Summary: Tsetse-transmitted trypanosomiasis is one of the major constraints on the expansion of the livestock and agricultural industries in Africa. The disease affects animals and man, with direct and indirect losses estimated in billions of dollars annually. Because of the phenomenon of antigenic variation, no vaccine is available. Current prophylactic efforts must rely on tsetse control by the use of insecticides and on trypanocidal drugs. However, recent advances in our knowledge of tsetse and trypanosome biology are offering hope for alternative methods of trapping tsetse, new drugs and even vaccination. Possibly of even greater significance is the increasing sense that Africa herself might be able to contribute to the resolution of this problem. Over a period of several thousand years, she has generated cattle, such as the taurine N’Dama and West African Shorthorn breeds of West and Central Africa, that are now known to possess a significant degree of innate resistance to trypanosomiasis and several other important infectious diseases. These cattle are extremely well adapted to the environment and are now recognised as having considerable production potential. The ability to resist the development of anaemia in the face of infection, as assessed by packed red cell volume percent (PCV), has been shown to be correlated with the capacity to be productive, thereby identifying regulation of PCV as a key trait of trypanotolerance. Thus, an estimate of the ability of an infected animal to maintain PCV, following either experimental or field infection, could be used as a method for identifying trypanotolerant individuals. This could provide a means of estimating trypanotolerance heritability, thereby permitting rational breeding programmes to be instituted. Africa may thus provide the answer.


INTRODUCTION

Pathogenic species of salivarian trypanosomes are present throughout vast areas of Africa, Asia, Latin America and the Middle East and cause disease in cattle, sheep, goats, water buffalo, pigs, horses, camels, wildlife and man. In Africa, the major pathogenic trypanosome species are transmitted by the tsetse fly (genus Glossina) and include Trypanosoma congolense, T. vivax, T. brucei and T. simiae. The closely
related subspecies of *T. brucei*, *T. b. rhodesiense* and *T. b. gambiense* cause sleeping sickness in man. Non-tsetse transmitted forms of trypanosomiasis also occur in Africa, as well as in the Middle East, Asia and Latin America. The most important pathogen, under these circumstances, is *T. evansi*. This parasite can cause severe disease in horses and camels and lead to significant losses in production and performance in cattle and water buffalo.

Currently, tsetse infest eleven million km² of Africa, about 37% of the continent, affecting forty countries (15). It is considered that seven million km² of this area would be suitable for livestock and mixed agriculture without stress to the environment, if trypanosomiasis could be controlled (30). No other continent appears to be dominated by one disease to the same extent as Africa is by tsetse-transmitted trypanosomiasis. This disease not only results in severe losses in production in domestic livestock due to poor growth, weight loss, low milk yield, reduced capacity for work, infertility and abortion, but also excludes domestic livestock from large areas of Africa. Currently, of a total population of approximately 140 million cattle, only about 30 million are located in the tsetse-infested zone. The situation with regard to sheep, goats, pigs, horses, donkeys and camels is probably as serious but it is poorly documented.

It is essential to note that domestic animals and wildlife also act as reservoir hosts for the human pathogens *T. rhodesiense* and *T. gambiense* and that trypanosomiasis in humans is an important constraint on rural development in Africa, acting as a major factor in the depopulation of large areas. It causes disruption of communities with the resultant depletion of human resources upon which viable agricultural communities depend. At present, it is estimated that some fifty million people in some 36 countries are at risk (33). There are several serious active foci of the disease in Africa, e.g. in Uganda, Sudan, Zambia, Côte d'Ivoire, Zaire, Angola and Mozambique. The number of new cases reported every year has increased to around twenty thousand (33).

Thus, the presence of tsetse results in widespread rural instability and causes severe production losses in a massive area of Africa. The annual loss in meat production alone has been estimated at US$ five billion (40), but this figure excludes milk, hides and mixed agriculture. In Africa, 80% of traction power is non-mechanised. It has been calculated that the availability of a draught ox to a family unit can increase agricultural output six-fold (29). Furthermore, the manure provided by livestock is essential for the production of food and cash crops and is a potential source of energy in the form of biogas. If all these factors are taken into consideration, it has been estimated that livestock and agricultural development of tsetse-infested Africa could generate a further US$ fifty billion annually. Because of the paucity of reliable data, these calculations can only be taken as conjectures and are probably a gross underestimate.

