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Vickerman K. On the surface coat and flagellar adhesion in trypanosomes. *J. Cell Sci.* 5:163-93, 1969.
[Department of Zoology, University College London, England]

A 12-15 nm thick coat envelopes the body and flagellum of bloodstream sleeping sickness trypanosomes. It is suggested that the replacement of one coat by another of differing antigenic specificity enables the parasite to evade the host's immune response. [The *SCI*® indicates that this paper has been cited in over 245 publications.]

How Trypanosomes Evade the Immune Responses

Keith Vickerman
Department of Zoology
University of Glasgow
Glasgow G12 8QQ
Scotland

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The way in which sleeping sickness trypanosomes survive their host's immune response by changing their antigens first fascinated me as an undergraduate. As the 1960s dawned, I was working on this problem at the East African Trypanosomiasis Research Organisation Laboratories in Uganda. Using cryopreserved trypanosome populations, Matt Cunningham and I[1] were able to show that the same variable antigen types (VATs) were produced by trypanosomes from man and a variety of local animals. On returning to University College London, however, I became enthralled by how trypanosomes adapt to conditions in mammal and vector by cyclically activating and repressing their single mitochondrion.

The antigenic variation work was continued by Ross Gray in Nigeria. He demonstrated[2] that a particular trypanosome stock gave rise to a remarkably predictable sequence of VATs in the blood of mammalian hosts of different species, with apparent reversion to a "basic antigen," and restart of the series, when the trypanosomes were transmitted through the tsetse fly vector. This finding had exciting implications for the vexing problem of how to vaccinate man and animals against trypanosomiasis.

The trypanosome undergoes a complicated cycle of development in the fly, culminating in the production in its salivary glands of the metacyclic form, which alone among the vector stages can infect a mammal. In the mid-1960s it was virtually impossible to conduct experimental tsetse transmission of trypanosomes in the UK as no British laboratory was breeding tsetse flies and, with a transmission rate of less than 5 percent, large numbers of flies were needed to produce the odd salivary gland infection. Infected flies had to be flown in from Africa and slaughtered on arrival to obtain stages in trypanosome development. It was while examining some of this precious salivary gland material with the electron microscope to ascertain the state of the trypanosome mitochondrion that I noticed that the metacyclic had a thick, compact surface coat similar to that which I had seen previously on mammalian bloodstream forms; their noninfective predecessors in the gland had no such coat, neither did earlier stages of parasite development from the fly midgut.

Contemporary thinking held that the variable antigen of trypanosomes was secreted as "exoantigen" into the blood of the host. It immediately crossed my mind that the variable antigen was more likely organised into the coat. Loss of the variable antigen coat in the fly gut would explain the assumption of common antigenic identity at this stage by trypanosomes derived from different VATs:[3] reacquisition of the coat by the metacyclic accounted for Gray's observed reversion to a "basic antigen." That the coat is composed of variable antigen was confirmed while working with Tony Luckins from the University of Edinburgh, after I had moved to the University of Glasgow in 1968.[4]

My group in Glasgow (David Berry, Scott Crowe, Steve Hajduk, Dominique Le Ray, Laurence Tetley, and Mike Turner) went on to show that the metacyclics of a trypanosome clone, instead of expressing a single VAT, express a restricted (12-25) mixture of VATs,[5] which changes with repeated fly transmission, complicating further any plans for vaccination against the African trypanosomiases.

The nature of the variable glycoprotein comprising the coat and the extraordinary gene-switching mechanisms that enable the trypanosome to replace one coat with another went on to become big business in the 1970s and 1980s;[6] and now relevant papers appear regularly in the molecular biology journals. But molecular biology alone cannot reveal the entire story: the sociology of trypanosome populations—how different VATs interact with the immune response so that one fraction of the parasite population lays down its life to enable the rest to survive—remains an unsolved mystery.

Alas for flagellar adhesion: we know little more about it than we did in 1969!

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2. **Gray A R.** Antigenic variation in a strain of *Trypanosoma brucei* transmitted by *Glossina morsitans* and *Glossina palpalis*. *J. Gen. Microbiol.* 41:195-214, 1965. (Cited 130 times.)
3. **Seed J R.** Antigenic similarity among culture forms of the *brucei* group of trypanosomes. *Parasitology* 54:593-6, 1964. (Cited 30 times.)
4. **Vickerman K & Luckins A G.** Localization of variable antigens in the surface coat of *Trypanosoma brucei* using ferritin-conjugated antibody. *Nature* 224:1125-6, 1969. (Cited 125 times.)
5. **Tetley L, Turner C M R, Barry J D, Crowe J S & Vickerman K.** Onset of expression of the variant surface of glycoproteins of *Trypanosoma brucei* in the tsetse fly studied using immunoelectron microscopy. *J. Cell Sci.* 87:363-72, 1987.
6. **Borst P & Cross G A M.** Molecular basis for trypanosome antigenic variation. *Cell* 29:291-303, 1982. (Cited 250 times.)

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