

## Heartwater: an abridged historical account\*

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### ABSTRACT

Heartwater was first recognised and recorded in South Africa as early as 1838. Since then the disease has been described from almost all the countries in Africa south of the Sahara, from certain islands around Africa and from a number of islands in the Caribbean. Most of the research on the disease, at least until fairly recently, was conducted in South Africa. Progress in research on the disease has been slow but a few important findings are highlighted in this paper.

**Keywords:** Cowdriosis, *Ehrlichia ruminantium*, heartwater, history of veterinary diseases, tick-borne diseases.

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Heartwater is a disease of cattle, sheep, goats and some wild ruminants caused by a rickettsia, previously known as *Cowdria ruminantium* but recently reclassified as *Ehrlichia ruminantium*, which is transmitted by the bont tick (*Amblyomma*). Typically the disease, which usually results in death, is characterized by high fever, nervous signs, and the accumulation of fluid in the lungs, brain, thoracic cavity and pericardial sac. It is one of the major causes of stock losses in sub-Saharan Africa.

The first reference to what probably could have been heartwater was made in South Africa by the Voortrekker pioneer Louis Trichardt in 1838 while trekking through what is now Limpopo Province. On the 9th of March he mentioned a fatal disease, 'nintas', amongst his sheep, following a massive tick infestation approximately 3 weeks earlier, as described in his diary on the 17th of February 1838<sup>12</sup>. Almost 50 years later, a farmer, John Webb, reported to the Cattle and Sheep Disease Commission in Grahamstown on a disease that apparently was then generally known as heartwater. He was of the opinion that the disease was introduced into the Eastern Cape at about the same time that William Bowker found a bont tick on a cow that was imported from Zululand in approximately 1837<sup>12</sup>. The disease was subsequently reported from various parts of South Africa, but owing to confusion with

other conditions, such as verminosis and pasture deficiencies, all the earlier information about the incidence of heartwater cannot be fully relied upon. It should be interesting to study other historical documents of the previous century in order to fill the gaps in our knowledge concerning the possible introductions and spread of the disease in South Africa, or for that matter, Africa. Confusion with other prevalent diseases with unknown aetiologies at that time will, however, make this a very difficult task.

There is, therefore, still no definite answer to the question whether heartwater is indigenous to the African continent or whether it has been imported. The resistance to heartwater exhibited by Persian sheep which were introduced into South Africa during 1872 suggests that a possible reason for their resistance could have been previous contact with the disease in their countries of origin<sup>12</sup>. However, heartwater was known in South Africa long before the first importation of Persian sheep and although certain *Amblyomma* species occur on the Asian continent, there is no evidence that the disease exists in that part of the world. To date the occurrence of heartwater has only been confirmed in parts of Africa, islands around Africa and on certain Caribbean islands, where it 'was probably' introduced with animals from Africa during the slave trade. Apart from the distribution of 2 American *Amblyomma* species (*A. maculatum* and *A. cajennense*), which were found to be capable of transmitting the disease in the laboratory, the distribution of heartwater, in general, corresponds closely to that of its recognised vectors. All the existing information

has been consolidated in the form of a global distribution map by Provost and Bezuidenhout<sup>12</sup> and, although not conclusive, suggests that heartwater is an indigenous disease of Africa.

The history of heartwater research is a story of great dedication and perseverance of many workers in this field. Progress has, however, been relatively slow and there have been few significant breakthroughs. The mere fact that research over more than a century has still not provided a satisfactory method of control is a clear indication of the great difficulties that have confronted researchers.

The first major breakthrough came when it was shown by the end of the 19th century, by Dixon and Edington, that the disease could be produced artificially by the intravenous inoculation of blood from sick to susceptible animals<sup>1</sup>. Despite the fact that no organisms could be demonstrated in the blood or other tissues of diseased animals, it was concluded by Hutcheon<sup>8</sup> that heartwater is caused by a living microorganism, at that time believed to be a filterable or ultraviolet virus. At about the same time the long-standing suspicion that the bont tick (*A. hebraeum*) is the vector of heartwater in South Africa was confirmed by Lounsbury<sup>9</sup>. These discoveries made it possible to reproduce heartwater in the laboratory and from then on much attention was given to defining the disease in order to develop some form of control.