Many factors contribute to the magnitude of the problem of African trypanosomiasis. One major factor is the complexity of the disease itself. In cattle, for example, three species of trypanosome, *T. congolense*, *T. vivax* and *T. brucei*, cause the disease, either individually or jointly. These trypanosomes are transmitted cyclically by tsetse, of which there are some 36 species and subspecies, each adapted to different climatic and ecological conditions (16). While tsetse are not the only vectors of African trypanosomes, cyclical transmission of infection represents the most important problem because, once the tsetse fly becomes infected, it remains infective.
for a long period, in contrast to the ephemeral nature of non-cyclical transmission. At the same time, trypanosomes infect a wide range of hosts including wild and domestic animals. The former do not suffer severe clinical disease but become carriers and constitute an important reservoir of infection. The success of the trypanosome as a parasite is to a large extent due to the ability to undergo antigenic variation, i.e. change a single glycoprotein (VSG: 6) which covers the pellicular surface, thereby enabling evasion of host immune responses and the establishment of persistent infections. Added to the complexity of multiple variable antigen types expressed during a single infection, each trypanosome species comprises an unknown number of different strains or serodemes, all capable of elaborating a different repertoire of variable antigen types (60). As a result, no vaccine is available for use in the field.

**BACKGROUND TO CONTROL**

In addition to the complexity of the disease and its epidemiology, other factors contributing to the failure to contain and reduce the problem include the enormous area affected and the limitations of methods currently available for control.

Control has mainly been directed towards eradicating or reducing the number of tsetse and towards the use of trypanocidal drugs. Both approaches have been shown to be effective if properly applied, but all too frequently they cannot be sustained and the net effect to date at the continental level has been limited. However, recent developments in the understanding of tsetse biology, in the strategic use of drugs, trypanosome biology and, in particular, host genetic resistance have identified promising new approaches.

**Tsetse**

Attempts to control tsetse have been made for over sixty years. Initially, they included eradication of wildlife, clearing of fly barriers to prevent the advance of the vector, and widespread bush clearing to destroy breeding habitats. The principal method now employed to control tsetse is by the use of insecticides. The insecticides used fall into two categories, residual and non-residual. Residual insecticides (DDT and more recently dieldrin) are usually applied as a single application by hand-operated sprays that deliver the insecticide to sites where resting tsetse are known to alight. Non-residual insecticides (endosulphan) require several applications, and are applied mainly by fixed wing aircraft or helicopters. Where insecticide control measures have been properly implemented, significant success was achieved, e.g. in Nigeria, Zimbabwe, Botswana and Zambia (30, 31). Despite the potential efficacy of tsetse control by insecticides, there are severe limitations to this approach. In Africa, there is a lack of trained personnel to implement insecticide control programmes. The costs are high, e.g. ground spraying in Zimbabwe costs between US$ 325-525/km² and aerial spraying can cost as much as US$ 750/km². Natural or man-made barriers are required to defend sprayed areas and prevent reinvasion, and constant surveillance for early detection of reinvasion is essential. Finally, there are increasing demands for restricted use of insecticides because of possible environmental impact on fauna and flora. In this respect it should be emphasised, however, that although non-target organisms can be affected by anti-tsetse spraying and quantities of insecticide remain
in the environment, these effects appear to be transitory, rarely lasting for more than a year (24). Current research involves the development of potent new insecticides with low toxic environmental effect, e.g. synthetic pyrethroids.

A completely new approach to tsetse control has recently been developed. Traps and screens have been used for many years as a means of sampling tsetse populations. However, with advances in the design, and the identification of colours and odours which attract tsetse, increasing attention is being given to the use of traps and targets as a method for tsetse control. Elegant studies carried out in Zimbabwe (59) have culminated in the development of simple insecticide-impregnated visual targets incorporating chemicals such as acetone and 1-octen-3-ol to attract tsetse. These developments are of considerable importance for the introduction of a simple and environmentally safe method of control. However, this approach has not been successful with all species of tsetse and costs are estimated at between US$ 320-620/km². There is hope that future research may remove these constraints.

