EQUINE VETERINARY JOURNAL
Equine vet. J. (2003) **35** (2) 118-120

Strangles, bastard strangles, vives and glanders: archaeological relics in a genomic age

In this issue (p 146), Spoormakers *et al.* (2003) describe 4 cases of *S. equi* metastatic brain abscesses and the application of magnetic resonance imaging as a diagnostic aid in two of them. The detailed pathogenesis of *S. equi* infections and events that result in metastatic abscessation are, at present, only partially understood although the puzzle is just beginning to be unravelled at a molecular level (Harrington *et al.* 2002). The first step in pathogenesis involves bacterial adhesion to the epithelium of the upper respiratory tract. A large number of adhesins have been identified in other streptococci (Fischetti 2000) and homologues for several of these are present in the *S. equi* genome, for example 'sfs', 'zag' and 'fne' encoding fibronectin binding proteins (Lindmark *et al.* 1996, 1999, 2001). The hyaluronic acid capsule of *S. equi*, encoded by the 'has' A,B,C operon (Walker and Timoney 2002) also mediates adherence to host cells (Srivastava and Barnum 1983) and noncapsulated strains are less pathogenic in mice and horses (Anzai *et al.* 1999a). The second step involves invasion of respiratory epithelium to gain access to the lymphatics and blood vessels in the *lamina propria*. *S. equi* produces a number of degradative enzymes, including hyaluronidase (Sting *et al.* 1990), and also cytolytic toxins, notably its streptolysin-S like haemolysin (Flanagan *et al.* 1998), that may assist this invasion. Third, and key to the development of abscesses, is evasion of killing by phagocytes. The major cell wall-associated M-like proteins SeM and SzPSe are antiphagocytic and prevent bacterial opsonisation, a prerequisite for efficient phagocytosis, by inhibiting complement deposition on the bacterial surface and binding fibrinogen (Timoney *et al.* 1997; Meehan *et al.* 2002). The degree of resistance of *S. equi* to killing by neutrophils is also dependent on the level of hyaluronic acid capsule expression; nonencapsulated strains are more susceptible to killing (Anzai *et al.* 1999a). In addition, *S. equi* produces, as yet uncharacterised, leucocyte cytotoxins and peripheral blood mononuclear cell mitogens (Timoney 1988; Mukhtar and Timoney 1988; Anzai *et al.* 1999b) which may contribute to abscess development. However, the regulation of many key events in pathogenesis remain unaddressed, not least the mechanisms of bacterial adhesion and invasion into host epithelium and the interaction between *S. equi* and phagocytes.

Strangles is one of the oldest recorded equine diseases and is notable not just as a disease with enduring clinical significance (Chanter 1997) but also one whose associated clinical terminology has remained resolutely medieval and resistant to modernisation. The terms 'strangles' and 'bastard strangles' are two of the few examples of terms that have survived in the equine veterinary literature for hundreds of years and are still in common usage (Yelle 1987; Timoney 1993; Spoormakers *et al.* 2003) in the modern scientific era.

The earliest surviving European veterinary manuscripts date from the 13th century and the term 'strangles' (appearing in the latin text as *strangulina*) was used by both Giordano Ruffo in his manuscript *De Medicina Equorum*, dated between 1251 and 1256, and Albertus Magnus in his magnum opus on zoology, anatomy and animal disease *De Animalibus*, dated between 1258 and 1262. In their descriptions of strangles, Ruffo, farrier to Emperor Frederick II of Italy, and Albertus, a Dominican bishop, describe the acute clinical disease but not its sequelae; the term 'bastard strangles' was not used although *De animalibus* tantalisingly hints that chronic sequelae 'delayed after effects' were recognised.

The term 'bastard strangles' first appeared in European veterinary literature in the late 17th century. At the time, veterinary medicine was a primitive art practised mainly by unskilled farriers although there were notable exceptions, most famously Jacques de Solleysell, Andrew Snape, William Gibson and Henry Bracken. During this period the terms 'bastard', 'false' and 'imperfect' were used interchangeably to describe atypical forms of disease and there are numerous examples of their use in both the veterinary and medical literature. Writing almost 200 years before the discovery of *Streptococcus equi* subsp. *equi* (Sand and Jenson 1888; Schutz 1888), and with a limited understanding of pathology, it is not surprising that there was disagreement between authors with the term 'bastard strangles' used inconsistently and the terms 'vives' and 'glanders' also used to describe strangles sequelae.

