protein loss through kidney damage. Interference between two unrelated stocks of *T. congoense* has been described by Morrison et al. (36), and tumour necrosis factor in *T. musculi* infections (26). Van Miert et al. (64, 65) did some comparative studies in goats on fever mechanisms during trypanosomiasis and the regulation of feed intake. They did not find the decrease in serum zinc and iron during the acute febrile periods of trypanosomiasis as compared with infections with Gram negative bacteria.

In rabbits the lipid metabolism can be severely disturbed, with a lipoaemia (47, 57). In ruminants, a lowering of the lipids has been found (58). Lipids may play a role in the non specific resistance of man against *T. brucei brucei* (46). The hypothesis has been advocated that the evolutionary development of lipoprotein factors in man against trypanosomes also implies directly or indirectly, a toxic effect on the host’s own aortic smooth muscle cells (43).

There is increasing evidence that the accumulation of end products of amino acid metabolism. contributes to the clinical pathology of trypanosomiasis. Stubbs and Seed (55) suggested that a reduced brain tyrosine level accounts for some of the neurological symptoms seen in *T. brucei gambiense* infections. Equally a fall in tryptophan could disturb the sleeping pattern during trypanosomiasis (39). Seed and Hall (52) are of the opinion that apart from immunological factors, major physiological changes are responsible for the pathology of African trypanosomiasis.

In conclusion, it can be stated, that all these processes are not unique for trypanosomiasis. The constant antigenic variations of the trypanosomes result, however, in the release of large amounts of biological active products and the formation of immune complexes, which are certainly major factors in triggering a variety of clinical and pathological changes.

REFERENCES