Trypanocidal drugs

Along with the non-availability of a vaccine, escalating costs and other constraints on initiating and maintaining tsetse control campaigns have led the livestock industries in the vast tsetse-infested areas of Africa to rely almost completely on the use of trypanocidal drugs to prevent or treat the disease. Without these drugs, the situation would be disastrous. Despite the need and demand for effective trypanocides, no new drug has been produced for commercial use in the last thirty years and there would appear to be no immediate prospects of new drugs becoming available. The cost of registering a new drug for use in animal trypanosomiasis is regarded by pharmaceutical companies as too high in relation to what is forecast as the likely financial return. This is despite the fact that it can be estimated some 120 million cattle, sheep and goats are exposed to infection. Even if animals were treated only twice annually, 240 million doses would be required. This figure is ten times the number currently used, as estimated by the FAO. Furthermore, there is an increasing number of reports of the successful use of trypanocidal drugs in cattle under ranch or village management. Thus, some 12,000 Boran are maintained in Mkwaja Ranch in Tanzania in an area where Boran cattle rapidly succumb to trypanosomiasis if left untreated. As a result of the strategic use of isometamidium chloride (a prophylactic trypanocidal drug) in combination with diminazene aceturate (a therapeutic trypanocidal drug), the level of productivity achieved was close to that of Boran reared in tsetse-free conditions on ranches in Kenya considered among the best in the world (55). At the same time, a similar drug strategy was implemented in East African Zebu cattle (700 head) under village management in Kenya and resulted in a 20% increase in performance (32). In both these situations, the level of tsetse challenge was considered high. In contrast, where disease risk is low and where it is possible to examine individual animals at regular intervals, therapeutic trypanocidal drug control strategies have been successfully employed, e.g. at Kilifi Plantations on the coast of Kenya. This dairy ranch is one of the biggest in Africa, supporting 800 breeding females based on Sahiwal x Ayrshire. The owner was virtually out of business because of trypanosome-induced abortion storms until he successfully introduced a systematic therapeutic drug strategy which he has maintained for over twenty years (61).

The fact that these control programmes were carried out in villages and ranches, on large numbers of cattle, over a long period of time, with financially successful results and with no evidence of significant drug resistance, offers some hope in the
short term for livestock and, consequently, for socio-economic development programmes in tsetse-infested areas of Africa. Nevertheless, it must be emphasised that the implementation of drug control programmes requires a degree of competent management and the constant availability of trypanocidal drugs. At the same time, if no new drugs are developed, there must be concern that the repeated use of the drugs currently available could lead to serious drug resistance problems in the long term.

**Prospects for vaccination**

The major constraint to the development of a vaccine against trypanosomiasis is the phenomenon of antigenic variation (36). However, while the repertoire of these antigens generated by bloodstream forms of the parasite is large (greater than 1,000), the repertoire of antigens produced by metacyclic parasites following transmission through the tsetse is much more limited and would appear relatively constant (7). Thus, it has been possible to immunise cattle and goats against tsetse-transmitted homologous (but not heterologous) strains of *T. congolense* and *T. brucei* (35), but not *T. vivax* (12), by prior exposures to metacyclic parasites. Nevertheless, the feasibility of production and the efficacy of a vaccine against metacyclic trypanosomes will depend on the relative stability of the metacyclic antigen repertoire for each species of trypanosome and on the number of strains which occur in the field. Currently, research is directed towards these objectives. It is thought, however, that the number of different strains is likely to be prohibitively large for the production of a cocktail vaccine containing the appropriate metacyclic antigens. As a result, the development of a vaccine against African trypanosomiasis has been considered unlikely.

As most research has concentrated on the VSG's of the trypanosome, data on the subcellular distribution and properties of other antigens are surprisingly scarce. Recently, a flagellar pocket membrane fraction has been identified in *T. rhodesiense* on the parasite surface at the emergence of the flagellum from the flagellar pocket. This would appear to be non-variable between different serodemes and to have protective potential (43). At the same time, receptor-mediated endocytosis of low-density lipoprotein (LDL) and transferrin has been demonstrated with *T. brucei* (4, 5). While cholesterol is the major sterol in the membrane of the trypanosome, there is no evidence that it can be synthesised by the trypanosome de novo. Cholesterol is not freely available in the mammalian bloodstream but is buried within LDL particles. As a result, it was hypothesised and confirmed by in vitro studies that the ability to endocytose LDL is essential for optimal trypanosome growth: removal of LDL or addition of antibodies against the purified LDL receptors inhibits growth. The receptor appears to be highly conserved and to be localised to membrane of the flagellar pocket and to be completely absent from the rest of the pellicular membrane.

It has also been demonstrated that *T. brucei* parasites bind Epidermal Growth Factor (EGF) and that binding modifies protein kinase activity and the growth rate of the parasites in vitro (19). Furthermore, antibodies to mammalian EGF receptor were found to precipitate a surface polypeptide of the parasite which in turn bound EGF. It would therefore appear that trypanosomes possess a surface growth factor receptor with considerable homology to the EGF receptor, although its location in the parasite remains to be identified.