One of the most important discoveries was made at Onderstepoort by Cowdry, a visiting rickettsiologist from the Rockefeller Institute for Medical Research in New York. He confirmed the suspicion of Sir Arnold Theiler that heartwater is caused by a rickettsia, by successfully demonstrating the organisms in the tissues of affected animals and in infected ticks<sup>5</sup>. He also named the aetiological agent of heartwater *Rickettsia ruminantium*<sup>5</sup>. The name was later changed to *Cowdria ruminantium*<sup>12</sup>.

This discovery also led to the development of an easy and practical method for the diagnosis of the disease, the so-called brain squash technique which is still widely used for the diagnosis of heartwater today<sup>1</sup>.

Over the years it was proved that many

\*The information is drawn freely from a previous article by Provost and Bezuidenhout referred to in the text<sup>12</sup>.

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wild, but also some laboratory animals, are susceptible to heartwater, or that they can act as asymptomatic carriers of the disease<sup>1</sup>. Since the earliest days it was realised that animals that recovered from the disease were subsequently immune. Extensive studies on the immunity of heartwater by Neitz and coworkers merit special mention<sup>11</sup>. These studies formed the basis of our knowledge of the immunity to heartwater for a very long time. They also provided evidence that circulating organisms are detectable in the peripheral circulation of immune sheep following reinfection, irrespective of whether a demonstrable reaction is produced or not.

A major breakthrough with regard to the control of heartwater was the discovery by Neitz of an effective chemotherapeutic agent, the sulphonamide drug 'Uleron', against the disease<sup>10</sup>. Subsequently other drugs, especially the tetracyclines, were also found to be effective and together they have saved the lives of many animals naturally or artificially infected with heartwater<sup>1</sup>.

Between 1945 and 1970 relatively little new information on the disease became available. During this time a blood vaccine was developed at the Veterinary Research Institute at Onderstepoort, which is still the only commercial vaccine against heartwater<sup>1</sup>. Since 1970 a number of findings have stimulated new interest in heartwater research. Very important was the discovery by Du Plessis and Kümme of an isolate of *Cowdria* which is highly pathogenic for mice<sup>7</sup>. Because of its somewhat atypical immunogenicity and pathogenicity its identity was initially viewed with some suspicion. The discovery nevertheless led to the development of a usable screening and serological test. More recent techniques and information that have become available during research on this organism later led to the isolation of other, more typical murinotropic *Cowdria* isolates<sup>1</sup>. The discovery of heartwater on certain islands in the Caribbean, and the threat of its possible introduction onto the American mainland, has led to the establishment of a number of

international research teams, and the generation of a wealth of very important scientific information on heartwater<sup>1</sup>.

The successful *in vitro* cultivation of *C. ruminantium* by Bezuidenhout and co-workers was another milestone in heartwater research. It opened many new avenues, including improved diagnostic and serological methods<sup>2</sup>. Advanced PCR tests revealed unsuspected genetic diversity in isolates of the organism and a phylogenetic relationship to *Ehrlichia* species. This led to a revision of the order Rickettsiales which abolished the genus *Cowdria* in favour of *Ehrlichia* and the causative agent of heartwater is now called *Ehrlichia ruminantium*<sup>6</sup>.

Genomic libraries were produced for the organism and various genome segments cloned and sequenced. Expression libraries were constructed and tested for immunizing ability, leading to the identification of a genomic locus containing four genes which, when presented as a DNA vaccine, conferred total protection in sheep against a laboratory challenge with virulent organisms<sup>4</sup>.

In 1998 Allsopp attracted substantial funding which enabled him and his co-workers to start an ambitious project aimed at determining the complete nucleotide sequence of the *E. ruminantium* genome. In 2004 the genome project was successfully completed and the fully annotated sequence published, the first bacterial genome to be sequenced in Africa<sup>3</sup>. The genetic information thus obtained allowed a more rational selection of genes with potential for vaccine production. Several genes have been identified which code for proteins which stimulate T-lymphocytes and interferon production and therefore are promising vaccine candidates. Vaccine trials utilising these genes are ongoing but it is a long and expensive process. These more recent molecular advances have been reviewed by Allsopp, Bezuidenhout and Prozesky<sup>1</sup>.

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