Originally, 'bastard strangles' referred to nonsuppurating submandibular and retropharyngeal lymphadenopathy, often in older horses (de Solleysell 1717; Gibson 1727; Bracken 1737), and not metastatic abscessation as it does in current usage (Spoormakers *et al.* 2003); enlarged, nonsuppurating lymph nodes were described as 'bastard kernels' (Gibson 1727). At this time, rather than 'bastard strangles', metastatic abscessation was referred to as 'glanders' (Snape 1683; de Sollysell 1717; Gibson 1727). Later in the 18th century, although the pathology was not characterised, 'bastard strangles' referred to retropharyngeal lymph node (RPLN) abscesses draining into the pharynx or guttural pouch "*...the most dangerous kind is when besides the above symptoms*

[RPLN swelling] the horse runs at the nose; this by some is called the bastard strangles..." (Bartlett 1777). Furthermore, Bartlett accurately described the pathology of metastatic abscessation "*...for want of properly effecting suppuration, the humours frequently settle or are translated to the lungs, the fleshy bowels or falling on the fleshy parts of the hindquarters…which sometimes kill the horse...*" as a distinct clinical entity, referring to it as 'glanders' and not 'bastard strangles'. The term 'vives' was also in use the 18th century to describe parotid lymph node abscessation (Gibson 1727; Bracken 1737), diffuse retropharyngeal swelling and possibly also guttural pouch empyaema (Gibson 1727; Bartlett 1777), although it subsequently disappeared from use.

At the beginning of the 19th century 'bastard strangles' still referred to RPLN abscess rupture and possibly guttural pouch empyaema "*...the swelling appears on the upper part of the throat or the head of the windpipe…this disorder sometimes discharges itself at the nose, which is very troublesome to cure and is then called the bastard strangles...*" (Clater 1809). Metastatic abscessation continued to be referred to as 'glanders' and not 'bastard strangles' (Clater 1809). Later in the 18th century 'bastard strangles' disappeared from the veterinary literature and was replaced almost exclusively by the term 'irregular strangles' (Cartwright 1849; Wallis 1852; Marshall 1864; Barnet 1865; Blakeway 1870; Cresswell and Cresswell 1885) although 'metastatic abscess' (Tombs 1838; Haycock 1858), 'anomalous strangles' (Hales 1833) and 'suppressed strangles' (Hudson 1853) were used occasionally. Abscesses in the thorax (Barlow 1854), abdomen (Hudson 1853; Nobbs 1836) and nervous system (Hales 1833; Blakeway 1881) were widely reported together with guttural pouch empyaema, ocular disease and laryngeal hemiplegia (Blakeway 1870). Victorian scientific opinion discouraged the use of the term 'bastard strangles' although acknowledged its value as a lay term (Blakeway 1870). Writing in 1861, Professor G. Armitage of Glasgow Veterinary College decried the use of the term 'false' or 'bastard strangles' stating "*...it would be better for veterinary science if we had the moral courage to sweep off the cobwebs of meaningless words and actually say what we mean when speaking of disease, than to submit to the use of word heirlooms of generations almost forgotten...*"

'Bastard strangles' reappeared in the 20th century, initially as a lay term (Hayes 1906; Wortley Axe 1906). Once again, there was little consensus between authors with the term used to describe metastatic abscesses (Hayes 1906), mild disease (Wortley Axe 1906) and retropharyngeal and parotid lymph node abscesses (Isherwood 1926). 'Bastard strangles' was not adopted universally, with some authors refering to atypical strangles with metastases (Meissner 1917), metastatic strangles (Anon 1931) and irregular strangles (Udall 1933). However, 'bastard strangles' persisted in lay texts (Lyon 1950) and is now, unfortunately, embedded within both the lay and the professional equine scientific literature where it refers to metastatic abscessation.

Several research groups are currently exploiting the *S. equi* genome sequencing project (www.sanger.ac.uk) and applying cutting-edge genomic technologies (Chiang *et al.* 1999) to elucidate the molecular basis of pathogenicity for this bacterium. Perhaps, as suggested by Professor Armitage nearly 150 years ago, it is time to apply modern terminology, as well as modern technology, to *S. equi* and consign the term 'bastard strangles' to the archives.

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