Thus, possible target(s) for either chemotherapy or immunotherapy do exist and renewed consideration can be given to the feasibility of developing new drugs or a vaccine.
Because of the limitations of the current methods for control and the likelihood that a vaccine will not become available in the foreseeable future, increasing consideration is now being given to the use of trypanotolerant breeds of domestic animals as a sustainable approach to livestock development in tsetse-infested areas. It has long been recognised that certain breeds of cattle, as well as many species of wild Bovidae and Suidae, possess the ability to survive and be productive in tsetse-infested areas without the aid of treatment where other breeds rapidly succumb to the disease (47, 39). This trait is termed trypanotolerance and is generally attributed to the taurine breeds of cattle in West and Central Africa, namely, the N'Dama (Fig. 1; 51) and the West African Shorthorn (52). While there is also evidence that significant differences in resistance to trypanosomiasis occur among various Zebu-\textit{Bos indicus} types (8, 42), most \textit{Bos indicus} cattle in tsetse-infested areas require regular treatment or are found only on the fringes of fly belts. Imported breeds cannot be maintained even in areas of low tsetse risk without intensive drug therapy.

\textbf{FIG. 1}

N'Dama bull reared from an embryo obtained in the Gambia and implanted in a surrogate Boran mother in Kenya
It is thought on the basis of rock paintings and engravings that the taurine Hamitic Longhorn breed, from which the N'Dama is descended, arrived in the Nile Delta from the Near East at about 5000 BC, while the taurine Shorthorn cattle were introduced into the same area between 2750 and 2500 BC (46, 13). In contrast, Bos indicus cattle, which are the most prevalent cattle type in Africa, did not become numerous in Africa until after the Arab invasions of AD 669, although they were recognised in Egypt between 2000 to 1500 BC. It is worth recalling that wild Bovidae, which are extremely resistant to trypanosomiasis (38), emerged in Africa some twenty to forty million years ago (26) and that tsetse probably originated even earlier (16).

While trypanotolerant breeds of cattle are a well-recognised component of livestock production in West and Central Africa, they represent only a small proportion (about 5%, or 8 of 147 million) of the total cattle population in the countries infested with tsetse (21, 22, 23). Failure to exploit these breeds can be attributed to the belief that because of their small size they were not productive and to the view that their trypanotolerance was limited to resistance to local trypanosome populations and that, as a result, their “tolerance” would break down if they were moved to distant tsetse-infested locations where different trypanosome strains were present.

However, these views have not been substantiated by more recent detailed investigations. In a survey on the status of trypanotolerant cattle in eighteen countries in West and Central Africa, indices of productivity were computed using all the production data available for different breeds (21). It was found in areas where the tsetse fly risk was low or zero that the productivity of the N'Dama and West African Shorthorn was equal to that of the trypanosusceptible Zebu which are physically larger. Directly comparable data between breeds were not available in many areas because the level of tsetse challenge was such that breeds other than trypanotolerant ones did not exist. Furthermore, it has been found at the International Trypanotolerance Centre (ITC) in the Gambia that supplementary feeding of N'Dama with local by-products, which are normally discarded, resulted in growth rates of as much one kg per day, producing two-year-old animals weighing over 300 kg. At the same time, little attention has been paid to milk production in N'Dama and it has generally been assumed to be too low even to record. However, preliminary results at the ITC have shown that the average milk yield of 65 N'Dama cows over a practical extraction period of ten months was 313 kg (K. Agyemang, ITC, personal communication). Such a yield is remarkable for animals which had an average bodyweight of 230 kg and which were exposed to tsetse challenge.

As far as resistance is concerned, evidence that trypanotolerance is due not only to resistance acquired to local trypanosome populations has been provided by the successful establishment of cattle from West Africa in distant tsetse-infested areas of West and Central Africa. Examples include the introduction of Lagune (a West African Shorthorn) in 1904 and N'Dama (Fig. 2) in 1920 into Zaire and more recently N'Dama into the Central African Republic, Gabon and Congo (21).

Furthermore, both field and experimental studies carried out on several different breeds of cattle, including Ayrshire, Friesian, Holstein, Hereford and their crosses, as well as indigenous African breeds such as Zebu, Boran, West African Shorthorn and N'Dama have confirmed the superior resistance, or trypanotolerance, of the latter two breeds, as judged by the ability to resist the effects of infection, i.e. not only to survive, but to gain weight and reproduce (47, 52, 39, 41). Anaemia is a well recognised and inevitable consequence of trypanosome infection in domestic animals
in general and cattle in particular \((20, 37)\), and it has been consistently noted that trypanotolerant cattle when they become infected develop less severe anaemia \((41)\). At the same time, it has been noted that the intensity, prevalence and duration of the accompanying parasitaemia are less than that observed in more susceptible breeds \((9, 39)\). Thus, it has been concluded that the ability to resist anaemia and to control parasitaemia are key indicators of the trypanotolerance trait.

![N'Dama cattle ranched in a tsetse-infested area of Zaire](image)

**FIG. 2**

**N'Dama cattle ranched in a tsetse-infested area of Zaire**

The validity of the foregoing experiments and the conclusions drawn have been and must be called into question for several reasons. In many studies, the disease history, in particular whether or not a previous infection with trypanosomes had been experienced, was not known. In some cases, groups of animals were exposed to field challenge or wild caught tsetse, a situation in which it is not possible to guarantee a uniform infective challenge. In other experiments, cattle were infected by syringe inoculation with bloodstream forms of the trypanosome; some workers, excluding ourselves, believe that this method of infection might give misleading results as the skin in which the tsetse deposits the infective organisms, is by-passed by syringe inoculation.

However, all these questionable factors were eliminated in an experiment carried out at the International Laboratory for Research on Animal Diseases, Kenya \((44)\). The N'Dama in this study were obtained as embryos from donors in the Gambia
and implanted into surrogate Boran mothers in Kenya (25). All cattle were born and reared in an area of Kenya free from trypanosomes. Starting at one year of age, eight of these N'Dama were each infected on four consecutive occasions with one of four clones of *T. congolense* transmitted by the tsetse *Glossina morsitans centralis*. While each clone was known to belong to a different antigenic serodeme of *T. congolense*, all had been proven to be equally virulent. The infectivity of every tsetse used was confirmed prior to use on cattle. Boran cattle of corresponding age were challenged at the same time. All animals were maintained on a high *ad libitum* plane of nutrition. To prevent death any infected animal with a PCV value equal to 15% or less was treated with the trypanocidal drug, diminazene aceturate; previous experience had shown it was at this PCV value or less that death might occur.

This investigation completely confirmed the superior resistance of N'Dama cattle when compared to Boran. Thus, N'Dama with no previous experience of trypanosomiasis born to Boran dams that had never encountered the parasite, nevertheless resisted the effects of infection by trypanosomes. During the course of the four different challenge experiments, no N'Dama required trypanocidal drug treatment; in contrast, 77% of all Boran infected did. Moreover, while severe weight losses were experienced by all the trypanosome-infected Boran, compared to uninfected controls, trypanosome infection did not affect liveweight gains in the N'Dama. In contrast to the Boran, infected female N'Dama continued to show normal oestrous cycle activity and were even successfully superovulated.

As in previous studies, the superior capacity of the N'Dama in resisting the effects of infection appeared to lie in the ability to control parasitaemia and resist anaemia (Table I). Previous workers (9) have suggested that the N'Dama's resistance to anaemia was in fact directly correlated with its capacity to control parasitaemia, in terms of intensity, prevalence and duration. However in Paling's studies (44), when mean parasitaemia and PCV values of N'Dama were computed for individual animals over four infection periods, no direct correlation could be established, i.e. certain N'Dama demonstrated higher PCV values during all four infections while others showed better parasite control (Table II); individual animals displayed the ability to resist anaemia or to control parasitaemia in a consistent and repeatable fashion for all four experiments. It was therefore concluded that while both processes are under genetic control, they are not directly linked.

### Table I

<table>
<thead>
<tr>
<th><em>T. congolense</em> clone</th>
<th>Mean parasitaemia score* and packed red cell volume percent (PCV) of N'Dama and Boran cattle infected with <em>Trypanosoma congolense</em> during four consecutive periods (44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean parasitaemia score</td>
</tr>
<tr>
<td></td>
<td>N'Dama</td>
</tr>
<tr>
<td>1</td>
<td>1.90</td>
</tr>
<tr>
<td>2</td>
<td>2.23</td>
</tr>
<tr>
<td>3</td>
<td>2.05</td>
</tr>
<tr>
<td>4</td>
<td>2.20</td>
</tr>
<tr>
<td>Overall</td>
<td>2.10</td>
</tr>
</tbody>
</table>

* scored as described by Paris et al. (45)
TABLE II

Mean parasitaemia score and packed red cell volume percent (PCV) of N'Dama cattle during four periods of infection with Trypanosoma congolense (44)

<table>
<thead>
<tr>
<th>Animal no.</th>
<th>Parasitaemia score</th>
<th>PCV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Ranking</td>
</tr>
<tr>
<td>1</td>
<td>1.12</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>1.93</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>2.46</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>2.03</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>2.13</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>2.10</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>2.14</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>1.86</td>
<td>1</td>
</tr>
</tbody>
</table>

One further important new finding to emerge from this work (44) was that the N'Dama also had a greater capacity to mount better secondary and tertiary erythropoietic responses. Thus, over the course of each of the four infection periods the overall mean of all PCV values progressively increased (Table I). This improved responsiveness was not observed in the Boran nor was it related to improved control of parasitaemia or to a difference in virulence among the four clones of *T. congolense* used.

As parasitaemia wave remission is effected by antibodies directed against the surface coat antigens of the trypanosome (36), it is generally assumed that the superior capacity of trypanotolerant animals to control parasitaemia is associated with a better immune response. There are preliminary studies in N'Dama infected with *T. vivax* (11) and Baoule (West African Shorthorn) infected with *T. congolense* (1, 49) which indicate that this might be the case; this is an important area requiring further research.

Thus, the trypanotolerance trait is associated with at least three characteristics which may or may not be related, namely, the ability to resist anaemia, the ability to control parasitaemia and possibly the ability to mount a more effective immune response to the trypanosome. It is important to know how each of these processes relates to the capacity of the animal to perform and be productive, and if any of them could be used as a marker to select for the trypanotolerance trait.

While it has now been definitely established that the trypanotolerance characteristic is an innate trait, there is evidence that its stability can be affected by environmental factors. Several have been incriminated, including overwork, intercurrent disease, repeated bleeding, as well as pregnancy, parturition, suckling and lactation. However, probably the most important single factor is nutritional status. Thus, when infected village N'Dama in the Gambia were supplemented even with only small amounts of groundnut meal, a local by-product, not only were their growth rates improved but they were significantly less anaemic than non-supplemented animals (K. Agyemang, ITC, personal communication).

At present, no estimates of heritability of trypanotolerance are available. Stewart (54) reported cross-breeding studies involving N'Dama, Zebu and Ghanaian Shorthorn (a trypanotolerant genetic mix) in which he produced a larger, more productive animal that retained its resistance to trypanosomiasis. Similarly, it was found that
N'Dama × Zebu crossbreeds retained a significant degree of trypanotolerance when exposed to natural tsetse challenge (3). In breeding experiments in the Côte d’Ivoire involving large numbers of N'Dama and Jersey, it was observed that the F1 cross produced an excellent animal as regards growth and milk production (27). It was stated that such crosses retained their tolerance, although no information was given on the level of tsetse challenge or on the prevalence of trypanosomes. However, crossbreeds with greater than 50% Jersey background appeared to be less hardy.

Several studies have been carried out on a range of inbred strains of mice, exhibiting a spectrum of susceptibility to *T. congolense* (34, 48) and to *T. rhodesiense* (28, 17). The underlying genetic basis of susceptibility was examined in F1 hybrids and backcrosses derived from mouse strains of high and low susceptibility, while the influence of H-2 haplotype was evaluated using H-2 congenic strains of mice. The general conclusions of these studies were that resistance represented a polygenic model of inheritance and that it was not under the influence of H-2 haplotype. However, it should be emphasised that the mouse infections with high parasitaemias and inevitable death may not be a good model system for cattle.

A major constraint in estimating the heritability of trypanotolerance in cattle is the difficulty of defining and measuring the trait, i.e. what precisely is trypanotolerance. It has now emerged that at least two factors are associated with the trait, the ability to control parasitaemia and the ability to resist anaemia. Furthermore, evidence has been accumulating that the severity of anaemia, as measured by PCV value, in trypanosome-infected cattle is correlated with production traits, such as reproductive performance and growth, suggesting that the PCV values, and possibly parasitaemia profiles, during the course of a trypanosome infection might serve as selection criteria for trypanotolerance.

Recently, Trail et al. (57, 58) have investigated these possibilities, in field research involving N'Dama cattle in Zaire and Gabon. These programmes were designed to measure the effect of control of anaemia on animal productivity relative to that of other aspects of trypanotolerance, e.g. control of parasitaemia; to look at the practicality of its assessment early in an animal’s life; and to evaluate the possibility of its improvement through a genetic selection programme or by use of marker genes, or both.

In Zaire, breeding cows were maintained for three and a half years under a mean monthly trypanosome prevalence (the percentage of animals detected as being parasitaemic at a monthly examination) of 10% per month (57). The comparative influences of time detected parasitaemic, parasitaemia intensity (representing control of development of parasitaemia) and PCV value (representing control of development of anaemia) were measured on calving interval, calf weaning weight and cow productivity (weight of weaner calf per cow per annum).

Significant findings showed that cows with transient parasitaemia had a 14% shorter calving interval and a 15% higher productivity than their contemporaries with prolonged parasitaemia. The effects of parasitaemia intensity were not significant. In contrast, animals maintaining a high PCV value had an 11% shorter calving interval, a 9% heavier calf weaning weight and a 24% superior cow productivity over those maintaining a low PCV value. Control of development of anaemia, as measured by average PCV level, thus appeared to be the criterion of trypanotolerance most closely linked to overall cow productivity. The repeatability of PCV values between calving intervals was reasonably high (0.33) and almost equal to that of calf weaning
weight. The ability of individual N'Dama to maintain PCV values over several different challenge infections has also been demonstrated experimentally (Table II), as discussed earlier (44). The repeatabilities of the various traits measured between successive calving intervals set upper limits to their degrees of genetic determination and heritabilities (14). Thus, the ability to control the development of anaemia, as indicated by PCV value, might well be a reliable criterion of trypanotolerance with which to identify more trypanotolerant individual animals. The fact that calf PCV values were at least as important as dam PCV values in their effect on calf performance suggested that evaluation of this criterion of trypanotolerance in an animal might well be feasible before it reached maturity.

As a result, in Gabon, one-year-old N'Dama cattle were tested by exposure to high natural tsetse challenge for varying lengths of time (58). In three tests, involving over 400 animals, the effects of PCV values on animal growth were confirmed. While a low parasitaemia score was associated with 10% superior growth rates, a high PCV value showed a 44% advantage. It was computed that the major differences in the capacity to control anaemia could be determined within six weeks of detection of parasitaemia and it was proposed that this approach could be used as a field test on young animals to select for trypanotolerance. Alternatively, if satisfactory correlation could be obtained between natural infection effects and those of an experimental infection, such an approach might become even more feasible.

These results are extremely encouraging and suggest that efforts should now be directed towards evaluation of the degree of genetic determination in measures of control of development of anaemia, and their heritabilities and genetic correlations with animal performance traits. Consideration should also be given to the possibility of identification of marker genes associated with anaemia control or with aspects of performance under high trypanosome challenge. To date, the search for markers has concentrated on the major histocompatibility complex and on a polymorphic system of common leukocyte antigens. One major histocompatibility complex encoded phenotype (ECA 121) and two common leukocyte antigens (IL-A37 and IL-A39) have given indications of important associations with maintenance of PCV values and animal performance under trypanosome challenge (56).

In addition to the trypanotolerance trait, trypanotolerant breeds of cattle and in particular the N'Dama would appear to have other genetic advantages that must contribute to their potential for use in livestock development programmes in the tropics. They are reported to be resistant to several other important infectious diseases, including a number of tick-borne infections such as streptothricosis (53), heartwater, anaplasmosis and babesiosis (13). These findings might indicate a greater resistance to ticks per se. N'Dama may also possess some degree of resistance to helminthiasis (H. Kaufmann, ITC, personal communication). In this respect, the Red Maasai sheep of Kenya have been shown to be significantly more resistant than the Merino not only to trypanosomiasis (18) but also to haemonchosis (50). Similarly, it appears that indigenous African cattle such as the N'Dama as well as wild Bovidae are more resistant to environmental constraints because of superior physiological adaptation in terms of food utilisation, heat tolerance and water conservation (39).

Another important aspect when considering the exploitation of the genetic resistance resource in livestock development is that it is likely that chemotherapy might be more effectively and economically applied both in terms of numbers of doses needed and also on the level of dose required. In this respect, it has been shown, at least
in mice, that trypanocidal drugs are more efficacious in mice which are innately more resistant and whose immune system is intact (2, 10). It is also of interest that in trypanosome-infected N'Dama, trypanocidal drug treatment resulted in a rapid and complete recovery of PCV values in one month, with a 70% recovery in nine days (58). While there were no trypanosusceptible controls, in the experience of the authors, infected Boran cattle would have taken much longer to achieve normal PCV values after trypanocidal drug therapy.

DISCUSSION

It is being increasingly recognised that Africa possesses animal genetic resources probably unparalleled on any other continent. These resources have begun providing sustainable and environmentally sound solutions for the vast disease problems currently confronting Africa. Thus, the natural innate resistance to trypanosomiasis and to several other important infectious diseases possessed by breeds of cattle such as the N'Dama and the West African Shorthorn is now accepted as an important additional approach to national and regional disease control programmes. The fact that these breeds also possess considerable production potential offers at a stroke an unparalleled opportunity to improve livestock production in the vast areas of Africa dominated by tsetse, ticks and helminths.

It must also be appreciated that genetic resistance does not mean refractoriness and that high levels of resistance and production need to be supported by adequate management and nutrition. Nevertheless, it is likely that the more resistant breeds will be less demanding from a management point of view, e.g. it is likely that drug requirements will be both less in amount and in frequency. One might even speculate that where vaccines are or do become available, they will be more effective in animals which also possess an innate natural resistance to the disease in question.

While there is an increasing number of examples of innate resistance to disease being identified in domestic livestock, trypanotolerance is one of the best recognised and one of the most thoroughly investigated. Recent experimental (44) and field studies (57, 58) reported in this review are starting to provide the basic tools with which the trypanotolerance trait can be identified and exploited. Thus, the control of the development of anaemia as measured by PCV value during the course of a trypanosome infection has a major effect on production; the repeatability of PCV values between calving intervals has been shown to be reasonably high and almost equal to that of calf weaning weight; the effect of calf PCV values on performance are at least as important as dam PCV values. As major differences in the capacity to control anaemia can be determined within six weeks of infection, the possibility now exists of carrying out selection tests for trypanotolerance on young animals.

It should now be possible to evaluate the degree of genetic determination in the measures of control of development of anaemia, and their heritabilities and genetic correlation with animal performance traits. At the same time, marker genes associated with anaemia control and/or with aspects of performance following trypanosome infection might also be identified.

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Résumé: La trypanosomose transmise par les glossines est l'une des contraintes majeures de l'élevage et de la production agricole en Afrique. L'homme et les animaux peuvent être atteints par cette maladie dont les conséquences économiques sont graves : les pertes, directes et indirectes, se comptent en milliards de dollars par an. En raison de l'existence de variations antigéniques, il n'existe pas de vaccin et, actuellement, les mesures prophylactiques se limitent à l'emploi de trypanocides et d'insecticides. Cependant, les progrès récents dans notre connaissance des glossines et de la biologie des trypanosomes laissent espérer la mise au point de nouvelles méthodes pour piéger les glossines, ainsi que de nouveaux médicaments et même d'un vaccin. Plus important encore, est le fait qu'il apparaît de plus en plus certain que l'Afrique pourrait elle-même contribuer à résoudre ce problème. En effet, en quelques milliers d'années, sont apparues sur le continent africain certaines races de bovins, telles que la race N'Dama et la race des Lagunes, qui sont répandues en Afrique occidentale et centrale. On sait maintenant que ces races présentent une certaine résistance naturelle à la trypanosomose et à plusieurs autres maladies infectieuses graves. Elles sont très bien adaptées aux conditions du milieu et offrent un potentiel de production considérable. La barrière qu'elles opposent au développement de l'anémie résultant de l'infection (évaluée par l'hématocrite) est en corrélation — comme ceci a été démontré — avec la productivité. De ce fait, on peut considérer que la régulation de l'hématocrite est une caractéristique majeure de la trypanotolérance. Ainsi, en évaluant la capacité d'un animal infecté, naturellement ou expériemtalement, à maintenir constant l'hématocrite, il pourrait être possible de mettre au point une technique permettant d'identifier les sujets trypanotolérants, et d'évaluer l'héritabilité de la trypanotolérance. Des programmes de sélection rationnels pourraient alors être instaurés. C'est peut-être l'Afrique elle-même qui a apporté la réponse au problème de la prophylaxie de la trypanosomose.


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Resumen: La tripanosomiasis transmitida por las moscas tsetse es uno de los mayores obstáculos al desarrollo de la ganadería y de la producción agrícola en Africa. Ataca a los animales y al hombre y trae aparejadas pérdidas directas e indirectas estimadas en miles de millones de dólares anuales. Debido al fenómeno de variación antigénica no hay vacunas; en la actualidad, las medidas profilácticas se limitan al uso de insecticidas y trypanocidas. Sin embargo, los progresos recientes en cuanto al conocimiento de la mosca tsetse y de la biología de los tripanosomas permiten esperar que se establezcan nuevos métodos de captura de las moscas tsetse, nuevos medicamentos e inclusive vacunas. Más importante aun es la convicción creciente de que Africa podría contribuir por si misma a la resolución del problema. En efecto, han aparecido en el continente en un período de algunos miles de años ciertas especies bovinas, como las razas
N'Dama y de las Lagunas de África occidental, que se han difundido en África occidental y central. Se sabe en la actualidad que esas razas tienen una cierta resistencia natural a la tripanosomiasis, además de otras varias enfermedades infecciosas graves, están bien adaptadas a las condiciones del medio ambiente y ofrecen un potencial de producción considerable. Se ha demostrado que el obstáculo que oponen al desarrollo de la anemia como consecuencia de la infección, evaluada por el hematocrito, está en correlación con su productividad. Esto permite considerar la regulación del volumen globular como una característica fundamental de la tripanotolerancia. De esta manera, al evaluar la capacidad de un animal infectado para mantener constante el volumen globular tras una infección natural o provocada, se podría poner a punto una técnica capaz de identificar los animales tripanotolerantes y de evaluar la heredabilidad de la tripanotolerancia, e instaurar entonces programas de selección racionales. Tal vez la misma África ya ha aportado la respuesta al problema de la profilaxis de esta enfermedad.

PALABRAS CLAVE: Hematócrito - N'Dama - Producción - Raza de las Lagunas de África occidental - Resistencia genética - Selección de razas - Tripanosomiasis - Tripanotolerancia.

** REFERENCES **


